How Self-Expanding Bare-Metal Stent Design Can Affect Procedural Results

Clinical outcomes in treatment of femoropopliteal artery disease with the Pulsar-18 stent.

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The use of self-expanding nitinol slotted-tube stents for the treatment of femoropopliteal stenotic and occlusive disease has been an essential part of endovascular therapy for the last 2 decades. With the advent of drug-coated balloons, the use of self-expanding stents has decreased, and currently, there is a tendency to follow a leave-nothing-behind approach. This method has led to a shift from primary stenting in the superficial femoral artery (SFA) and proximal popliteal artery toward a bailout-only stenting strategy. In daily practice, however, and especially when dealing with long, calcified lesions, there is still a need for stenting. Therefore, it is important to be aware of the stent design factors that influence clinical outcomes, a role that is typically underestimated. This article provides an overview of these design features and how they relate to clinical results.

CHRONIC OUTWARD FORCE

Chronic outward force (COF) is the radial force that a self-expanding stent exerts at expansion and is related to the stent design, strut thickness, the stent material (the so-called spring constant), and also the amount of oversizing with respect to the vessel diameter. This is the force to which the artery will be continuously exposed after implantation. There are two more radial forces in addition to COF: the radial resistive force that occurs under concentric compression and the crush resistance that occurs under focal compression. COF applies for all self-expanding stents. The more a stent is oversized, the higher the COF will be. When looking at different stents, however, we can see that significant differences occur between the various stent designs depending on the degree of oversizing (Figure 1).

Figure 1 shows that there is a difference not only of the curve’s height that represents the COF under different amounts of oversizing but also in the curve’s steepness, with an almost horizontal course of the self-expanding stent with the lowest COF. The latter finding is especially of importance because it shows that even with an oversizing of 2 mm (which generally is considered to be too much oversizing), no significant increase of COF is perceived by the vessel wall. The relatively small increase in COF related to the degree of oversizing is important in clinical practice because in irregular lesions, stent expansion even after postdilation may not be homogeneous.

Implanting stents in arteries leads to a typical response that follows a response-to-injury sequence of events that is comparable to that of wound healing. In a numerical modeling experiment, it was found that, especially in arteries with heavily calcified plaques, oversizing should be avoided because the low stiffness of the plaque will lead to increased stress to the arterial wall. A similar
study revealed that a higher oversizing ratio will lead to a significant increase in wall shear stress and structural stress that can be associated with damage to the arterial wall and disruption of the laminar blood flow, while not contributing to a significant luminal gain. Given the continuous character of these radial forces (due to the self-expanding design), the damage will continue to accumulate, therewith creating a mechanical environment that is prone to induce restenosis. Therefore, the interventionalist should take care not to oversize nitinol stents in order to improve clinical outcomes.

Related Preclinical Animal Studies

Two animal experiments have shown the negative effect of oversizing on the occurrence of restenosis. The first study looked at the effects of overlapped nitinol self-expanding stents into the iliofemoral arteries of 14 swine. Because of variations in target artery size, the stent-to-artery ratio ranged from 1.2:1 to 1.9:1 (in clinical practice, oversizing of 1 mm is typically recommended, eg, a 6-mm stent in a 5-mm artery, which corresponds to a ratio of 1.2). During the implantation, quantitative angiography was used to assess the arterial lumen and stent diameters. At 6 months, an angiographic study and histologic analysis were performed.

Initially, stent expansion was not complete (ranging from 4.7 mm to 7.1 mm), and stents were seen to conform to the diameter of the target artery. At 6-month follow-up, it was noted that continuous expansion over time had led to an enlargement to nearly the nominal stent diameter (of 8 mm). Histologic examination showed significant effects of oversizing, with marked increases in injury and luminal area stenosis. A statistically significant linear correlation between the stent-to-artery ratio and area stenosis was found. The authors concluded that severe oversizing (eg, a stent-to-artery ratio of 1.4:1) resulted in a histologic response that includes exuberant neointimal proliferation and luminal stenosis.

In the second study, nitinol stents were implanted with a stent-to-artery ratio between 1 and 2.3 and showed similar results. Also, this study used quantitative angiography to calculate the arterial and minimal luminal diameter. Follow-up consisted of quantitative angiography and histomorphometry after 5 months. Stent segments were divided into “normal-sized” (stent-to-artery ratio < 1.4) and “oversized” (stent-to-artery ratio ≥ 1.4). All stent segments were seen to expand almost to their near nominal diameter during follow-up. Normal-sized stent segments increased their diameter by 6% and oversized segments by 29%. A significant correlation between oversizing and restenosis by both angiography and histomorphometry was observed. Again, oversizing was shown to correlate in a linear and positive fashion with neointimal proliferation and restenosis, and this is most likely due to the chronic physical stimulus exerted by the continuing expansion of the stents. Continuous expansion of a self-expanding stent may even lead to stent strut migration to the adventitia. In a study presented by M. Funovics during CIRSE 2017, a comparison was made in a swine model between a low-COF and a high-COF stent, using the same amount of oversizing. At 28 and 90 days, it was observed that the low-COF stent-treated segments demonstrated a smaller neointimal area and area stenosis, lower injury (evaluating the internal elastic lamina [IEL], media, and external elastic lamina), and inflammation scores (Figure 2).

The outcomes of the VIPER clinical study, which evaluated a heparin-bonded expanded polytetrafluoroethylene-covered stent graft in femoropopliteal artery disease, reflected the findings from these animal studies. A statistically significant difference in primary patency was seen between devices with a less than 20% oversizing at the proximal landing zone and those with more than 20% oversizing (88% vs 70%, P = .047). Figure 3 shows a fluoroscopic image after stent implantation (6- X 80-mm Pulsar-18 in 2011, Biotronik) in a severely calcified lesion, with lack of full stent expansion.
in an area of focal calcification, and an angiographic residual stenosis of less than 30% (circle; with a high-COF stent, the stress exerted on the vessel wall would be significant, potentially leading to neointimal hyperplasia); a fluoroscopic image that was obtained 5 years later when the patient returned for treatment of an ipsilateral iliac lesion shows full stent expansion and angiographically, a full patency of the stented segment. This figure illustrates the chronic impact of the stent and its COF on a long-term clinical outcome. With a constant low COF applied to the vessel, patency can be achieved over a long-term follow-up even if the vessel is not fully open immediately after the procedure.

**STRUT THICKNESS**

As mentioned previously, the strut thickness is an important factor that determines the COF of a stent. With a stent strut thickness of 140 µm, the Pulsar-18 stent has the thinnest struts of modern self-expanding stents (others range from 178–228 µm), leading to the lowest metal-to-artery ratio (Figure 4). Despite the fact that there is less material, bench testing has shown that fracture rates are similar to or lower than those with other nitinol slotted-tube stents (Data on file at Biotronik). This low fracture rate is of utmost importance, because it is known that with certain stent designs, there is a high risk of stent fractures, especially when treating long lesions in the femoropopliteal segment.9

The strut thickness also plays a role in the development of the inflammatory response, as a lower injury score for thin-strutted stents was demonstrated in a published study investigating the effect of endovascular stent strut geometry.10 The occurrence of early restenosis and the development of myointimal hyperplasia in stented blood vessels have been attributed to deep vascular injury with IEL fracture.10

This relation was demonstrated in a study that aimed to evaluate the vascular wall response to superficial injury (without IEL rupture) after balloon angioplasty and intravascular (balloon-expandable) stent placement in porcine arteries and the determination of the effect of stent strut geometry on the degree of vessel injury and early restenosis. Two different stents were used, one with rectangular struts and smooth corners, and the other with thicker struts and sharper corners. The latter stent was designed specifically to induce large wall stress concentrations. Intravascular ultrasound was used in all deployments to ensure accurate balloon sizing and to avoid stent overexpansion and deep vascular injury during the procedure. Histomorphometric analysis was performed 90 days after the implantation. Histologic examination showed that the arteries where thick-strut stents were implanted had a statistically higher incidence rate of deep vascular injury with IEL fracture. The arteries that incurred a deep injury showed a 10-fold increase in myointimal thickening as compared to the arteries where the IEL remained intact. This myointimal thickening resulted in a statistically higher restenosis rate than in the arteries without deep injury.

This phenomenon is even more present in vessels with a high plaque burden (where the occurrence of IEL injury is more likely). In cases where only a superficial injury was seen, there was no correlation between the amount of vessel wall/medial layer compression and the development of restenosis from myointimal hyperplasia.

The authors therefore concluded that the maintenance of an intact IEL is an important factor in the prevention of myointimal hyperplasia and restenosis in stented porcine iliac arteries.10 Stent strut profile can increase local vessel wall stress concentrations, which will lead to rupture of the IEL and eventually an exaggerated response to injury. Stent designs should therefore focus on low-profile struts with geometries that allow reduction of local stress concentrations. Several studies in the coronary arteries have demonstrated that the use of thinner struts will lead to a significantly lower restenosis rate.1,10

**THE PULSAR-18 STENT**

Pulsar-18 is a laser-cut self-expanding nitinol stent
loaded on a low-profile 4-F–compatible over-the-wire coaxial delivery system. The stent has a flexible, thin-strut, open-cell design with peak-to-valley segments and six radiopaque markers at each end (Figure 5). It is completely covered with a passive amorphous silicon carbide coating. It has been specially designed with high flexibility, thin struts, and low COF to fulfill the demands of the SFA anatomy.

Pulsar’s safety and efficacy has been investigated through an extensive clinical program in more than 1,000 patients treated with a 4-F endovascular approach across a range of lesion lengths and difficulties (Figure 6).

**4-F-COMPATIBLE ENDOVASCULAR MATERIAL IS SAFE AND EFFECTIVE IN THE TREATMENT OF FEMOROPOPILATEAL OCCLUSIVE DISEASE**

The 4-EVER (4-F Endovascular Treatment Approach to Infrainguinal Disease) multicenter, nonrandomized, prospective trial was designed to observe the safety and efficacy of treating symptomatic femoropopliteal occlusive disease using 4-F–compatible devices without any closure device. There were 120 patients (82 men; mean age, 71 ± 9.7 years; range, 47–90 years), primarily claudicants, treated for 120 femoropopliteal lesions (90% TASC A/B; mean lesion length, 71 mm ± 45.9 mm) in five European centers using 4-F Fortress sheaths, Pulsar stents, and Passeo-18 balloons (all from Biotronik).

Technical success was achieved in all 120 patients. No closure devices were used; the mean manual compression time was 8.1 minutes. There were access site complications (significant hematomas) in 3.3%, mostly in patients who were on warfarin therapy. The duplex-controlled 12-month primary patency rate was 81.4%, with a freedom from target lesion revascularization (TLR) rate of 89.3% and a survival rate of 93%. After 24 months, the primary patency rate of 72.3% and freedom from TLR rate of 82.7% confirmed the 12-month results and showed consistent outcomes over a longer follow-up period.

This trial demonstrated 100% technical success with a 4-F endovascular approach, with fewer access site complications (rate, 0.9% for patients who were not on warfarin) and reduced manual compression time compared to historical values for 6-F treatments, thus supporting the supposition that 4-F endovascular treatment is safe and effective for TASC A and B lesions in the SFA.

**TASC C and D Lesions**

To observe the Pulsar’s performance in difficult lesions, the TASC D study was initiated. The study included 22 patients with chronic total occlusions of the femoropopliteal arteries with an average lesion length of 245 mm, all presenting with critical limb ischemia (CLI) and successfully recanalized using the Pulsar-18 self-expanding stent.

Technical success, defined as establishment of an antegrade straight line flow to the foot through a reopened SFA, was achieved in all patients; 100% of patients had a complete wound healing of their lesions.
during 6-month follow-up. After 12 months, the primary patency rate was 77%, and no major amputation had to be performed, resulting in a 100% limb salvage rate.

A limitation of the trial was the small study population with only 22 patients; however, outcomes showed that a low COF stent like the Pulsar-18 stent can achieve beneficiary primary patency and freedom from TLR rates in long lesions.

The TASC D II study additionally confirmed these results. Thirty-six patients were enrolled in this all-comers registry. The average lesion length of 18.2 cm was longer than that in many of the competitive studies. After 12 months, a promising primary patency rate of 85.4% and a freedom from TLR rate of 87.5% were achieved, thus showing that the Pulsar-18 outcomes are consistent across different lesion lengths and lesion types (TASC A–D).

Furthermore, in the PEACE trial, a prospective, multicenter, all-comers registry including 148 patients with symptomatic femoropopliteal lesions, a subgroup analysis comparing TASC A/B to TASC C/D showed no difference in clinical outcomes \((P = .55)\). Overall primary patency was 87.4% after 6 months and 79.5% after 12 months. The overall freedom from TLR rates were 93.2% and 81% at 6 and 12 months, respectively. The dedicated subgroup analysis found no significant differences between patients with diabetes versus those without \((P = .92)\), with CLI versus non-CLI \((P = .92)\), patients with renal insufficiency versus the overall population \((P = .8)\), patients with lesion length > 100 mm versus the overall population \((P = .09)\), or patients with chronic total occlusions versus the overall population \((P = .67)\).

BIOFLEX PEACE has been designed to provide more answers to the PEACE study. It is a multicenter, all-comers registry investigating the effectiveness of the Pulsar-18 nitinol stent in the treatment of medium-length femoropopliteal lesions in 160 patients. Patients eligible for study inclusion included those with symptomatic peripheral artery disease of Rutherford category 2 to 5 due to > 70% stenosis or occlusion of the SFA or the popliteal artery. Clinical evaluation, duplex ultrasonography, painless walking distance, and ankle-brachial index were evaluated at baseline and after 6, 12, and 24 months (Figure 7). At baseline, 41.9% of the treated lesions were moderately to heavily calcified, and 39.8% were considered complex TASC C or D lesions. The patient demographics were mixed: 71.9% were smokers, 33.1% had diabetes, and 15.3% had CLI.

The 12-month results showed a primary patency rate of 86.4% and freedom from clinically driven TLR of 97.1%; 81% of patients showed an improvement of at least one Rutherford class and change in ankle-brachial index from 0.66 at baseline to 0.89 at 12-month follow-up. After 24 months, clinical success could be maintained, demonstrating a primary patency rate of 78% and a freedom from TLR rate of 92.4%.

Pulsar stents used in BIOFLEX PEACE were implanted with an oversizing of 0.8 mm, which shows that in the real-world setting, interventionalists are aware of the importance of low COF and thus apply as minimal oversizing as possible.

**CONCLUSION**

The importance of the relation between stent design and clinical outcomes in the treatment of femoropopliteal artery disease has been shown in multiple studies. Low COF in combination with a thin strut design of a self-expanding nitinol stent results in less vessel wall injury, leading to a low injury response of the vessel. This feature translates clinically in lower restenosis rates. When stents are used, design characteristics should be considered as an important factor when choosing a stent.

The positive results of the Pulsar-18 stent registries support the endovascular approach in patients with different disease complexities and lesion lengths. Modern next-generation nitinol stents like the Pulsar-18 demonstrate high primary patency rates and event-free follow-up, supporting the safety and effectiveness of this treatment concept.


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