Swirling Flow®: Nature's Ideal Alternative to Drug Elution

How swirling flow induced by the BioMimics 3D stent provides a drug-free solution for limiting restenosis and reducing the need for revascularization.

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When the Katsanos et al meta-analysis was published in *Journal of the American Heart Association* in 2018,[1] it would have been difficult to predict the impact on the use of drug-coated/drug-eluting devices by the summer of 2019. At the time of this writing, several regulatory bodies have made statements relating to the use of paclitaxel devices. At a panel meeting in June 2019, FDA continued to indicate that paclitaxel-coated and paclitaxel-eluting devices should be used with caution in peripheral artery disease (PAD) and that available data will continue to be reviewed. The United Kingdom Medicines & Healthcare Products Regulatory Agency has advised physicians to "not use paclitaxel drug-coated balloons (DCBs) or drug-eluting stents in the routine treatment of patients with intermittent claudication until further notice."[2] Germany's Federal Institute for Drugs and Medical Devices stated, "In all cases, other than in patients with a particularly high risk of restenosis, alternative treatments should preferably be considered."[3] The Cardiovascular and Interventional Radiological Society of Europe's position statement on the controversy said, "In the majority of patients undergoing lower limb recanalization therapies, alternatives to drug-eluting devices should be used."[4]

Fortunately, the challenging issue of limiting restenosis has a drug-free solution: swirling flow—nature's own vascular protection mechanism and the ideal alternative to drug elution.

USING SWIRLING FLOW IN THE FEMOROPOPLITEAL ARTERY

The distribution of atherosclerosis and the tendency of an artery to develop restenosis varies throughout the human arterial system. The femoropopliteal artery has both a high prevalence of atherosclerosis and a high tendency to develop restenosis.[5,6] Part of the reason for the variable distribution of native arterial disease was explained by Caro et al, who drew attention to the relationship between wall shear stress (WSS) and a reduced tendency toward atherosclerosis.[5] It is understood that normal arterial blood flow is laminar. In addition, the normal pattern of that laminar blood flow in the aorta and proximal branches is also spiral, and it is referred to as swirling flow.[6] WSS can be

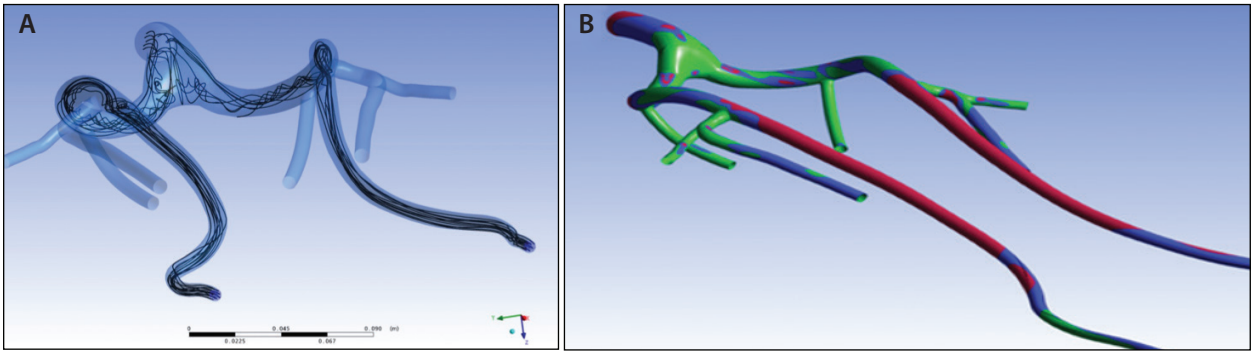

Figure 1. A computational fluid dynamics (CFD) model of swirling flow, showing it becoming dampened in the iliac arteries, resulting in straight laminar flow in the SFA (A). A CFD model of high WSS in the iliac arteries (as a consequence of swirling flow) and low WSS in the SFA; low WSS (pathogenic) represented in red, suboptimal WSS represented in blue, and high WSS (protective) represented in green (B).[7] Reproduced from Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. JAMA. 1999;282:2035-2042.

thought of as the velocity of blood against the internal wall of the vessel. Swirling flow increases WSS when compared with nonswirling flow, resulting in a reduced propensity to develop atherosclerosis and restenosis. Blood flow in the superficial femoral artery (SFA)—where natural curvature is limited, particularly when straightened by a straight stent—is naturally less swirling and has a reduced WSS (Figure 1)[7], hence the high prevalence of native disease and proliferative response to endovascular injury.

Animal studies have confirmed that areas of low WSS predict the development of neointimal hyperplasia (NIH) in grafts and stents.[8] Using straight nitinol stents to treat the SFA of patients with PAD has been shown to reduce WSS.[9] Evaluation of coronary stents in humans showed that the pattern of in-stent restenosis is determined by the distribution of WSS.[10,11] These observations led to the development of the BioMimics three-dimensional (3D) self-expanding nitinol stent (Veryan Medical Ltd.), which has a helical centerline that is capable of inducing swirling flow (Figure 2). The ability of this stent to reduce restenosis was first tested in a porcine model in which a straight stent was placed in one carotid artery and a helically formed version of the same stent was placed in the other carotid artery. The study demonstrated that (1) the helical centerline stent imparted nonplanar curvature to the implanted segment and generated swirling flow; (2) the swirling flow significantly reduced the development of NIH (Figure 3)[12]; and (3) a correlation between the degree of curvature and the reduction in NIH was established.[13]

The BioMimics 3D stent was subsequently tested in the first randomized controlled trial (RCT) to directly compare two nitinol stents in the femoropopliteal segment.[14] MIMICS-RCT was a multicenter, core lab–controlled, prospective, randomized trial in which the BioMimics 3D stent was compared with a conventional straight stent control (LifeStent, BD Interventional) in 76 patients with symptomatic occlusive disease of the SFA and proximal popliteal artery. Conventional radiographs and angiograms confirmed that the BioMimics 3D stent imparts nonplanar curvature

Figure 2. The BioMimics 3D stent.

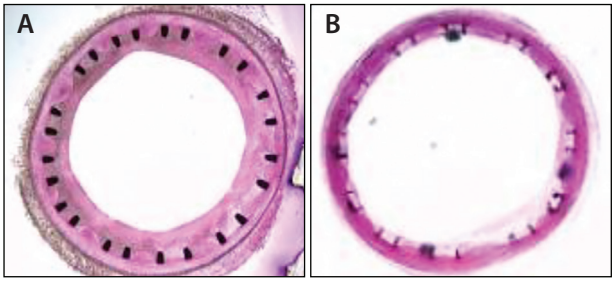

Figure 3. Thirty-day histology of a straight nitinol stent (A) and the same stent with a 3D helical shape (B) in a porcine carotid model. Overall, in 10 animals studied, there was a 45% reduction in neointimal thickness ($P < .001$).[12]

to the diseased artery. Compared with the straight stent control, the BioMimics 3D stent had significantly better primary patency through 2 years (Figure 4). There was no clinically driven target lesion revascularization (CDTLR) in the BioMimics 3D arm between 12 and 24 months, whereas there was a threefold increase in CDTLR in the straight stent control arm over the same time period. This represents a significant difference between the two stents (Figure 5). The clinical validation of the BioMimics 3D swirling flow stent is continuing across a range of studies in the MIMICS clinical program. Recently presented 2-year data from the MIMICS-2 investigational device exemption study have validated the clinical outcomes of the earlier randomized study in a larger (271 patient), more challenging patient population.[13]

DRUG-COATED BALLOONS

Current DCBs use paclitaxel to address the biological mechanisms that lead to restenosis. The drug is combined with an excipient or carrier to provide uniform dosage and rapid uptake into the vessel wall. Variations in the excipient, formulation, and dosage of the paclitaxel result in the different behavior of individual DCBs.

The pivotal DCB trials showed improved performance over simple angioplasty, but these were regulatory studies in carefully selected patients with uncomplicated lesions, and the importance of that in terms of the generalizability of DCBs' value deserves some attention.[15-19] Severe calcification and an inability to completely predilate the lesion were exclusions in these studies, and they effectively removed those lesions from any analysis. Furthermore, because only 12% to 26% of lesions were total occlusions, vessels in these populations were predominantly noncalcified, with simple disease that was unlikely to recoil after angioplasty, resulting in a bailout stent rate of only 2.5% to 7%.

When the same DCBs are used in patients who are more representative of routine clinical practice and documented within the global registries, the lesion patency and CDTLR rates remain good because these more clinically generalizable cohorts are measuring the outcome of using a DCB

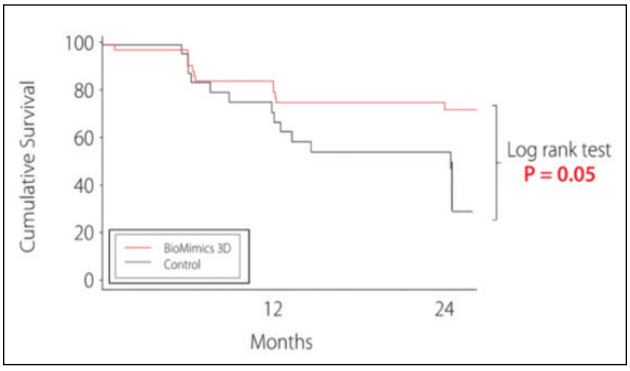

Figure 4. Kaplan-Meier survival estimate from loss of patency (MIMICS-RCT study).

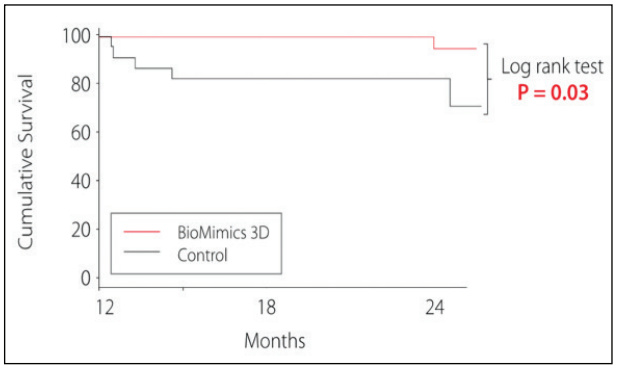

Figure 5. Kaplan-Meier estimate of survival from CDTLR between 1 and 2 years (MIMICS-RCT study).

plus a stent.[20,21] Registry patients were characterized by more complex disease than those who were recruited to the pivotal regulatory trials, resulting in an average stent rate of 28% to 35.5%.[20-23] This stent rate was related to both lesion length and the chronic total occlusion rate. For instance, in IN.PACT Global, the stent rate was 53% when the length of lesion exceeded 25 cm and 47% in total occlusions.[22,23] The Kaplan-Meier survival estimates from the pivotal regulatory trials demonstrated that the patency benefit and reduction in CDTLR over simple angioplasty occur between 6 and 12 months; but after 1 year in IN.PACT SFA, the Kaplan-Meier curves were parallel.[24] This trend is also seen in the global registries.[20-23]

A DCB-only approach has never been an adequate solution for clinical practice outside of pivotal trials. Although the bailout stent rate was low in pivotal trials, the global registries demonstrate that a much higher use of stents is required to maintain patency and low CDTLR rates. Vessel recoil and late negative remodeling are common contributory factors in the loss of patency, which compromises a DCB-only strategy.

CONCLUSION

Besides providing the required scaffolding, swirling flow generated by the BioMimics 3D stent has been shown in the MIMICS-RCT trial to significantly reduce the need for revascularization compared with a straight nitinol stent over 2 years of follow-up.[14]

With physicians now being advised to find alternatives to the use of paclitaxel in femoropopliteal intervention, swirling flow induced by the BioMimics 3D stent would appear to be nature's ideal substitute.[25] ■

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The BioMimics 3D Vascular Stent System has FDA and CE Mark approval. Not available for sale in Japan.
US Federal law restricts this device to sale by or on the order of a physician.

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