From Drug-Eluting Balloon to Drug-Coated Balloon … to Eradication of Intracoronary Metal, a New Ending Story

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In October 1993, the team of the Thorax Center in Rotterdam transmitted three live cases to TCT in a 90-min session: the first one was a three-vessel disease treatment with three Palmaz-Schatz stents (not yet approved in the USA by the FDA) [1]; the second one was a recanalization of a CTO with a laser wire in a patient included in the TOTAL trial [2]; the third one was a drug-eluting balloon treatment (the Dispatch balloon) post balloon angioplasty [3].

Indeed, drug-eluting balloons have existed before drug-coated balloons. The first local drug delivery device for coronary application was the porous balloon, consisting of an angioplasty balloon with laser-made perforations around its circumference. This catheter, however, caused jet-stream lesions to the vessel wall because of the high local infusion pressure. Other infusion methods and a variety of infusion catheters were designed to overcome this limitation, such as controlled low-pressure infusion, microporous balloon, dual balloon, multi-channel balloon, drug delivery sleeve, or iontophoretic balloon. However, all devices had the drawback of not allowing simultaneous distal arterial perfusion. The duration of infusion and the amount of drug administered were thereby limited. The potential hazards of local arterial damage and absence of coronary perfusion while the drug is being delivered confined the use of these devices to the animal experimental laboratory. A quarter of century ago (in 1995), a new local drug infusion catheter (Dispatch Soimed Systems Inc.) was designed to overcome these aforementioned limitations by combining infusion and perfusion characteristics.

At that time, we used to administer 99mTc-labeled heparin through the drug-eluting balloon and during the live case (for the TCT) and as routine we used to push a gamma camera into the cath lab to visualize online, on the screen of the gamma...
camera, the increasing local radioactivity at the site of the balloon angioplasty [4] (see Figs. 1.1 and 1.2).

Yes, indeed, more than 10 years before the use of drug-coated balloon we had a wave of research and hype with drug-coated balloons.

Heparin was known as a powerful inhibitor of smooth muscle cells—in vitro, and for sure we were impacting the vessel wall with the drug, as demonstrated by the remnant radioactivity for 24 h (Fig. 1.2).

Unfortunately, despite the scientifically documented administration of the drug into the vessel wall, it did not affect the neointimal hyperplasia.

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**Fig. 1.1** Distal part of the local drug delivery catheter (Dispatch) showing the deployed 20-mm-long nondilatational coil balloon. The coil consists of six balloon loops wrapped in a nonporous polyurethane sheath. When the loops are inflated, a central conduit for blood perfusion was deployed, and five external blood-free compartments were created. Drug solution entered these compartments through isolated slits in the catheter shaft located between the inflated coils.

**Fig. 1.2** Offline image reconstruction at four different periods during the acquisition: (1) last 15 min of infusion; (2) 15 min, (3) 3 h, and (4) 6 h after infusion and coil-balloon removal. A single image represents 15 min of acquisition.
I lost my interest in drug-eluting balloon and in 1997 Elisabeth Nabel from NHI tried to convince me that upregulation of P27 by a drug called Rapamycin would eliminate the exuberant neo-intimal hyperplasia induced by the baro-trauma of balloon angioplasty.

In 1999, Robert Falotico drew my attention to the neo-intimal inhibition obtained from a pig model treated with a stent-eluting Rapamycin. The rest is history—with Eduardo de Sousa we ushered into the era of drug-eluting stents. There were two drugs: one cytostatic Sirolimus and one cytotoxic Paclitaxel. My preference went to Sirolimus although I tested Paclitaxel in TAXUS II and III trials [5–8]. What was not my astonishment when in 2006 I was asked to review for the *NEJM* a paper on prevention of neo-intimal hyperplasia in patients with in-stent restenosis treated by Paclitaxel drug-coated balloon. I could not detect any methodologic flaws in the paper and I accepted the paper of Bruno Scheller in the *NEJM* [9].

It was in itself the start of a new era, exploring drug-coated balloon versus BMS or DES in restenosis, in primary lesion, in large vessel, in small vessel, in bifurcation, and so on. Fortunately, drug-coated balloon does not have to face the specter of late or very late thrombosis. Paclitaxel was initially used because of its lipophilicity. In the early days of drug-eluting stent era, we used to say that “it sticks to the metal as benzene does.”

A recent meta-analysis on the use of paclitaxel in the peripheral circulation has surprised some clinicians [10]. And, the saga about the correct report of the data is worrisome, but I have to remind the clinicians that animals, such as horses, chewing leaves of a Taxus hedge, may die—it is a powerful drug. But, as beautifully described in the monography of Bernardo Cortese, the technology has evolved. Limus are now used; biolimus A9, because of its lipophilic nature, could have a certain edge on the hydrophilic sirolimus. However, sirolimus encapsulated in lipidic microsphere would do the trick [11] (Figs. 1.3, 1.4, and 1.5) although nano-technology is luring around the corner to make its entry into the field. It seems like yesterday, but it was in 2013 that Pedro Lemos, Renu Virmani, and myself reported the preclinical work on that methodological approach. Figures 1.3, 1.4, and 1.5 describe the salient features of this technology, now widely applied in the clinical arena.

The precise tailor-made use of the principle of drug-coated balloon is also described in detail in the monography. Nowadays, OCT imaging can provide precise dimensions of the vessel and guarantee correct fitting between the balloon dimension and the vessel size (Fig. 1.6).

At some point, at least for stable angina the percutaneous treatment, even without implantation, will be challenged by powerful systemic pharmacological agents, such as monoclonal antibody against PCSK9, aiming at regression of coronary artery disease. Today, a reduction of 22% in revascularization rate has already been documented in the FOURIER trial [12]. Soon we will have to re-think our strategy of treatment and synergy of local and systemic treatment without permanent caging of the vessel with metal—a new Holy Grail!

Since the first stent implantation in 1969 by Dotter [13, 14], it took us more than 50 years to learn how to properly cage a coronary vessel [15]. It may take us as long to abandon the metallic cage as the method of treatment. This is one of the perspectives sketched in this remarkable monography by Bernardo Cortese.
Fig. 1.3  Schematic illustration of the ultrastructure of the nanoparticle containing sirolimus (nucleus, in green), incorporating the combination of two excipient carriers to allow penetration and release of the active agent. Excipient 1 is a lipid-based component with a hydrophilic head and two lipophilic tails, which is the basic unit of a bilayer membrane that encapsulates the particle (note the detail in the right upper panel). Excipient 2 is integrated in the particle envelope, comprising ~5% of the coating mass. It is a calcium-phosphorus-based component with enhanced hemocompatibility that is readily absorbed into the vessel wall and releases the encapsulated drug on variation in pH.

Fig. 1.4  (a) Scanning electron micrography of the nanocarrier drug-eluting stent formulation. From left to right: pre-crimped coated stent; balloon after removal of stent. (b) Scanning electron micrography of the nanocarrier drug-eluting balloon formulation (left panel). Right panel: high magnification microphotography of the nanocarrier coating.
Fig. 1.5 Temporal penetration of DTF-labeled sirolimus nanoparticles after drug-eluting balloon inflation, as assessed by confocal microscopy. The left panels show a diagrammatic representation and the mid- and right panels the actual cross-sectional images. At 1 h (upper panels), 60–70% of circumferential area was marked with DTF signal. No particle was seen below the internal elastic lamina. At 3 days (mid-panels), 30–40% of circumferential area presented DTF signal. The majority of particles were below the internal elastic lamina (some positive signals deeper in media). At 7 days (lower panels), 30–40% of circumferential area had DTF signal. Particles primarily in deep media, with rare extension into adventitia. A: adventitia; EEL: external elastic lamina; IEL: internal elastic lamina; L: lumen; M: media
Fig. 1.6 QCA (quantitative coronary angiography) underestimates the real dimension (laminal flow of contrast medium in contact with the vessel wall is assessed by brightness profile; 2.8 mm, see figure). QIVUS (quantitative intravascular ultrasound) imaging overestimates the real dimension (ultrasound wave has to penetrate the vessel wall over 200 μm before being reflected; 3.2 mm, see figure). OCT (optical coherence tomography) measures the real dimension (light wave has to penetrate the vessel wall only over 20 μm before being reflected; 3.0 mm, see figure).

References