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Coronary bifurcation stenting: insights from *in vitro* and virtual bench testing

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Abstract

The various techniques and devices that have been proposed for the treatment of coronary bifurcation lesions have differing levels of complexity and each has one or more limitations. Two highly complementary ex vivo methods are available to study the treatment of bifurcation lesions: *in vitro* and virtual bench testing. Both methods can be used to develop, evaluate and optimise bifurcation stenting techniques and dedicated devices. The basics, the evolution, the advantages and limitations of both methods are discussed in this paper. Subsequently, a literature overview of the main insights gained from *ex vivo* testing in the field of bifurcation stenting is given.

Introduction

When treating coronary bifurcation lesions percutaneously under ideal circumstances, the stents (and balloons) (i) are easy to insert and deploy, (ii) provide adequate scaffolding, (iii) are not distorted (iv) result in perfect strut apposition (v) are not obstructive and (vi) do not have multiple layers of struts. One of the key factors for the achievement of this ideal scenario is the control of postprocedural stent deformation. Despite the advances being made in the field of bifurcation stenting during the last decade, this ideal scenario is not achieved in common clinical practice and consequently there is room for improvement. Nowadays, state-of-the-art imaging modalities (e.g., OCT) are available to visualise the deformed stent *in vivo*. However, these imaging techniques provide little information regarding the occurring 3D stent deformations. Therefore, *ex vivo* assessment of stent deformations during bifurcation stenting is very important to further improve and refine the treatment of bifurcation lesions. In addition to the accurate quantification of postprocedural stent deformations, it can also be used for the optimisation of procedural parameters (e.g., inflation pressure, balloon inflation sequence, etc.) and it gives valuable insights in the different available stent platforms. Finally, it can play a significant role during the development of dedicated devices.

Currently, two highly complementary *ex vivo* methods are available to assess accurately stent deformations: *in vitro* and virtual bench testing. In brief, *in vitro* bench testing of bifurcation stenting involves the deployment of one or more stents within a bifurcation model and subsequent visualisation of the resulting lumen and stent deformations using for example micro computed tomography (microCT). The prerequisites are physical stent and balloon samples, a phantom bifurcation model, high-resolution imaging facilities and of course expertise. To quantify virtually stent deformations during bifurcation stenting, a numerical technique, called Finite Element Analysis, is used. These virtual bench tests

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require virtual geometrical and material models for every component involved, dedicated hard- and software and of course the necessary skills and experience. The virtual tests allow for example assessment of the stress state of the stented vessel, which is impossible to measure experimentally. However, proper experimental validation is needed to determine whether all model assumptions are justified. If the assumptions cannot be justified, the validity of the model can be challenged. In this paper, both methods are discussed and an overview is given of the main insights gained from *ex vivo* testing.

In vitro bench testing compared with computer simulations

In vitro bench testing has a much longer tradition in the domain of bifurcation stenting compared with computer simulations. In this section, the fundamentals and the evolution of both approaches will be discussed, as well as their advantages and current limitations.

In vitro bench testing

Briefly, *in vitro* bench testing of bifurcation stenting involves the deployment of one or more stents within a bifurcation model and subsequent visualisation of the resulting lumen and stent deformations. Based on these observations, new techniques can be developed, existing ones can be modified and guidelines can be formulated regarding stent choice and procedural parameters (e.g., inflation pressure, balloon size, inflation sequence, etc.). The basis of this approach has remained unaltered since the first publications[1,2], but considerable progress has been made regarding the bifurcation model and the visualisation, two crucial aspects of *in vitro* bench testing.

IMAGING

Initially, conventional photography with a conventional lens or using a paediatric endoscope was the main tool to visualise and analyse bifurcation stenting techniques[3,4], while microCT has become the standard visualisation method. This allows generation of detailed three-dimensional reconstructions which can be used to examine the stents from different perspectives. Parts of the reconstructed geometry can be removed to improve the clarity, cross-sections can be easily obtained and "fly-through" movies can be created.

BIFURCATION MODELS

The first *in vitro* bifurcation models were completely rigid and constructed by, for example, cutting troughs in a flat plexiglass sheet[2]. Another plexiglass plate was fixed over the troughs to constrain the stent and balloon during inflation. Removing this second plate allowed direct visualisation of the deformed stent, which is necessary to avoid light distortion when using conventional photography. These rigid models have been replaced by flexible silicone models (tubes or blocks), as light distortion is not an issue when using microCT. Until now, most bifurcation models had a planar structure. In a simple way, Murasato included the three-dimensional structure of the left main coronary artery bifurcation by gluing silicone tubes on the outer surface of a cylinder with a diameter of 7.5 cm[5]. Now anatomically correct phantoms can be created by stereolithography from materials that have similar characteristics to coronary arteries (Ormiston in press). It is now known that the bifurcation anatomy is not represented by joining simple tubes but the branches have a funnel like configuration at their origins (Figure 1).

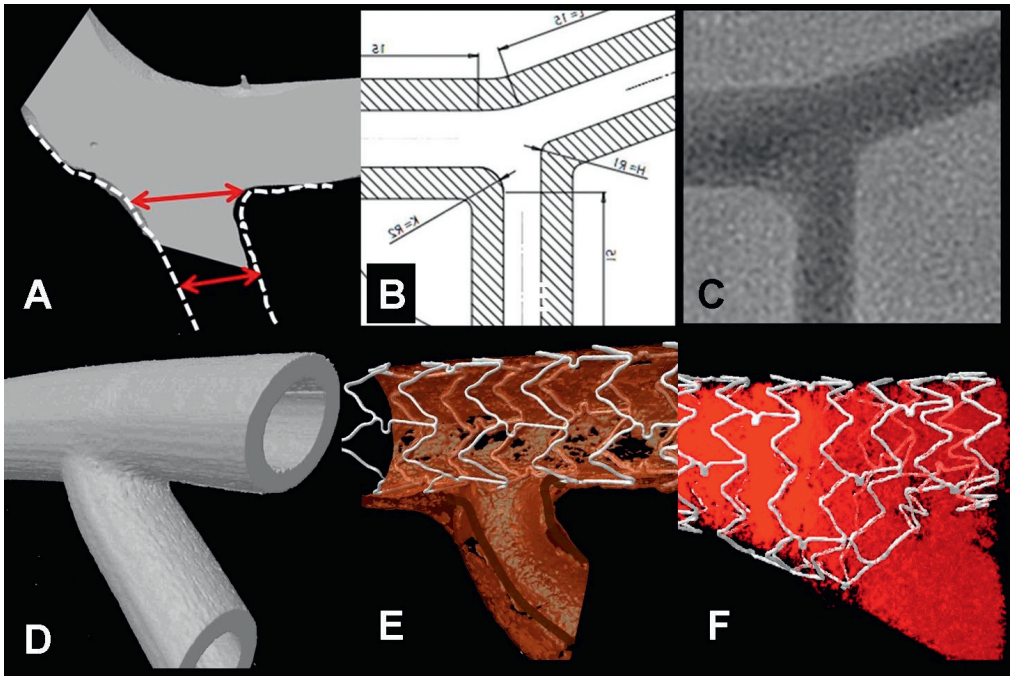

Figure 1. In A is a cast of a human coronary bifurcation (courtesy of Dr. Ormiston) showing that the origin of a branch has a transition zone that is not a simple connection of two tubes but is funnel shaped. From diagrams (B), any shaped bifurcation can be made by stereolithography (C and D). In E the phantom wall is differentiated from the lumen and the stent using microCT. In F the lumen of a phantom is distinguished from the stent by exploiting differences in Hounsfield number.

ADVANTAGES AND LIMITATIONS

In vitro bench testing has a long tradition in this field and the resulting observations are easily accepted by the interventional cardiology community as they are based on real stent deployments. Although proper use of *in vitro* bench testing for bifurcation stenting requires considerable expertise, it is a technique that can be used by a large number of researchers, engineers and physicians. Another advantage of *in vitro* bench testing is that one can really experience and feel things, such as difficulties of advancement of a balloon catheter through the side of a stent. Finally, investigating a large number of cases by *in vitro* bench testing is feasible, as demonstrated by Ormiston et al[6], who deployed 116 stents to study the crush technique.

Although the introduction of microCT has been a great step forward, it is still associated with a number of limitations. First, microCT imaging and the related reconstruction are expensive and time-consuming[6]. Second, simultaneous visualisation of the stent(s) and the phantom arterial wall is feasible but proves to be difficult, although this provides additional insight into the apposition of the stent struts (Figure 2). Differentiating the balloon(s) from the stent(s) is even more challenging when using microCT. A third limitation is related to the fact that only the final stent configuration has been visualised up to now, although information of the evolution of the strut deformations with increasing pressure would be very useful. This would be difficult and time-consuming since every frame would require a complete scan and, moreover, the sample should be stable (i.e., no movement) during each scan. Finally, conducting large studies requires a substantial number of stents and balloons.

Virtual bench testing (finite element simulations)

Finite element analysis is a numerical technique used to investigate virtually the mechanical behaviour of structures, such as medical devices, using dedicated software. The main steps required to perform such a simulation are: (i) the construction of a virtual geometrical model for every component involved, (ii) the definition of realistic material behaviour for these components, and (iii) the assignment of realistic boundary and loading conditions. The application of finite element simulations to study stents (and medical devices in general) could be defined as virtual bench testing. This research domain has undergone a major transformation during the last few years, thanks to increased computer power and innovative simulation strategies, and can now be used to predict accurately strut deformations occurring during bifurcation stenting.

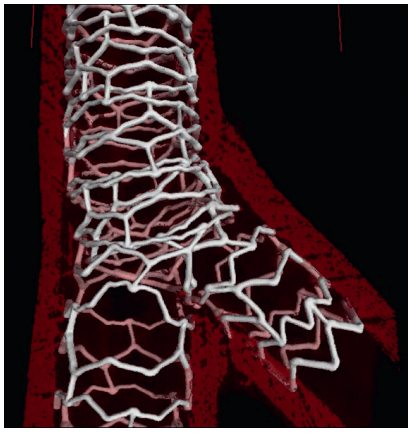

Figure 2. Simultaneous visualisation of the stent(s) and the phantom vessel wall is feasible as shown in this example of culotte stenting (courtesy of Dr. Hikichi).

VIRTUAL BALLOON AND STENT MODELS

Virtual stent models can be created using CAD (computer-aided design) data provided by stent manufacturers or, when no geometrical information is available, by accurately assessing all stent dimensions starting from high resolution microCT stent images (voxel pitch of 1 µm)[7]. The different mechanical behaviour of the currently used alloys (e.g., stainless steel, cobalt-chromium or platinum-chromium) can be incorporated in the models. Similarly, virtual balloon models can be created that accurately mimic the geometry and the behaviour of conventional and dedicated, compliant and non-compliant balloons[8].

VIRTUAL BIFURCATION MODELS

Different approaches can be followed to generate virtual bifurcation models, each one having its own specific benefits (Figure 3). Idealised or artificial models are useful to assess the impact of certain geometrical parameters (e.g., percent area stenosis or bifurcation angle) on the deformations occurring during bifurcation stenting[9,10]. Alternatively, patient-based models can be constructed starting from clinical data (e.g., 3D QCA)[7]. These models allow investigating the stent behaviour within a more realistic environment (Figure 3).

ADVANTAGES AND LIMITATIONS

Although the use of computer simulations to study bifurcation stenting is a relatively recent trend, the initial studies have demonstrated the potential of this approach. Virtual bench testing provides additional information compared with *in vitro* evaluation (e.g., stresses within the vessel wall) and many procedural parameters can be studied without requiring a large number of stent and balloon samples. Virtual bench testing can also incorporate the fluid domain in the bifurcation model, thus allowing the calculation of local fluid dynamic quantities, such as wall shear stresses. Moreover, new device concepts can be evaluated and optimised without having to manufacture every design iteration.

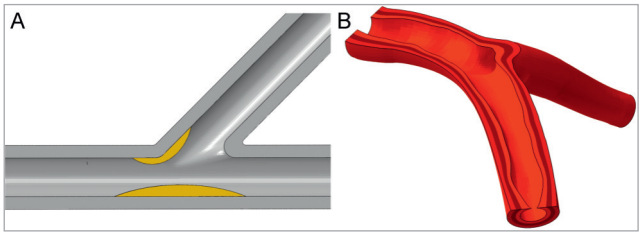

Figure 3. Overview of the different approaches available to generate virtual bifurcation models. Panel A shows an artificially created model (courtesy of Dr. Dubini), while panel B gives an example of a patient-based bifurcation model (courtesy of Dr. Mortier). The type of model should be chosen depending on the application.

Other advantages are that the different parts (balloon, stent and vessel wall) can be simultaneously visualised and that deformations during balloon inflation and deflation can be monitored.

These computer models are based on a number of assumptions and this logically raises questions about the credibility of the simulation results. The only way to get these virtual data verified and accepted by physicians is to put a considerable effort into the validation of these models using experimental *(in vitro)* data. In addition, virtual bench testing remains an engineering tool that requires a solid background in finite element analysis and therefore, this tool is only available to a limited amount of people. In contrast with *in vitro* bench testing, the feasibility of virtually performing large scale studies (including double stenting techniques) still needs to be demonstrated.

Insights from *ex vivo* testing

Ex vivo testing of bifurcation stenting techniques has provided useful insights into the advantages and drawbacks of the different techniques available and has been used to optimise these procedures. In addition, it has led to a better understanding of the behaviour of both conventional stent designs and dedicated devices. The main observations obtained from *in vitro* and virtual bench testing are briefly summarised in this section.

Stent design

The many factors that influence clinical outcomes after drug-eluting stent implantation include the type of drug, the coating and the stent platform. One particularly important aspect of the stent platform when treating bifurcation lesions is the size to which the cells can be expanded by balloon dilatation through the side of the stent. Using stents with large potential cell sizes reduces the possibility of compromising the main vessel (MV) or side branch (SB) lumen after postdilatation. This potential cell size has been reported for a number of stents using different approaches: (i) by inflating a balloon through the side of a stent and measuring the size of the expanded cell on a photograph[4] and (ii) by deriving the theoretical maximal cell diameter from the cell circumference, measured on a 3D reconstruction obtained by microCT imaging[11]. In practice, nowadays almost all contemporary stents have cell sizes more than adequate for bifurcation stenting.

Different stent platforms also cause different stresses within the vessel wall. This was clearly shown in by Mortier and colleagues[7] for three stent platforms virtually implanted in a patient-based left main bifurcation model. The feasibility of using these virtual models to develop stents leading to lower stress levels (and thus ultimately to less injury) was also demonstrated.

Single MV stent

The first *in vitro* bench testing studies focused on the deformations occurring after dilatation through the side of a stent, which is a commonly applied procedure to improve SB access[1,2]. It was shown that such a dilatation markedly improves the SB lumen but also distorts the stent within the MV, resulting in a reduced MV lumen. Redilatation within the main vessel stent or final kissing inflation (FKI) restores the MV lumen.

The first virtual bench study in the field of bifurcation stenting also focused on the effect of inflating a SB balloon through a MV stent[10]. The obtained results were in agreement with the previous *in vitro* observations and thus confirmed the feasibility of using computer simulation to study bifurcation stenting techniques. More recently, Gastaldi et al[9] studied the impact of different stent positions with respect to the SB ostium following to SB dilatation and FKI using an atherosclerotic bifurcation model. Their results correlate well with previous experimental tests in terms of observed deformations of vessel and stent. An interesting finding of this work is that the relative position of the deployed MV stent strongly affects the occurring strut deformations. For the closed cell design which was studied, optimal SB access was only obtained when a cell was centrally placed with respect to the SB ostium. Since the relative position of the stent can not be controlled, it is important to understand that FKI does not guarantee a perfect apposition of all struts. This is also true for open stent designs, as illustrated in Figure 4.

The amount of ostial scaffolding after dilating through the side of a stent is affected by the site of guidewire recrossing. For Y-shaped bifurcations, it has been shown that optimal ostial scaffolding is obtained by inserting the guidewire through a "distal cell" at the SB ostium[12,13].

Two-stent techniques

Many two-stent techniques have been developed, evaluated and optimised using *in vitro* bench testing. In this section, the attention is focused on bench testing observations related to the most frequently applied two-stent techniques.

CRUSH

Bench testing has provided many essential insights into the complex stent deformations induced by crush stenting or a related technique[3]. The crush technique has been introduced with the aim of providing complete ostium scaffolding and optimal drug delivery, but (wedge-shaped) gaps in strut scaffolding have been observed at the distal side of the SB ostium after postdilatation[6,13]. One factor responsible for this incomplete coverage is the position where the wire crosses into the SB. In contrast to the observations in case of a single MV stent, a distal recrossing should now be avoided as this may cause the guidewire to go outside the SB stent, leading to an additional crush of the SB stent within the SB. However, recrossing at the appropriate point is not easy[14]. These gaps are less common when using a mini-crush[6]. Stent cell size also plays a crucial role during crush stenting, as clearly demonstrated by Ormiston et al[6]. They observed a significantly lower residual stenosis after crush stenting when using stents with potential cell sizes that are greater than 3.5 mm in diameter.

CULOTTE

Culotte stenting requires postdilatation through both the SB and MV stent in order to reduce the number of "floating" struts within the vessel lumen. It is therefore important to select stents with an open-cell design, especially when dealing with large daughter vessels. Using stents with cells that can not be sufficiently enlarged will lead to the so-called "napkin ring" behaviour, as demonstrated with microCT imaging[13,15,16].

T-STENTING AND TAP

Bench testing has revealed the main problem with T-stenting, which is the precise placement of the SB stent[4]. A too distal deployment results in incomplete scaffolding, while a too proximal position leaves struts in the MV. Protruding stent struts may hinder the insertion of a balloon catheter within the MV and thus complicate FKI. For that reason, the T-stenting and the small protrusion technique (TAP-stenting) have been proposed, during which the SB stent is intentionally positioned with a small protrusion to fully cover the proximal side of the SB ostium[17]. By placing an uninflated balloon within the MB before deploying the SB stent, FKI can easily be performed and generates a small neo-carina. Stent design may also play an important role during TAP-stenting, as illustrated in Figure 5.

V-STENTING AND SIMULTANEOUS KISSING STENTS TECHNIQUE

The V-stenting technique consists of the simultaneous deployment of two stents in the two daughter vessels. These two stents are positioned with their proximal ends at the carina, and may form a small metallic "neo-carina" when these two ends touch each other. The term simultaneous kissing stents (SKS) is used when there is a

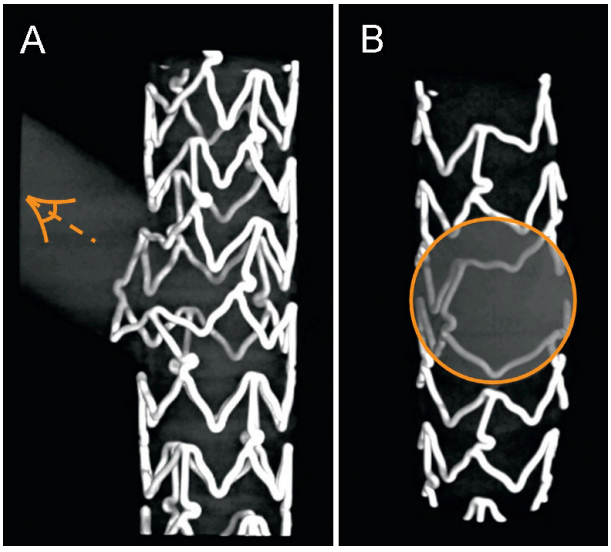

Figure 4. MicroCT visualisation of a Multi-Link Vision stent (Abbott Vascular, Santa Clara, California) after FKI (Courtesy of Dr. Mortier). Panel B gives the view from within the SB (as indicated in panel A) and clearly illustrates that FKI does not guarantee optimal strut apposition[8]. One of the determining factors is the relative position of the stent with respect to the SB ostium[9].

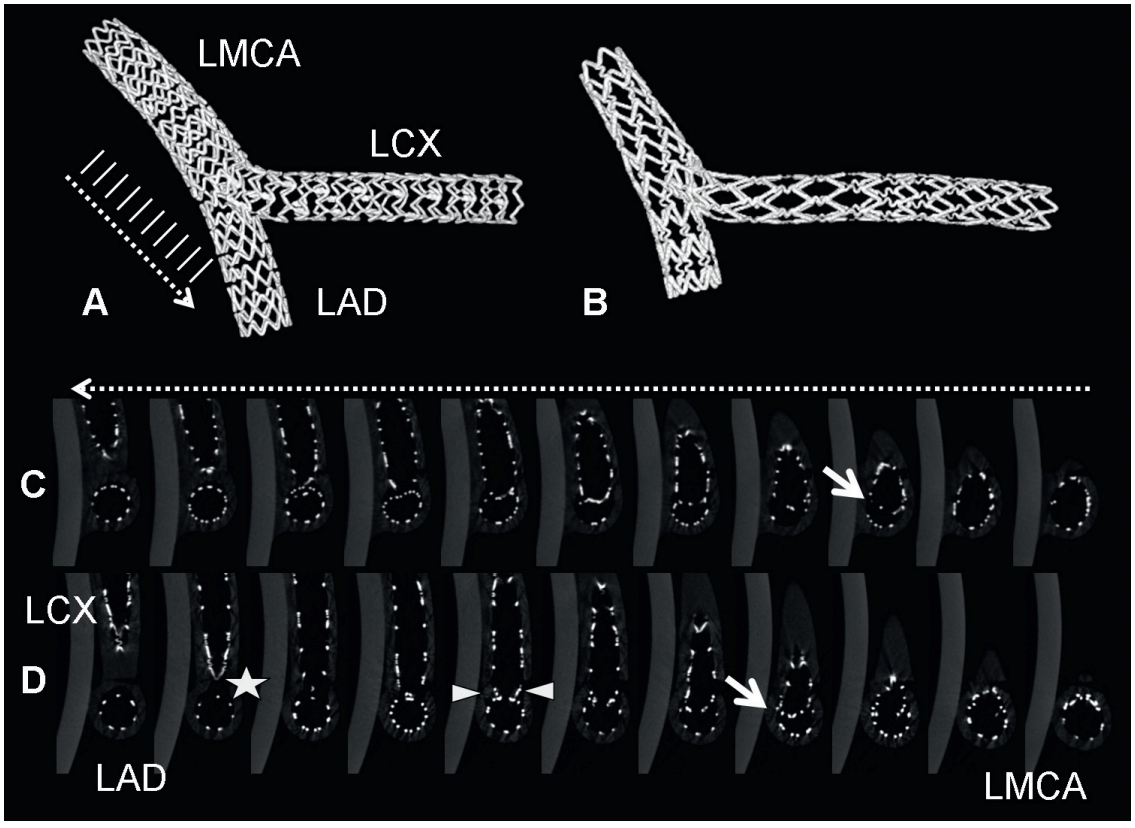

Figure 5. In vitro bench test of T-stenting and minimal protrusion (TAP) technique in the left main coronary artery bifurcation model (Courtesy of Dr. Murasato). (A) A three-dimensional image of micro focus computed tomography of the case using open-cell stents. MV: Driver 3.5/24 mm (Medtronic, Santa Rosa, CA, USA), SB: Multilink Penta 3.0/23 mm (Abbott Vascular, Santa Clara, CA, USA). (B) A three-dimensional image of the case using closed-cell stents. MV: Cypher 3.5/18 mm (Cordis, Miami Lakes, FL, USA), SB: Cypher 3.0/28 mm. (C) Cross-sectional view of model A. Each view was obtained according to the dotted arrow. (D) Cross-sectional view of model B. The Cypher stent was squeezed in the SB ostium (D, triangles) and an unstented area was observed at the carina (D, star). Metallic carina was deviated to the opposite side of the SB in the model A (C, arrow), while it was in the centre of MV in the model B (D, arrow).

large protrusion of both stents in the proximal MV forming a relatively long neo-carina. Although both techniques are quick and easy (guidewire recrossing is not necessary), bench testing has revealed some limitations caused by the generation of this "neo-carina". A typical problem observed with microCT imaging is the uneven expansion of the two stents in the proximal MV segment. It has been suggested that this behaviour occurs when using different stent sizes, which is often required to match the two distal vessel diameters[18]. In addition, twisting of the stents may occur if the length of the stent overlap is large (Figure 5). Therefore, rewiring one of the vessels (e.g., for repeat treatment) while avoiding the guidewire to go through the side of one of the stents may be challenging. Furthermore, the substantial metallic neo-carina with the SKS technique may predispose to stent thrombosis (Figure 6).

Optimising kissing balloon inflation

Final kissing balloon postdilatation is highly recommended when using a two-stent approach as it results in a better apposition of the stents struts and corrects distortion within the MV. The deformations after FKI depend on many factors (balloon pressure and size, inflation and deflation sequence, etc.) and it is extremely important to realise that small procedural variations may have a large impact. *In vitro* bench testing is of great value when attempting to optimise FKI as demonstrated by Ormiston et al[6], who compared a "one-step postdilation" with a "two-step postdilation". One-step postdilation was defined as a single simultaneous kissing balloon postdilation, whereas a two-step kissing postdilation involved a high pressure postdilation in the SB followed by simultaneous kissing inflation. It was shown that a two-step kissing postdilation significantly reduces the remaining ostial stenosis after crush stenting.

It is still a matter of debate whether or not to systematically perform a final kissing postdilation for a single stent technique, mainly because of the Nordic III trial, which showed that there is no benefit of using a routine kissing inflation[12]. This finding is on one hand surprising as FKI improves the strut apposition, but on the other hand, makes sense as this procedure has a number of negative side effects. A computer simulation of final kissing balloon inflation clearly reveals some of these drawbacks (Figure 7): (i) FKI causes and elliptic deformation of the proximal segment. (ii) Direct balloon-artery contact occurs at the entry of the SB which may cause arterial injury. (iii) The simultaneous inflation of the two balloons leads to high stresses within the vessel wall which may in turn trigger an excessive healing response. Some other limitations of final kissing postdilation were highlighted during *in vitro* bench testing studies. Guérin et al[19] observed a significant increase of the coating damage in the proximal stent segment that has been overstretched by the two balloons. Finally, it has been shown that extremely oversized postdilation, for example caused by a kissing postdilation, considerably modifies the strut configuration[20]. This clearly illustrates the need for dedicated devices as stents are currently being expanded to a diameter they were not designed for. In order to minimise the elliptic deformation after kissing postdilation, a minimal balloon overlap is recommended[13]. In addition, a high pressure proximal inflation using a short noncompliant balloon could be used to correct proximal stent distortion[12].

Dedicated stent systems

The use of *in vitro* and virtual bench testing during the development of dedicated bifurcation stent systems may help to better understand and to improve the products in an early phase[8,21]. A particular advantage of using a virtual approach is that several device iterations can be investigated without having to manufacture every intermediate design. On the other hand, *in vitro* bench testing facilitates the "feel" of product behaviour, for example, how easy is accurate positioning. In conclusion, a good combination of thorough *in vitro* and virtual bench testing early in the development process can reduce costs, timescales and risks associated with the development of a new device.

An example of the use of computer simulations to optimise a novel bifurcation stent system has been described[8]. The simulations were used to investigate the feasibility of a novel dedicated stent design and procedure for provisional stenting, that has been developed by Boston Scientific in collaboration with Dr. Sjögren (Falun Hospital, Falun, Sweden). The Liberté based stent design has an adapted strut pattern in the central stent region providing the possibility to reach a larger diameter at the SB ostium. A postdilation with a short oversized compliant balloon was thought to be useful for improving SB access and facilitating guidewire introduction through a distal cell. Simulations proved to be valuable in assessing the feasibility of this concept and in quantifying the impact of several design and procedural parameters such as balloon size, pressure, and strut width.

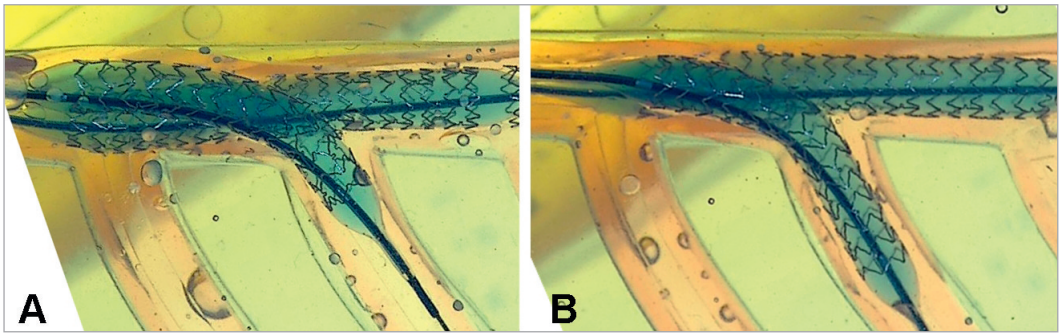

Figure 6. In vitro bench testing of the simultaneous kissing stent (SKS) technique (Courtesy of Dr. Murasato). Stent twisting may occur within the proximal MV when there is a long overlap of the stents (Panel A). This phenomenon is less pronounced when using minimal stent overlap (Panel B).

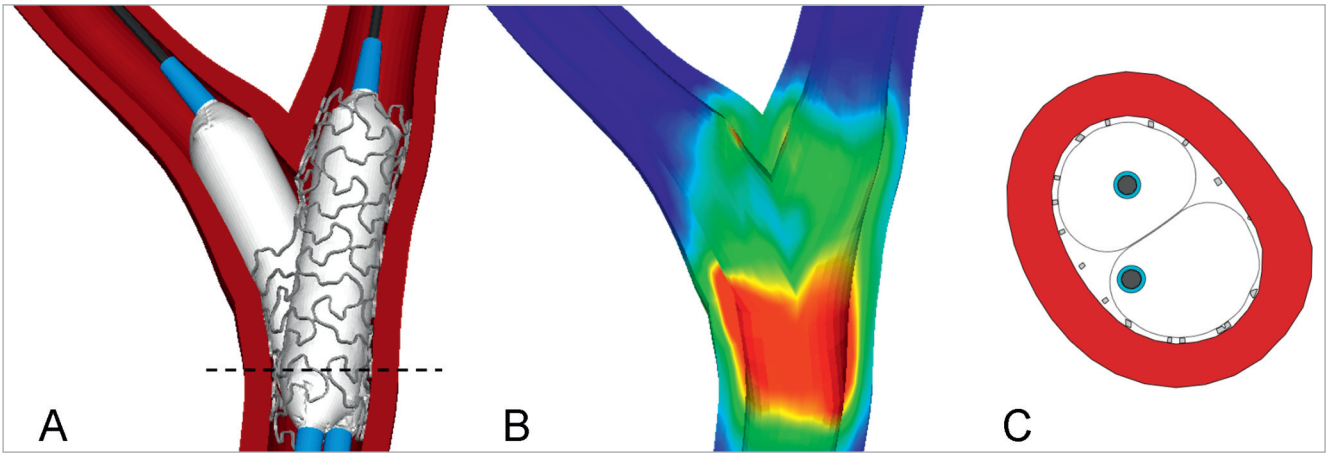

Figure 7. Virtual bench testing of FKI illustrates some of the current negative side effects of this procedure (Courtesy of Dr. Mortier). Panel A shows the virtually predicted deformations, while the resulting vessel wall stresses are depicted in panel B (a red colour reflects a high stress, blue corresponds with a low stress). The high stresses within the proximal MV may lead to an increased arterial injury. The ovalisation caused by the simultaneous inflation of the two balloons is shown in Panel C. This panel also nicely illustrates the possibility to simultaneously visualise the balloons, the stent and the bifurcation model.

Conclusions and future prospects

This review illustrates the large impact of *ex vivo* evaluation of bifurcation stenting techniques and dedicated devices on the treatment of bifurcation lesions. Two complementary methods are available, *in vitro* and virtual bench testing, each one having its own specific advantages and drawbacks. Current insights are mainly based on *in vitro* bench testing, which has been used for many years in this domain, but computer simulations certainly have the potential to provide additional insights.

A continuous effort should be made to improve both methods further. For *in vitro* bench testing, an evolution towards patient-based silicone models (e.g., based on stereolithography) seems a logical next step and could help to investigate the different techniques and devices within a more anatomically correct environment. Progress could also be made by including stenoses in the silicone models and by using different materials with varying mechanical behaviour. Virtual bench testing of bifurcation stenting is a promising technique, but a number of steps need to be taken before its full potential can be realised. Getting the virtual results verified and accepted is crucial and therefore, more extensive validation of the computer simulations by comparing the results with *in vitro* data is required. In addition, these simulations should be further automated and optimised in order to be able to study a larger number of cases (including two-stent techniques).

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