Development in Intracoronary Stents

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Key words:
Coronary artery disease, intracoronary stents, PTCA.

Manuscript received:
June 5, 2001;
Accepted:
November 13, 2001

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In 1964, Dotter et al[1] used the term "stent" to describe wire tubular implants that could be placed in femoral arteries of animals with non-surgical techniques for the first time. The first reports on the use of intravascular stents were made much later, in 1983, by Dotter et al[1] and Gragg et al[2] who placed a wire spring of nitinol in arteries of dogs using a catheter. These reports served as a catalyst for the conduction of experimental research in order to develop such novel devices. In 1985, Gianturco et al[2] published their conclusions on implantation of self-expanding intravascular wire stents in animals. In the same year, Palmaz et al[3,4] introduced the concept of transferring the intravascular stent in a non-deployed balloon and placing it exactly at the lesion site. In 1987, Roussau, Roubin and Schatz[2,4] reported placements of various types of intravascular stents in animals in their publications. A common finding of all researchers, was the severe problem of acute or subacute thrombosis despite intensive anticoagulative treatment. These reports in cardiology, but not radiology reviews, signaled a change of orientation for the intravascular stent technique from the vascular radiology field towards the interventional cardiology domain. In 1986, the first implantation in a human subject was carried out by Jacques Puel[2,4] (Toulouse, France) and soon after that, Ulrich Sigwart[2,4] announced the implantation of 24 self-expanding, intracoronary mesh type stents in 19 patients. The initial indications of intracoronary stent placement were: a) restenosis of prior angioplasty, b) stenosis of aortocoronary grafts, and c) acute artery occlusion, due to dissection during balloon angioplasty. The first favorable results came from a new, so called "Giantourco-Roubin"[2,4], stent. In 1991, Schatz[4,5] announced the results of a multi-center study on 229 intracoronary stent placements in 230 lesions, on 213 patients, using a new, so called "Palmaz-Schatz" stent. Subacute thrombosis reached a rate of 14%, and restenosis 40% in 6 months, i.e. the rates of conventional angioplasty, despite the use of a high-dosage anticoagulative treatment that caused bleeding disorders and prolonged hospitalization. High thrombosis rates convinced cardiologists that intracoronary stents, being foreign bodies, exhibited high thrombogenicity. Using high pressure balloons, Antonio Colombo[4,16] achieved the best, most symmetrical deployment of intracoronary stents, improving blood flow through them. This resulted in lower thrombosis rates and reduction of anticoagulative treatment.

Using high-dosage antiplatelet treatment[4] and without using anticoagulative drugs, subacute and acute thrombosis have been restricted today to acceptable levels. The Benestent and Stress studies established intracoronary stent implantation as a method that reduces restenosis rates at least in one lesion class, and allowed researchers to focus on the enhancement of intracoronary stent features and concomitant medication, in

order to further limit complications resulting from their use. Over time, thrombosis and restenosis issues, combined with technical challenges for the successful positioning of intracoronary stents, helped to determine the features of the ideal stent that may today be briefly described as: flexible, easy to advance, low profile, radiopaque, clot-resistant, histocombatible, easy to deploy and with an adequate support strength.

Restenosis following stent angioplasty

Restenosis is defined as the decrease of the vessel lumen diameter by 50% at the site of balloon angioplasty, either conventional or using an intracoronary stent. There are more than 80 different types of intracoronary stents available today and each has its own, special features, advantages and disadvantages. Typically, they are made of stainless steel and, based on the manufacturing technique, they are classified[4] as follows: 1) tubular form, e.g. Velocity, V Flex, V Flex plus, Bio-Di v Ysio, Be stent, Jo stent Flex, Jo stent plus, Multi Link; 2) coiled plaiting made of metal wire, e.g. Freedom, Wiktor, GR II; 3) repeated rings, e.g. AVE, XT Bard; 4) multiple design, e.g. NIR stent; 5) mesh form e.g. Wallstent etc.

Despite the fact that intracoronary stent placement results in a larger lumen and prevents the elastic retraction of the vessel, the presence of the stent stimulates the restenosis mechanism even more, hence intimal hyperplasia is more significant compared to that with simple balloon angioplasty. Restenosis following an intracoronary stent angioplasty is due to: a) injuries induced to the inner elastic membrane; b) the secretion of mitotic substances and growth factors; c) the prolonged and continuous stress of the stent, and d) the presence of a foreign body (chronic irritation). This complex mechanism of restenosis in each phase remains within the scope of the researchers, in order to reduce the incidence of (acute or subacute) thrombosis and restenosis. Nowadays, researchers try to invent new intravascular stents with particular properties against restenosis, beyond the vessel support. These stents are: 1) coated with various substances or materials; 2) biodegradable; 3) radioactive; and 4) releasing pharmaceutical substances.

Coated intracoronary stents

Numerous pharmaceutical substances have been tested to manage restenosis, either systemically or locally using local catheters (local drug delivery). The local use of methylprednisolone or other steroids, oligonucleotides, heparin and other substances, has not yielded the expected results in the reduction of restenosis. As intracoronary stents remain in permanent contact with the vascular wall, it has been attempted to transfer substances that inhibit thrombosis and reduce restenosis, from the stent to the vascular wall. In order to transfer the active pharmaceutical substances from the stents, the latter must be coated with appropriate polymer substances that slowly release the contained pharmaceutical substance. Such polymer substances may be self-degradable or not. The advantage of a self-degradable polymer is that it disappears after completion of transfer of the active pharmaceutical substance. However, polymers cause an inflammatory reaction that results in contributing to restenosis. As a result, research will be continued until the ideal polymer is developed.

The first attempt was made in the Benestent II[4,12,16] study. Heparin-coated Palmaz-Shatz stents were used in order to reduce the thrombogenicity of the metal surface of the stent. Today, following the improvement of the polymer substance covering the various types of stents, in multi-center studies, where heparinized intracoronary stents are used (Benestent II phase IV, PAMI stent, Tosca), subacute thrombosis reaches 0%. The following coated intracoronary stents are readily available: 1) CBAS[4,16] (Johnson & Johnson: heparinized Palmaz Shatz[5] stent); 2) BX Velocity-Hepamed Coated (Johnson & Johnson); 3) Wiktor-HEPAMED (Medtronic), and 4) Jostent (JOMED, Sweden). Clinical studies are in progress on the application of heparinized stents in elongated stenoses and small diameter vessels <2.5 mm.

Inactive and tissue-friendly substances that do not cause platelet accumulation and inflammatory reactions and, therefore, do not trigger restenosis have been used as coatings for the metal surface of intracoronary stents. Inactivate carbon[4,10] (Carbostent), gold (Goldstent[4,15]), diamond scrapings (Phytis) have been tested as coatings on the surface of various metal stents in clinical practice with relatively good results. BiodiVysio (Biocompatibles, UK) uses phosphatidylocholine[4,16], a natural component of the cell membrane, as a coating of the metal surface of the intracoronary stent. Phosphatidylocholine is the main phospholipid of the biological cell membrane and, therefore, the hydrophilic environment that it

creates, inhibits platelet accumulation and subsequently subacute thrombosis, possibly affecting chronic restenosis. There are clinical studies (CE Mark Study, OPENS Registry, DINSTICT Trial) determining subacute thrombosis <1% and restenosis <20% with the use of Biodivysio. The potential of phosphatidylocholine to act as a polymer, i.e. to bind and release pharmaceutical substances at the angioplasty site, contributes to the management of restenosis.

In the Cardiology Clinic of the University of Athens, Stefanadis et al[6,13,16] have invented an intracoronary stent, where the metal surfaces of the stent are covered with an autologous venous (cephalic vein) or arterial (radial artery) graft. The indications of this combined surgical and subcutaneous technique for the placement of intracoronary stents, are: vessel rupture during angioplasty, acute myocardial infarction, stenoses proximal to the coronary arteries origins, and venous grafts. Intra-hospital thrombosis, infarction or death rates with this method were 0%. Some 87% of these patients did not undergo any revascularization technique (percutaneous revascularization procedure or aortocoronary bypass) in the following two years, and angiographic restenosis was approximately 13.3%. Then, an intracoronary stent became commercially available, that used a thin film (sandwich technique) of synthetic PTFE material (Jostent Coronary Stent Graft, JOMED, Sweden) as a means of coating. This intracoronary stent has been used with favorable results in coronary arteries aneurysms, in venous grafts to prevent thrombus dislodging and embolization, and in coronary vessels perforations during angioplasty. According to the experience gained at many centers, and the French database, it appears that they are appropriate for the above indications, in vessels of diameter >3 mm, and antiplatelet treatment is recommended to extend beyond 3 months, due to high rates of acute or subacute thrombosis.

Biodegradable intracoronary stents

The two primary reasons for the use of intracoronary stents are: vessel dissection, and prevention of restenosis. The dissection healing process lasts at least 6 months. Thus, the presence of a permanent intravascular stent seems to be unnecessary beyond this period. In an 3-year angiographic retest, Kimura et al[4,16,17] determined that the presence of intracoronary stents did not correlate with the lesion progress, nor with the acceleration of atheromatosis in general. Furthermore, the extension of the Benestent I retest to 5 years proved that the enhanced angiographic result is maintained. Although no clear disadvantages are evident due to the long-term presence of the intracoronary stents on the vascular wall, there are clear advantages when they are absent: potential for remodeling of the vessel in case of a new lesion, potential for surgical revascularization for elongated lesions where multiple elongated intracoronary stents had been placed. The first biodegradable intravascular stents[17] were developed by Stack et al at Duke University, of poly-L-lactase. Other similar stents were developed under the combined efforts of Cleveland University, Mayo-Clinic and Thorax Center. D- and L-lactase, polycaprolactone and polyorthoester polymers were used for their manufacturing. All of them, however, caused a moderate inflammatory reaction, exhibited prothombotic properties, and caused a measurable intimal hyperplasia in the experimental models used. Lincoff et al invented a biodegradable intravascular stent made of poly-L-lactase (PLLA), that they enriched with pharmaceutical substances which inhibit the proliferation and differentiation of smooth muscle cells of the tunica media, thus developing the PLLA Igaki-Tamai stent. This was the first biodegradable stent used in humans. Tamai et al. assessed the safety and effectiveness of this stent, by placing 25 stents in 19 lesions of 15 patients. In these cases, no thrombosis, death or myocardial infarction was observed in the first 30 days. Also, no elastic retraction of the vessel was observed in the next 24 hours, as well as in three and six months, as shown by the intracoronary ultrasonograph study. The angiographic restenosis with this stent reached 30%.

Radioactive intracoronary stents

It has been shown that a low dose of radiation[4,7,16] is effective in the treatment of vegetative cell populations, by inhibiting or decelerating their proliferation. This knowledge has led to the assumption that low radiation doses could cause a reduction of intimal hyperplasia and consequently of restenosis following angioplasty. The favorable results of the first (randomized) study for the application of radioactivity in patients with intracoronary stent and restenosis (SCRIPPS Trial) encouraged Herlein et al.[4,7,16] to use radioactive intracoronary stents in ani-

mals. These stents were made of steel "bombarded" with Co, Mg, Fe ions in a cyclotron, and emitted γ and β radiation. The stents used were capable of emitting various radiation doses (0,15 to 23 μCurie). After using the above stent, a reduction of intimal hyperplasia was observed for low and high doses. The intermediate doses caused an increase of hyperplasia, thus proving the complexity of the vascular wall response to radiation. Nevertheless, the regeneration of the endothelium was found to be possible, even though delayed, despite the prolonged exposure to radiation. In order to assess the safety and effectiveness of the Palmaz-Shatz (Fischell ISO) radioactive stent (P^{32}) implantation in humans, the IRIS study was designed and performed. In a 6-month angiographic retest, restenosis was found to be 31%, and the need for a new revascularization was 21%. The above results were considered not particularly encouraging. The European experience comes from the multi-center study of Milan, Vienna and Rotterdam, where radioactive stents (P^{32}) emitting higher radiation dose (24 μCi), were used. Restenosis inside the stent was only 4%, but at its edges >30% (edge effect). Other radioactive intracoronary stents that have been used are: Inflow (0.2-20 μCi), and Act One (1.5-10 μCi). In general, the use of radiation, either in the form of short-therapy, or in the form of radioactive stents, introduces unresolved problems. The therapeutic and toxic limits have not been accurately determined, and the delayed results of ionizing radiation are not clear, while restenosis at the edges of the radiated area remains a particular problem.

Intracoronary stents releasing pharmaceutical substances

The future seems to belong to intracoronary stents with combined properties of support and drug release. The drugs to be released should have genetic and antimitotic[8] properties in order to limit local inflammatory reaction, inhibit proliferation and differentiation of smooth muscular fibers of tunica media and promote rapid regeneration of the endothelium. The pharmaceutical substance Taxol (Paclitaxel) is of particular importance. This is an antineoplastic[9,10,11,18] substance with a dose-related effectiveness. The QuaDs-Qp2 is a stent that releases Taxol. The results from the use of this stent are highly encouraging, based on the first clinical study data of QUANUM phase 1. Multi-center studies are still in progress, such as SCORES Trial and ELUTES Trial (V-Flex+Paclitaxel), where the activity of Taxol-releasing intracoronary stents is tested. RAPAMYCIN[10,18] (Serolimus) is a similar antineoplastic drug. Initial small-scale clinical studies showed that the use of Rapamycin-releasing stents is combined with a 0% thrombosis and restenosis in 6 months. The RAVEL (Sirolimus Coated Bx-Velosity) multicenter study is also in progress. Stents that release NO, which in turn promotes regeneration of the endothelium, have also been tried.

Conclusions

The use of intracoronary stents has undoubtedly facilitated the generic use of percutaneous revascularization methods in coronary arteries disease. However, although they have substantially eliminated the peri-interventional complications and have reduced the restenosis rate, the restenosis issue remains the vulnerable spot of percutaneous revascularization methods. In recent years, various development attempts to develop intracoronary stents have been made in order to reduce restenosis (coating with various substances or materials, use of biodegradable materials, radioactive stents, and stents releasing pharmaceutical substances). Stents coated with various substances or materials, biodegradable stents, and radioactive intracoronary stents do not seem to have particularly contributed to combating restenosis. Stents that release pharmaceutical substances are of particular interest, as precursor studies have showed highly encouraging results regarding restenosis rates following their use. The first substances that seem to be particularly helpful are the antineoplastic drugs. Clinical studies that are expected to be announced soon, will show the real dimensions of the achievements and the challenges of the use of intracoronary stents releasing various pharmaceutical substances.

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