Stents in the Second Decade — Meshes Maturate?

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Summary

Since the refinement of antiplatelet therapy to reduce the occurrence of acute and subacute thrombosis following stent implantation, stents have become an essential device in the armament of interventional cardiologists to combat the unsatisfactory restenosis rates after plain old balloon angioplasty. It has been established that stents offer a superior outcome compared to PTCA in short, de-novo lesions of native vessels, chronic total occlusions, venous bypass grafts, bail-out situations, acute myocardial infarction, and restenotic lesions. New developments in stenting include the use of stents as drug delivery systems for substances with various modes of action (anticoagulative, antiaggregatory, antiproliferative, radioactive, and others), improved mechanical designs, addition of polymer membranes, and the introduction of new coating and stent body materials. Above all, however, the ideal stent should exhibit various properties such as excellent biocompatibility, hemocompatibility, antithrombogenicity, and flexibility. Further aspects comprise good radioopacity, customization in length, design, expandability, and others.

Key Words

Coronary stenting, technical perspectives, clinical perspectives

Introduction

Since the advent of percutaneous transluminal coronary angioplasty (PTCA) in 1977 by Andreas Grüntzig, restenosis rates have remained in the range of 15-47% [1-10]. The initial, limited indication of the technique to non-calcified, proximal, single lesions in large native vessels has been greatly expanded over the last two decades. Nowadays the improved technology of balloons and guide wires combined with increased operators experience reduced the relative and absolute contraindications for percutaneous coronary angioplasty to only a few clinical scenarios, including elective PTCA in unprotected left main stenosis, bifurcation lesions supplying a large amount of myocardium, and diffuse, three-vessel coronary artery disease [11-16]. The most dramatic development leading to this rapid expansion of indications has been the technique of scaffolding the diseased arteries with stents.

Clinical Issues of Stenting

Based on the work of Charles T. Dotter in 1969 [17] and 1983 [18], deployment of stents, named after the English dentist C.T. Stent [19], was pioneered in human coronary arteries in 1986 by Jean Puël in Toulouse and Ulrich Sigwart in Lausanne [20]. The initial indications were limited to bail out situations, unsatisfactory results (e.g. elastic recoil), and to recurrent and complex stenoses [21-25].

The major breakthrough for elective stenting was achieved with the BENESTENT and STRESS-trials, which documented reductions of restenosis rates with the Palmaz-Schatz stent in comparison to balloon angioplasty from 31.6% to 22% [26] and from 42.1% to 32% [27]. These benefits lasted for a minimum of one year [28]. Nevertheless, it must be emphasized that in both trials only de-novo lesions of the proximal left anterior descending artery with a minimum reference diameter of 3 mm and a maximal length of 15 mm were included. Since these landmark studies, the Palmaz-Schatz stent has established superiority over balloon angioplasty alone in recurrent stenosis by reducing restenosis rates from 32% to 18% ($p = 0.03$) and target vessel revascularization from 27% to 10% ($p = 0.001$), and by increasing event free survival at 250 days from 72% to 84% ($p = 0.04$) [29]. It must be noted that this study included only symptomatic

patients with proven ischemia and lesion lengths smaller than 10 mm.

Recently, the Palmaz-Schatz stent showed a significant reduction in restenosis rates in chronic coronary occlusions (> 2 weeks) from 75% to 32% ($p < 0.001$) [30] as did the Wiktor-stent from 74% to 32% ($p < 0.002$) in occlusions older than 4 weeks [31].

Balloon dilatation of stenoses in venous bypass grafts is technically simple [32] but confounded by high periprocedural myocardial infarction (< 12%) and death rates (4%) [33], especially in older grafts. This is due to the fragile fibrous caps covering lesions which are rich in intercellular matrix relative to vascular smooth muscle and lipid cells [34-44]. Stents, however, are also successfully deployed in venous grafts (95-99%) and exhibit lower restenosis rates (17-40%) in comparison to balloon angioplasty (23-68%) [32][39-55].

In acute myocardial infarction the Gianturco-Roubin II-stent was superior over balloon angioplasty with regard to major adverse clinical events in the hospital (3.2% vs. 19.8%, $p = 0.03$) and at one year (17.3% vs. 34.6%%, $p = 0.002$). This was paralleled by an improvement of at least one grade from Grade 3 TIMI flow after 7 days (98% vs. 83.3%, $p = 0.028$) and a reduction of target vessel revascularization of 9.6% vs. 13.4% (ns) at one year [56]. A similar trend was observed in the PAMI Heparin Coated Stent Pilot Trial [57] and other studies [58,59]. Although the results are encouraging, their limits (e.g., sample size, patient selection, follow-up, and others) justify large scale multi-center trials.

Stent Related Issues

As an alloplastic material, stents instigates platelet activation by various mechanisms [60-63] which may induce acute and subacute (< 14 days after deployment) thrombosis in up to 20% of implants [54] [64-80]. Hence, aggressive antiaggregation and anticoagulation were instituted with some progress in reducing (sub-) acute thrombosis but at the cost of increased local complications at the puncture site, leading to the need for surgical repair in up to 13.6% of cases [23][29][55][76-78][81-90].

Once high-pressure stent dilatation established itself as a common technique, with or without intravascular ultrasound, acute and subacute thrombosis rates plummeted to 1-2% [26][38][65][79][91-93]. Consequently, anticoagulation was dropped in favor of combined antiplatelet therapy based on Aspirin and ADP-inhibitors, such as ticlopidin, without any negative impact on (sub-) acute complication rates [34][38][65][84] [89-91][93-97].

Although dilatation of in-stent restenosis is usually not a challenge, the acute luminal gain is about 15% less than in stent deployment. The targeted stent-to-vessel ratio of 1.0-1.1 may only rarely be achieved with PTCA alone. This may explain the higher recurrence rates with in-stent restenotic lesions, especially long lesions, in the range between 30-85% [85][98-100].

Along with these technical and patient-related mechanisms, the architecture of the stent, defined by surface, bulk material and mechanical design, is a factor in stent procedure outcome as well [101]. During balloon inflation stents may form wings in a dog-bone-like manner [101-102]. Thus, penetration into or even perforation of the outer layers of the vessel [103] is a matter of concern. Furthermore, stents may stretch the artery with resulting vascular trauma at the edges. A crucial role in this issue may be attributed to the architecture of the device and the deployment balloon. The required inflation pressure is an additional variable of stent deployment and may have a wide range among the different balloon catheters and stents. As this difference in expansion behavior leads to various types and severity of vascular injury, it also influences restenosis [104]. Thus, once again, stent design (e.g., coil stents, slotted tube stents) plays a key role in the outcome of the interventional procedures. From a clinical point of view, this explains why restenosis occurs primarily at the margins and at the articulation of the tubular elements of slotted tube stents [105]. Analysis of the mechanical properties of the stent at various stages of its use (e.g., prior to inflation and at different diameters during deployment) is critical for predicting the short- and long-term performance of the stent. It is intriguing to speculate that, for different types of lesions and vessels, different stents may perform better than others in terms of clinical outcome.

During deployment, stents may have to withstand significant external forces. Threats to the stent structure and surface may include the PTCA equipment and the arterial system (e.g., calcified lesions). If stents are crimped manually onto the balloon by the operator, the devices are exposed to uncontrolled, unpredictable, non-standardized, and non-reproducible forces that may damage the stent architecture, thus making the design of stents that are not pre-mounted on the deli-

very balloon even more complex than for pre-mounted stents.

Another concern is antiaggregation therapy. Although considerable progress was made by discontinuing systemic anticoagulation, there are still patients who may not tolerate aspirin, ticlopidin, or successive "super-aspirins". One possible approach to this dilemma is to reduce thrombogenicity of the stent itself by covering it with a thin, antithrombogenic layer in a hybrid design. Amorphous silicon carbide showed a 2-3 fold prolonged clotting time in vitro by reducing cleavage of the fibrinogen molecule through electrochemical mechanisms [60][121]. A stainless steel slotted tube stent covered with a thin (0.5 µm) layer of amorphous silicon carbide was implanted in the iliac arteries of New Zealand White Rabbits. Histology revealed only limited smooth muscle cell proliferation and low restenosis rates [106]. Preliminary results in a prospective, non-randomized clinical trial showed a recurrence rate of 21% with the TENSUM® stent [107]. A prospective randomized clinical trial with sufficient power is ongoing (TENISS).

Many agents have potential as antiproliferative agents for stent procedures. The list of possible anti-restenosis drugs includes heparin, hirudin, prostacyclin, NO, glycoprotein IIb/IIIa receptor antagonists, the tissue factor pathway inhibitor (TFPI), and antisense oligonucleotides (c-myb, c-myc, PCNA, cdc2, cdk2, PDGFR-b) [108]. It must be emphasized that drugs which are antiproliferative in vitro only rarely exhibit clinically relevant antiproliferative effects when applied systemically [108]. One method of increasing local drug concentrations without systemic effect is to attach the antiproliferative agent to the stents directly or to incorporate the drug in a membrane sheathing the stents. Clinical trials examining this method are currently underway [80].

Another antirestenosis measure that is currently being researched is treating the lesion site with radiation, much as one would treat a proliferative tumor. Gamma and beta radiation emitting sources (^{192}Ir, ^{90}Y, ^{90}Sr/Y, ^{32}P, ^{138}Re, ^{166}Ho, ^{133}Xe) are being studied for this use, either as wires, gas/liquid filled balloons or stents. The key challenge for intravascular brachytherapy seems to be dosing: the treatment should reduce intimal cell proliferation without delaying endothelial coverage or leading to coronary aneurysm [30][110-111]. Current clinical trials demonstrating the feasibility and safety are preliminary; the long-term effects need further observation [109].

Stents may also be coated with various polymers or vessel allografts [108]. However, stent coatings negatively influence the mechanical properties of the device (profile, flexibility, elasticity, and others) in the majority of cases and often elicit an increased foreign body response.

Following implantation, stents are covered by the endothelial layer within four weeks. Thus, a stent may only need to be in place for a short time. Re-endothelialization rules out explantation due to the damage caused to the vessel wall upon removal of the stent, so researchers have focussed their interest on biodegradable stents instead of removable stents. Biodegradable stents have been deployed in animals with limited success due to increased intimal proliferation with severe restenosis during stent degradation [112]. In addition, the mechanical properties of biopolymer stents do not yet meet the requirements of conventional scaffolding devices (e.g. radial strength, elasticity, plasticity, elastic recoil).

Parameter	Property
Biocompatibility	Excellent
Hemocompatibility	Excellent
Antithrombogenicity	Excellent
Coating	Variable
Sheathing	Variable
Radioopacity	Good, without jeopardizing QCA* measurements
Radial strength	Customized
Profile	Low
Adhesiveness of stent on balloon	Excellent
Flexibility	Excellent
Expandability	Excellent
Lengths	Customized, limited foreshortening during inflation
Life time	Short living (about 4 weeks?)
Cost	Low

Table 1. Properties of the "ideal" stent.
*(*Quantitative Coronary Angiography).*

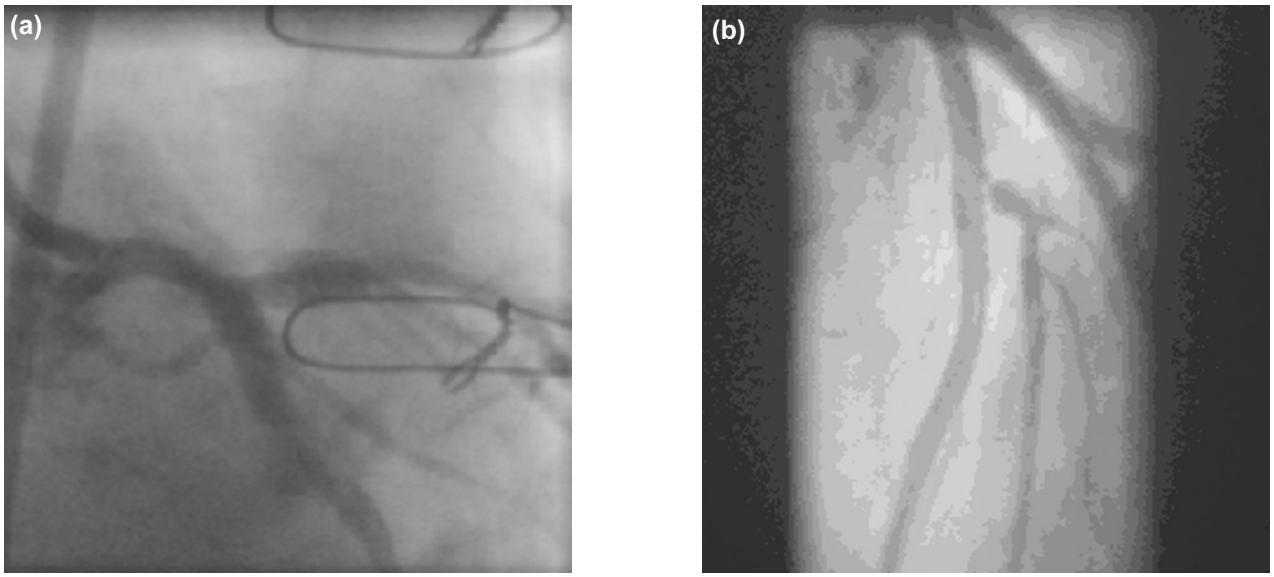

Figure 1. (a) A rather invisible stainless steel stent immediately after deployment into the left main coronary artery. The length of 7 mm emphasizes the importance of customization. (b) The good visibility of the spine of a stent at the cost of impaired quantitative coronary angiographic evaluation.

Beside of these medical aspects stents should also meet the more practical requirements of easy handling to facilitate deployment — and retrieval in case of misplacement — especially for the less experienced operators (Table 1). Cardiologists are primarily bothered by slipping of the stent off the balloon, a bulky profile and the inadequate radioopacity of the device (Figure 1). A sophisticated solution to increase the visibility would be the plating of a stainless steel stent with a radioopaque gold surface. But this may allow for enhanced corrosion with a significantly increased combined rate of death, myocardial infarction, or target lesion revascularization [113]. Covering the marker in a hybrid design with a layer complicates the issue by requirements such as low thickness and thrombogenicity, mechanical stability during deployment and others. On the other hand the hybrid design offers the opportunity of combining the pros of different materials while reducing their cons at the same time [114]. At present, trials in the rabbit are conducted with silicon carbide covering the entire hybrid design highly flexible slotted tube 316L stainless steel stent TENAX® (BIOTRONIK, Germany) with additional gold markers (Figure 2) to assess whether these theoretical reflections translate into any benefit in the animal prior to its application in man. This brief description of one issue substantiates the common experience that optimizing one parameter usually influences and — unless performed carefully — may jeopardize another, so that

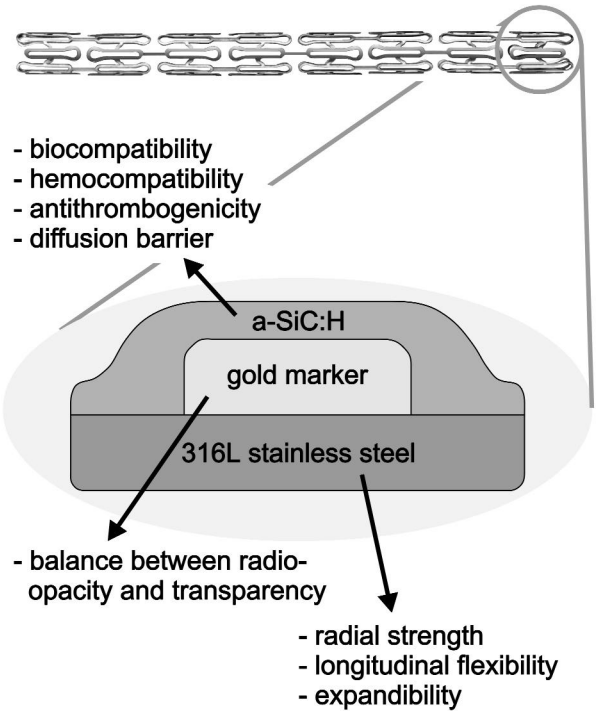

Figure 2. Future improved hybrid design of the Tenax® (BIOTRONIK, Germany) coronary stent with gold markers. At present trials are conducted in the rabbit regarding the biocompatibility.

the "ideal" stent always represents a compromise of the different aspects.

Conclusion

Stents have become a standard part of interventional cardiology practice, and the accepted indications for stenting are continuing to expand. Nevertheless, it should be realized that at present the only documented benefit of "stand alone" stenting in comparison to PTCA is the reduced need for repeat target vessel revascularization [26,27][115] and that repeat plain old balloon in the pre-stent era finally had a success rate of 90% [116]. The "oculostentotic reflex" [117] to smoothen the coronary arteries may not generally be beneficial on the long run. Current data show the future to be either modified stents in the various fashions described above, the combination with systemic drug application [118] or matching the type of stent with the lesion. New and complex technologies should be compared not only with plain old balloon angioplasty but should refer to the possible benefits of the combination of PTCA plus drug therapy [119,120]. Furthermore, not stents alone but, the synergism of stents, balloons and guide wires with complementary tasks may be successful in the restenosis issue.

In general, as doctors have discovered that coronary stenoses are dynamic instead of simple, mechanical obstacles in located indifferent human tubes. The unsatisfactory long-term results of balloon angioplasty or simple stenting has forced them — in collaboration with other disciplines — to search for a dynamic, multifactorial, and adaptive approach to coronary intervention.

This is not the end.
It is not even the beginning of the end.
But it is, perhaps, the end of the beginning.
(Sir Winston Churchill)

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