Modern Approach to Vulnerable Plaque and Bifurcation Stenting

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Abstract: *The goal of this animal trial was to test the first prototype of the Viller Stent Delivery System (SDS) for stenting vulnerable lesions and bifurcation lesions. Two male pigs were enrolled in the study. After premedication with aspirin and clopidogrel both animals were anesthetized and implantation of the stents was performed. The stents positioning was checked according to coronagraphy and optical coherent tomography. Pigs were sacrificed while under general anesthesia, their hearts harvested and stents explanted. Results: overall, five stents were implanted. The implantation was feasible in 5 out of 9 attempts. Failure of delivery was reported in two cases and resulted into stent loss. In two cases the balloon burst and devices had to be replaced. The carina match was obtained in 1 out of 4 cases. The protruding part (cone of the stent) was against the side branch in 4 out of 5 cases. In order to visualize the markers in the auxiliary balloon a 10-15% concentrationof contrast substance must be used.*

Keywords: vulnerable plaque, bifurcation lesion, stenting, atherosclerosis

1. Introduction

Despite all of the available diagnostic and treatment modalities atherosclerosis remains one of the most common healthcare problems worldwide with an estimated annual mortality rate of approximately 17,5 million cases [1]. In most cases acute coronary syndrome (ACS) appears to be linked to atherosclerotic lesion associated thrombosis of a vessel [2]. Despite the outstanding progress in the field of percutaneous interventions (PCI) modern interventional cardiology has been haunted for years by two elaborate problems: the problem of a vulnerable plaque (VP) and the problem of bifurcation stenting (BL). In an attempt to solve these problems many societies were formed and came up with different insights and ideas of how to contribute to the vast data necessary to create trustworthy clinical recommendations and patient-follow-up technics.

Concerning the problem of the VP, there is a lot of accessible information, but no strict rules or recommendations. If we regard ACS as a culmination of a pathological process, we may subdivide all of the coronary lesions into two distinct categories including culprit lesions, which by all means appear to be responsible for an ACS, and non - culprit lesions. The transaction of non-culprit lesions into the culprit ones may be described in terms of plaque destabilization. The latter being a rather complicated and largely underestimated phenomenon that encompasses poorly described interactions between plaque structure, hemodynamics and the system of hemostasis[3–5]. Most of the listed above entities can be assessed nowadays via multiple visualization technics including computed tomography (CT) angiography, optical coherent tomography (OCT), intravascular ultrasound (IVUS) and virtual histology etc. This allows us to assess not only the localization and number of lesions but inner structure of a plaque itself. This leads to an important conclusion that each individual might be carefully assessed and all his/her lesions compromising the blood blow in the coronary arteries might be evaluated and treated according to their structure, location and level of blood flow restriction.The treatment of any lesion calls for a combined therapy, which must include

an adequate systemic therapy and different surgical approaches. PCI is widely accepted as a gold standard of culprit lesion associated ACS. Some surgeons propose more aggressive tactics, which include simultaneous treatment of all the assessed during coronary angiography lesions. The results are still controversial, but in recent years it has become clear that a disease compromising all the blood vessels throughout the body is unlikely to be treated with a single stent. This calls for further investigation. The latter must include the mechanisms underlying restenosis and neoatherosclerosis which sometimes compromise the stented lesions.

CT of the heart with angiography allows to estimate CACS and calculate FAI, FFR and vascular remodeling index and combined with biochemistry (dsCRP) gives us an opportunity to evaluate the state of a patient and further tactics. Other necessary elaborations may be achieved with invasive technics as OCT or IVUS etc. All of the lesions might be treated simultaneously or one by one during several consecutive procedures. Considering the complexity of the problem each surgeon is to make this decision on his/her own with appreciation of his/her skills and available equipment. Prior to the intervention it is better to provide a patient with systemic plaque stabilizing therapy.

At this point it can be stated that we can assess and visualize VP, but are not still sure how to react to these findings and, what is also of great importance, if we actually use a correct tool to do treat them.

The stabilization of an unstable nonculprit lesion is a matter of a successful drug therapy[6][7]. But it is now clear that we must also use a correct surgical technic to achieve the following goals:
1) The excessive endothelial damage must be avoided. This means that stent characteristics must closely correlate with the size and topography of a vulnerable plaque. The best way to achieve this, considering the asymmetry of the vulnerable plaque itself, is to use the asymmetrical truncated stents.

2) The use of truncated stents is associated though with the need for specified stent delivery system usage, which would allow the precise positioning of a stent inside the vessel's orifice. Positioning can be achieved through stent delivery system designation with radiopaque labels.

The same things apply to the BL. The rate of incidence of coronary artery BL lies between 15% to 20% [8]. Treatment of them can be challenging and is associated with a high rate of adverse events [9], especially in patients with ACS[10], which implies a constant search for new perspective technics.

In this field clinical recommendations are available and a lot of new devices were introduced lately to simplify the working process and in an aim for the better results. These devises include Trytonside branch stent (SBS), BIOSS stent, Cappella Sideguard, Biguard Axxess.

Tryton stent is now approved by FDA and is included in multiple studies. First reports on long-term clinical results from the single center registry looked promising with acceptable rates of cardiac death, MI, TVR, TLR and ST [11]. The de novo coronary bifurcation lesions were proved to be safely and effectively treated in all cohorts of patients including patients with diabetes and unstable angina [12]. There were no cardiac deaths in the TRYTON trial, the rates of successful placement almost exceeded 95% with overall rate of thrombosis not exceeding 0,5% at 9 – 12 month[13].Trytone SBS was shown to be clinically non-inferior to positional stenting (PS) of left main bifurcation lesions and has favorable angiographic outcomes [14] but only if the orifice of the SBis greater than 2,25 mm and the lesion length of the SBshorter than 5 mm [15]. The system is safe to use with conventional drug eluting stents [16] and shows better results when used with DES [17]. Using everolimus – eluting stent of Trytone design was reported to be a success [18]. The MACE and MACCE for this stent were reported to be 9,8% and 13,9% at 5 years respectively with TLR 6,9% [19].

But there is still room for improvement. Every system has its limitations and Tryton is not exclusion. First of all the need for the target vessel orifice to be greater than 2,25 mm comes to be a major limitation, because Tryton SBS shows high rates of periprocedural myocardial infarction when used for treatment of smaller vessels. In TRYTON trail itself more than one-half of the enrolled lesions had diameter less than 2,25 mm. Later it was shown that Tryton stenting system may reach acceptable target vessel failure rates only when used for lesions with diameter of more than 2,25 mm [20].

The first IVUS studies reported high incidence of SB underexpension alongside with neointimal hyperplasia [21]. And even though the construction of the system seems to be rather simple some studies show that there is still a chance of malpositioning which might lead to unfavorable clinical results [22]. It has been shown that in more than 45% of implantations distal main brunch rewiring was performed through one panel instead of rewiring in-between the panels. However, authors imply that such occasions do not lead to unfavorable clinical outcomes [23]. This combined with

neo-intimal tissue growth makes it mandatory to further develop and upgrade the system. Target vessel failure remains high for Tryton[13], despite superior angiographic results [24].

Tryton has also failed to show any statistical difference in 9 month luminal dimensions, when compared to the SB-balloon angioplasty followed by main branch DES, when controlled using IVUS and 3D-QCA [25].

All the facts stated imply that the use of Trytone is somewhat limited only to LKA bifurcations with very specific characteristics, which makes the use of the stent challenging. Some researches state the question, if it is actually necessary to have such a stent at your disposal, if all the goals can be achieved using more conventional technics. The sirolimus – eluting BIOSSR LIMR is similar to Trytone but is constructed to treat the main brunch first. During the study POBOS II this stent failed to demonstrate better MACE and TLR rates when compared with standard bifurcation treatment with DES [26]. The stent also frequently requires SB rewiring and leaves the SBostium uncovered and implies the second SB stenting.

The Cappella Sideguard (CS) sidebranch stent is a self-expanding device primarily used for treatment of bifurcation lesions. The first studies evaluated its potency to treat bifurcation lesions and showed that although the stent is reported to cause NIH it can maintain sufficient blood flow through the SB [27][28]. The lumen gain is smaller compared with balloon – expendable stents [29]. On the other hand CS can successfully scaffold the ostium of the SB and allows to not to worry about side brunch jailing [30].

Other devices used to treat true bifurcation lesions (0,1,1 and 1,1,1) include Biguard S Bostial stent [31] and Axxess drug eluting stent.

The information on Biguard is somewhat limited. The first-in-man study had the occurrence of MACE as a primary endpoint [32]. Only 47 patients were enrolled in the study. The composite MACE at 12 months was reported to be as high as 10,6% and TLR 8,6%. Almost 33% of patients treated in this study with one stent and kissing balloon inflation experienced restenosis of the main vessel. Even though, the authors found the results of the study satisfactory, further studies are required to produce more reliable data.

The information of Axxess stent is more robust. The Axxess, introduce to the market by Biosensors Europe SA, is a self-expandable biolimus-A9 eluting conical V-shape stent, which is supported by a rapid exchange catheter running over a single wire. Such construction assures that stent can be successfully deployed at the level of bifurcation carina ensuring minimal pressure on the carina meanwhile opening up the orifices of both main and side branches. The stent can be used when the bifurcation angle does not exceed 70. The 3-year clinical results from the Diverge trial proved to be encouraging [33]. Long term results are also proved to be within acceptable ranges [34]. The reported MACE rate was 9,3% at one year and 16,1% at three years. Unfortunately later analysis showed no difference in MACE and TLR

between patients treated with Axxess and patients treated with provisional stenting [8]. COBRA trial failed to demonstrate any statistical differences between culottestentning with Xience and Axxess and Biomatrix stents in stent strut coverage at 9 month [35]. At the same time Axxess provides a better radiation safety and limits the amount of the used contrast fluid [36], which is by all means better for the patient. After the interpretation of analysis of CARINAX registry the list of limitations was updated and the Axxess stents were not recommended for use in cases of moderate-to-severe calcifications and distal lesions [37]. Nevertheless Axxess is to be tested in combination with bioresorbable scaffolds during COBRAII trial [38].

All these attempts share the common problems. They are trying to create a specialized device to meet each individual point, which make them hard to operate and to be of questionable value to possess.

We assume that there should be one more criteria to be met: the system to treat both conditions should be used to treat any lesion plus the stated ones.

To meet this criteria we designed the new stent delivery system (SDS) capable of not only stenting simple lesions but also of working with BL and VP. The need for such device is dictated by recent studies, which in turn show that selective stenting might be better than two stents technique. The throughout description of the basics of this over the wire stent delivery system's construction is not however the goal of this article. All the information can be found in our patent here: US 20100070014 A1 published in 2010.

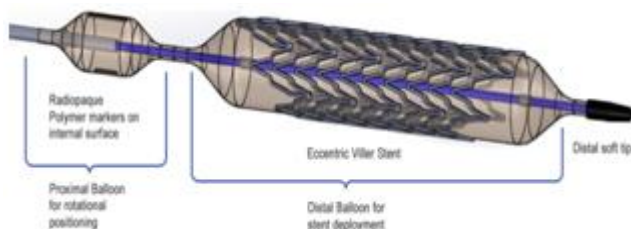The basic structure of the SDSs distal shaft is shown below (fig. 1).

Figure 1

Such SDS works in following order. Both balloons are connected consecutively to the compressor, but radiopaque label bearing balloon is more compliant and expands in the first place allowing the precise positioning of asymmetrical truncated stent in the orifice of the vessel. By applying sufficient force the operator can ensure that the stent is in position, meanwhile, by applying additional pressure, can start the expansion of the second stent- bearing balloon. After the implantation is complete the SDS is removed at once. The goals of the study were to evaluate acute feasibility of implantation and acute performance of a novel SDS on a swine model.

2. Materials and methods

This study was conducted at the Center for Cardiovascular Research and Development. Two female, domestic pigs, weighing 35-40 kg, and 3-4 months old were included in the study. Pigs were acclimated to the experimental facility seven days before the planned procedures. On the seventh day all the necessary procedures were performed, animals euthanized, hearts explanted and vessel segments with implanted stent harvested. Each animal received 150 mg aspirin and 150 mg clopidogrel orally at least two days prior to the start of the study.

After an overnight fast, the animal was anesthetized using a combination of Ketamine (10- 20 mg/kg, IM) and Xylazine (2 – 4 mg/kg, SC). After appropriate sedation, the pig was transported to the preparation room where two intravenous lines were placed in the auricular veins, and intravenous fluids (lactated ringers or 0.9% saline) were administered during the procedure. ECG electrodes were placed over the shaved metacarpal and metatarsal zones to monitor ECG. Throughout the procedure, vital signs were monitored (pulse oximetry, heart rate, respiratory rate and invasive blood pressure,). Propofol was administered (1-2 mg/kg, IV), and when the animal reached an adequate anesthetic plane an appropriate size endotracheal tube was inserted and cuff inflated to prevent leakage. The animal is then transferred to the Cath lab, placed on the table and attached to the anesthesia (Propofol, CRI 0,2- 0,3 mg/kg/min) and a mechanical ventilator unit.

After the proper depth of anesthesia was obtained, a vascular access sheath (6F) was placed in the femoral artery using Seldinger's technique. After the sheath is placed, a heparin bolus was administered.

The 6F guiding catheter was placed into the sheath, advanced via a guidewire under fluoroscopic guidance, and angiographic images of the target vessels obtained. Nitroglycerin (100 - 200 μg) was administered intra-arterially to prevent or relieve vasospasm. For visualization of coronary arteries, angiograms were obtained from at least two near- orthogonal angles. Identical angles were used throughout the implant procedures. The angles were recorded. After the initial identification of the target segments, QCA measurements were performed to determine the target segments diameters.

The SDS with a BM stent was inserted and the stents implanted. The consecutive angiographies were performed to evaluate the stent positioning. OCT was used to evaluate the stent implantation characteristics.

The animals were sacrificed afterwards by qualified staff. At the moment of euthanasia all the animals were under general anesthesia. 1 ml/10 kg intravenous injection of pentobarbital was performed. The case of death was confirmed be cessation of the heart electrical activity, which was assessed by means of ECG.

3. Results

First case
The implantation site was identified in distal LAD. The orifice of the vessel was measured and appeared to be 2,49 mm. The standard concentration of contrast solution was substituted with a lower one 10 – 15%, because of the issues

with visualization of radiopaque labels during the first implantation attempt. During the retraction process the stent fell off the SDS and another balloon was used to remove the stent avoiding further damage to the vessels. The second attempt was also unsuccessful.

During the successful third phase the stent was implanted in LAD. The moderate visualization of the radiopaque labels was achieved with 12 atm. Post-implant angiographies and OCT were performed without any problems. During the procedure the following OCT scans were obtained (Fig. 2), showing that the stent was correctly apposed and the protruding part was not located against SB orifice. QCA measurements were performed once again. Reference diameter 3,16 mm.
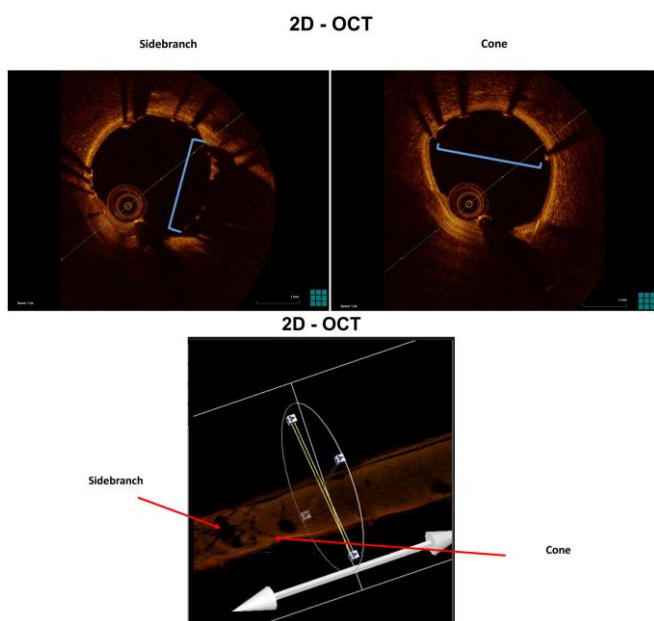

Figure 2

Second case

The study began with LAD. QCA was performed and reference diameter evaluated (2.0 mm). SDS was advanced without any problems. The markers remained visible during the whole procedure. Due to the system integrity issues balloon burst at 10 atm. During post-dilatation attempt implantation turned out to be a success. Once again the OCT study was performed (Fig. 3). OCT demonstrated that stent was correctly apposed and that the protruding part was against SB.
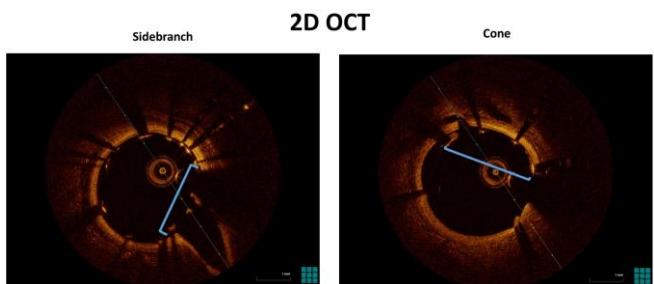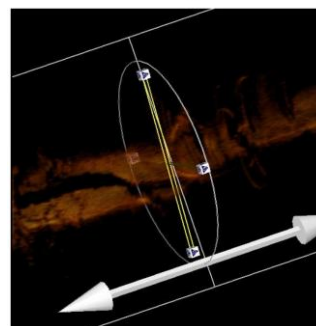

Figure 3

Than the implantation to the middle part of LCX was attempted. The mid-diameter turned out to be 2,6 mm. System was advanced to mid LCX and implanted without problems with the pressure not exceeding 10 atm. Unfortunately, even though the correct position was more or less achieved the carina match was not obtained (Fig. 4).
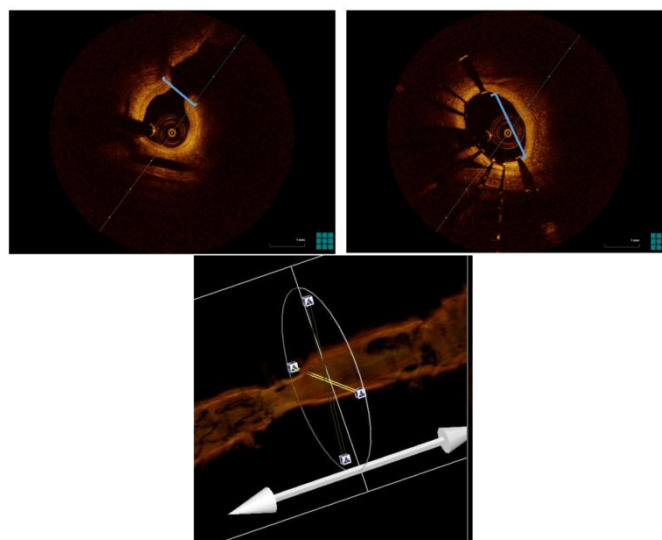

Figure 4

The stenting of the proximal segment of LCX was performed without any problems. The balloon inflated at 17 atm. In OCT the stent was correctly apposed with the protruding part nearly against the SB. The carina watch was no achieved though (Fig. 5).
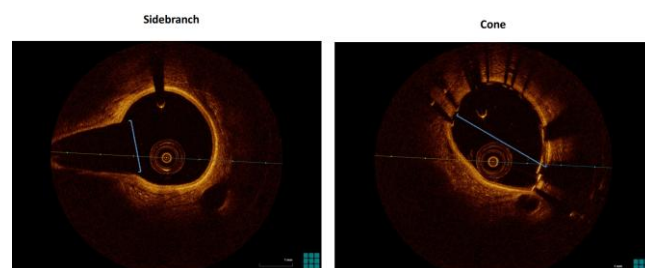

Figure 5

4. Conclusions

Overall, five stents were implanted. The implantation of the tested device was feasible in 5 out of 9 attempts. Failure of delivery was reported in two cases and resulted also into stent loss during removal from the vessel. In two cases the balloon burst and devices had to be replaced. The carina match was obtained in 1 out of 4 cases. The protruding part (cone of the stent) was against the side branch in 4 out of 5 cases.

In order to be able to watch the markers in the auxiliary balloon, a 10-15% concentration must be used, otherwise they are not visible under fluoroscopy.

It is obvious that the stenting system is in early development and needs further improvements. However, we were able to demonstrate that such an approach is possible and that using a system with such a construction might be beneficial in the cases mentioned above.

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