Relationship between hemodynamics and in-stent restenosis in femoral arteries

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Relationship between hemodynamics and in-stent restenosis in femoral arteries

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Anna CORTI, Monika COLOMBO, Diego GALLO, Josè Felix Rodriguez MATAS, Francesco MIGLIAVACCA, Stefano CASARIN, Claudio CHIASTRA

Although percutaneous transluminal angioplasty with stenting is one of the preferred treatments of lower extremity peripheral artery disease, this procedure suffers from a 66% 1-year primary patency rate. The unfavorable outcome is mostly attributable to in-stent restenosis, an inflammatory-driven arterial response, characterized by excessive smooth muscle cell proliferative and synthetic activity ultimately leading to lumen re-narrowing. The etiology of in-stent restenosis is multifactorial, involving different systemic, biological and biomechanical drivers. Among the biomechanical factors, a key role has been recognized to the stent-induced hemodynamic alteration, influencing smooth muscle cell activity both directly and through endothelium-dependent mechanisms. In this scenario, computational fluid dynamics simulations of stented femoral arteries allowed quantifying the local hemodynamics and identifying wall shear stress-based hemodynamic predictors of in-stent restenosis. This contributed to enhance the current knowledge of the fluid dynamic-related mechanisms of post-stenting lumen remodeling. However, given the multiscale and multifactorial nature of in-stent restenosis, multiscale mechanobiological modeling relating the intervention-induced mechanical stimuli to the complex network of biological events has recently emerged as a fundamental approach to decipher the underlying pathological pathways. This involves the analysis of interactions, cause-effect relationships, feedback mechanisms and cascade signaling pathways across different spatial and temporal scales, thus allowing tracking the effect of the intervention-induced perturbation to the molecular, cellular and finally tissue response. The present chapter examines the state-of-the-art of computational fluid dynamics studies of in-stent restenosis in femoral arteries and provides an overview on the emerging field of multiscale mechanobiological modeling of arterial adaptation following endovascular procedures.

Introduction

In-stent restenosis in femoral arteries

Percutaneous transluminal angioplasty (PTA) followed by stent placement is a common minimally invasive procedure used to open narrowed atherosclerotic femoral arteries and to restore the correct blood flow to the lower limbs. Nowadays, this procedure is performed and recommended for those patients who are susceptible to surgical risk and in presence of lesions with stenosis/occlusions shorter than 25 cm.[1] The incidence of adverse events is still high. In particular, in-stent restenosis (ISR), consisting in the re-narrowing of the stented segment in the months after intervention, is a major adverse event, with an incidence ranging from 15% to 32%, with a peak between 9 and 15 months post-intervention.[2]

ISR, often recalcitrant, is caused by excessive neointima growth and unfavorable inward vascular remodeling. PTA with stenting causes severe vascular injury including endothelial denudation. The healing process that begins after the endovascular treatment involves the activation of inflammatory and vascular cells leading to re-endothelialization, neointimal growth and remodeling.[3] However, this process can degenerate into a sustained inflammatory state and abnormal smooth muscle cell proliferation and extracellular matrix (ECM) deposition, potentially leading to neointima hyperplasia and ISR.[4–6] The mechanisms for the pathogenesis of ISR are not completely understood. ISR is promoted by several interrelated factors, including patient, biological, biomechanical, and operator-related factors.[7] Among the biomechanical factors, the stent-induced flow disturbances seem to play an important role on ISR development.[8–10]

Role of computer simulations in the study of in-stent restenosis

Over the past two decades, mathematical and computational modeling has emerged as a powerful tool to help elucidate the role of hemodynamic flow disturbances on ISR development. Such research has predominantly focused on two approaches. The first approach adopts computational fluid dynamics (CFD) modeling on three-dimensional (3D) patient-specific femoral artery geometries reconstructed from clinical images to address the impact of the altered hemodynamics after stent implantation on ISR. This approach has provided evidence on the role of stent-induced flow disturbances on ISR development.[8–10] In particular, the stent struts cause blood flow separation, creating recirculation and stagnation zones and expose the lumen to low and oscillatory wall shear stress (WSS), which promotes neointima regrowth.[8–10] The second approach aims to simulate the biological response of the artery following stent deployment, through a mechanobiological, multiscale model. The majority of the studies following this approach adopts agent-based models (ABMs) (*e.g.*[11–13]), whereby a natural description of cellular systems is obtained through the definition of a set of rules governing the agents' activities.[14] Thanks to this bottom-up approach, a complete understanding of the whole system is not needed but its behavior will naturally emerge from the imposed rules. ABMs easily capture spatial-related aspects such as tissue heterogeneity, composition and morphology, and can integrate phenomena at different scales within multiscale frameworks.[15] Moreover, ABMs can be coupled with hemodynamic models,[11,13,16-18] enabling the replication of hemodynamic-related cellular behaviors through the inclusion of rules depending on quantitative descriptors of flow disturbances, like the exposure to low and oscillatory WSS. In this way, it is possible to gain insights into the hemodynamic-driven mechanisms of tissue remodeling and ISR following stent deployment.

Chapter contents

The present chapter reviews the state-of-the-art in computational research on ISR of femoral arteries treated by endovascular intervention. In the first part of the work, the studies elucidating the relationship between altered hemodynamics and ISR via a CFD-based approach are described. In the second part, the general concept of vascular adaptation is introduced and the way in which multiscale models are revolutionizing the related research towards clinical translation is presented. Finally, the innovative approach, based on a multiscale computational framework, that our research group is pursuing to investigate the interdependent factors promoting ISR is presented.

Hemodynamics modeling of in-stent restenosis in femoral arteries

Recently, CFD models have been proposed to elucidate the direct link between the post-intervention altered hemodynamics and ISR in femoral arteries. Table 1 summarizes the aim of the studies, the clinical data available and the main characteristics of the developed models.

Table 1: Recent published studies on patient-specific hemodynamic modeling of in-stent restenosis in femoral arteries

First author, year [reference]	Aim	Arterial model (no. patient-specific cases)	Imaging data	Follow-ups	Analysis type (solver)	Boundary conditions	Blood model
Gokgol *et al.*, 2019 [19]	Impact of leg configuration (i.e. straight, flexed) on restenosis	3D patient-specific, FPA (20)	2D angiography (geometry), MRI (boundary conditions)	Baseline + Outcome (6M)	CFD (ANSYS CFX)	I: parabolic velocity profile O: zero pressure	Newtonian (μ=0.004 Pa·s), ρ=1050 kg/m^3
Colombo *et al.*, 2021 [20]	Impact of altered hemodynamics on restenosis progression	3D patient-specific, SFA with CFA bifurcation (10)	CT (geometry), DUS (boundary conditions)	Baseline, Follow-up (1M, 6M, 1Y) + Outcome (2Y)	CFD (ANSYS Fluent)	I: parabolic velocity profile O: flow-split	Non-Newtonian Carreau (μ0= 0 Pa·s $\mu\infty$=0.0035 Pa·s, λ=25 s, n=0.25), ρ=1060 kg/m^3
Colombo *et al.*, 2021 [22]	Restenosis prediction based on altered hemodynamics	3D patient-specific, SFA with CFA bifurcation (10)	CT (geometry), DUS (boundary conditions)	Baseline, Follow-up (1Y) + Outcome (2Y)	CFD (ANSYS Fluent)	I: parabolic velocity profile O: flow-split	Non-Newtonian Carreau (μ0= 0 Pa·s $\mu\infty$=0.0035 Pa·s, λ=25 s, n=0.25), ρ=1060 kg/m^3

Gokgol *et al.*[19] performed CFD simulations in patient-specific femoropopliteal artery models both in straight and flexed leg configuration. Twenty lesions were analyzed, half treated with PTA and the other half with self-expandable stents. The vessel models were reconstructed from two-dimensional X-ray angiographic images acquired immediately after the endovascular intervention. The lumen areas affected by low time-averaged wall shear stress (TAWSS) were larger in case of leg flexion (Figure 1) and also of lesions classified for restenosis at 6-month follow-up. However, none of the investigated hemodynamic descriptors

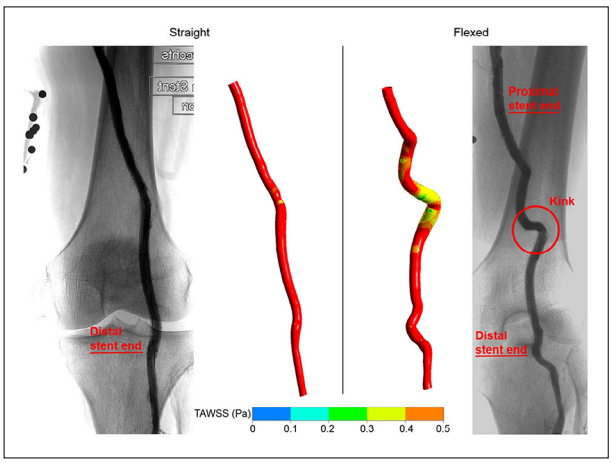

Figure 1: Time-averaged wall shear stress (TAWSS) distribution in an explanatory model of stented femoral artery exhibiting kinking during leg flexion. The X-ray images were acquired in the straight (left) and flexed (right) leg position and show the locations of the stented region and the kink when the leg is flexed. The lumen area exposed to low TAWSS (< 0.5 Pa) were located next to the kink or highly curved segment.

resulted significantly related to restenosis, possibly due to the limited resolution of the imaging modality used for the vessel reconstruction or by the lack of patient-specific boundary conditions imposed in the CFD simulations. Furthermore, the evaluation of success/failure of the endovascular treatment was based on a dichotomous information about the absence/presence of restenosis at 6-month follow-up. Thus, a local quantification of the lumen remodeling leading to restenosis was not possible.

To analyze the lumen remodeling trajectory over time after stent placement and to investigate the impact of altered hemodynamics on ISR initiation and progression, Colombo *et al.* [20] performed a longitudinal study by considering the data of 10 superficial femoral artery (SFA) lesions of 7 patients at multiple follow-ups, namely at post-operative 1 week, 1 month, 6 months and 1 year. Following the framework depicted in Figure 2, the patient-specific SFA models, semi-automatically reconstructed from computed tomography (CT) at the different follow-ups, [21] were used (i) to perform a morphological analysis (all the follow-ups), quantifying the lumen area change between the time-points, and (ii) to analyze the hemodynamics by means of transient CFD simulations (1-week, 1-month and 6-month follow-ups), computing several WSS-based descriptors.

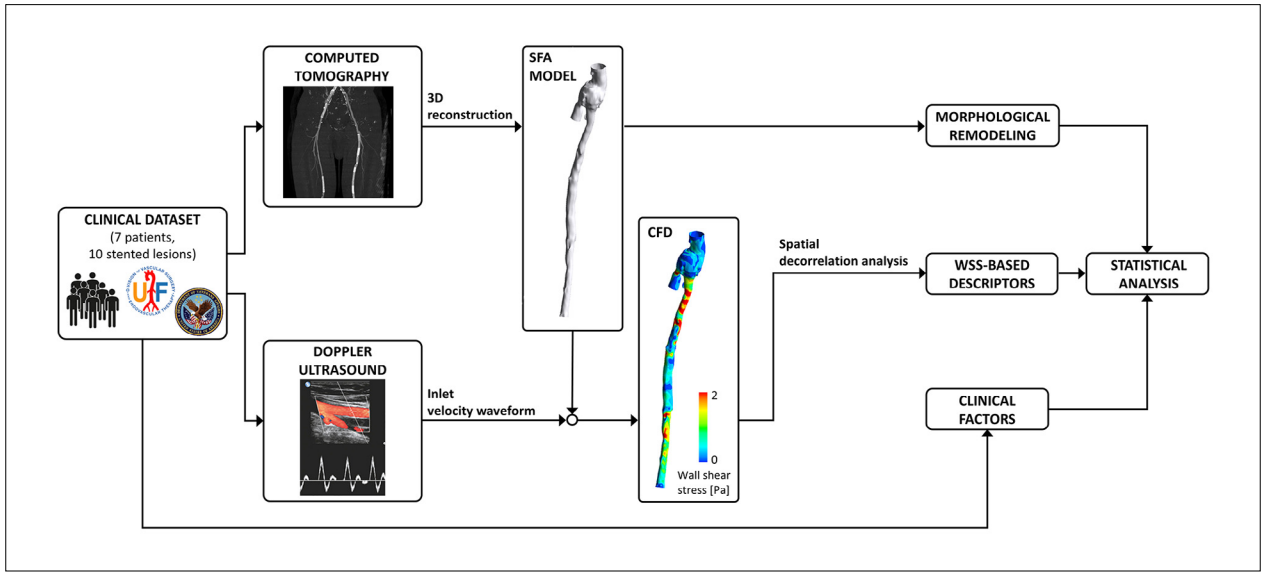

Figure 2: Schematic overview of the computational workflow adopted in the studies of Colombo *et al.* [20,22] to investigate the link between hemodynamics and in-stent restenosis in human superficial femoral arteries.

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Colombo and colleagues observed that the largest lumen remodeling occurred in the first post-operative month, with significantly larger inward remodeling in the fringe segments of the stented lesions, whereas focal re-narrowing frequently occurred after 6 months (Figure 3A-C). In exploring the impact of hemodynamics, the authors found that abnormal patterns of multidirectional WSS were significantly associated with lumen remodeling occurring both in the first- and last-time intervals (Figure 3D). In particular, TAWSS at 1 week was negatively correlated with lumen area change in the first-time interval (1-week:1-month), suggesting that for low TAWSS an inward remodeling occurred. Also, positive trends between oscillatory shear index (OSI) and relative residence time (RRT) and the lumen area change were observed at both first-and last-time intervals.

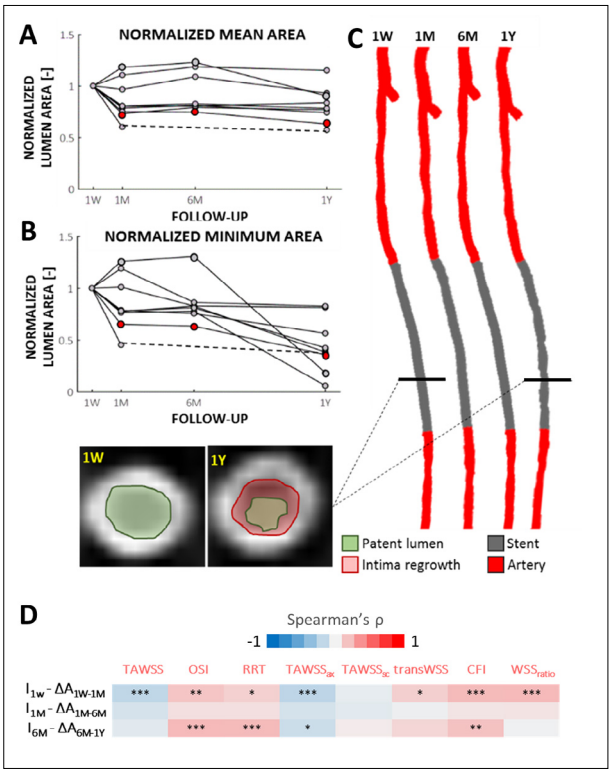

Figure 3:

A-B) Remodeling trajectory over time of the human superficial femoral artery (SFA) lesions analyzed in Colombo et al.20, reported as mean and minimum lumen area normalized with respect to the 1-month (1M) lumen area.

C) Reconstructed SFA models at 1-week (1W), 1M, 6-month (6M) and 1-year (1Y) follow-up and corresponding cross-sectional computed tomography images of one explanatory case.

D) Spearman's correlations between the lumen area change (ΔA) in the current time interval and the wall shear stress (WSS)-based descriptors (I) computed at the beginning of that time interval. TAWSS: time-averaged WSS; OSI: oscillatory shear index; RRT: relative residence time; TAWSSax: axial component of TAWSS; TAWSSsc: secondary component of TAWSS; transWSS: transverse WSS; CFI: cross-flow index; WSSratio: ratio between the cycle-averaged magnitude of the secondary and the axial WSS components; *: p<0.05; **: p<0.01; ***: p<0.001.

Adapted with permission from Annals of Biomedical Engineering, 2021, in press, Colombo M et al., In-stent restenosis progression in human superficial femoral arteries: dynamics of lumen remodeling and impact of local hemodynamics.
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Following the previous findings on the association between altered hemodynamics and lumen remodeling, Colombo *et al.*[22] evaluated the power of the WSS-based descriptors computed at 1 week to predict the inward lumen remodeling at 1 year (quantified as the lumen area change occurring during the time interval 1-week:1-year). From the findings of the study, it emerged that the TAWSS was strongly negatively correlated to the lumen area change (ρ = -0.75, p = 0.013), suggesting that low TAWSS is related to a large lumen area change. Furthermore, a positive strong correlation was found between the lumen area exposed to low TAWSS and the lumen area change (ρ = 0.69, p = 0.026), suggesting that the larger the lumen area exposed to low TAWSS is, the larger the lumen area change at 1 year is expected to be. Conversely, OSI and RRT were not correlated to the lumen area change (p > 0.05). Moreover, compared to the other WSS-based descriptors, the TAWSS was the best predictive marker with a positive predictive value (*i.e.* the probability that the lumen area subjected to altered hemodynamics can successfully identify corresponding regions of larger lumen area change) of ~45%.

In all reviewed studies, the image resolution of angiography and CT did not allow to detect the stent struts and, hence, to reconstruct the 3D stent geometry (*i.e.* detailed stent geometry with struts and links) and include it within the computational models. Moreover, the CFD simulations were performed assuming rigid arterial walls and fixed leg configuration (either straight/flexed in Gokgol *et al.*[19] or straight in Colombo *et al.*[20,22]). In the future, intravascular images could be combined with angiography or CT to reconstruct the stent geometry[23] and the leg movement could be simulated by using a methodology recently proposed for idealized femoral artery models.[24]

Multiscale computational modeling of in-stent restenosis in femoral arteries

Multiscale models of vascular adaptation: general concepts

Vascular adaptation is driven by a complex network of heterogeneous and interconnected mechanisms (*e.g.* mechanotransduction, gene pattern alterations),[25] a deep understanding of which is crucial to deliver personalized treatment, yet lacking. To cope with it, researchers have lately revolved to a "systems biology" approach, for which a biological system is seen as an interconnected web involving environmental conditions and mutual interactions among its components.[26–28] Multiscale models are the computational translation of the "systems biology" concept and thus they are suitable to bridge in-vitro models of single-scale phenomena to *in-vivo* models of whole systems of interest.[25,29] Such a detail level, together with late progress in biomedical technology, offers a powerful instrument for personalized medicine and fosters the establishment of *in-silico* models to drive biomedical research in a more robust fashion.

ABMs are a class of computational models well-fitting to represent heterogeneous populations and capture the behavior of systems with an intrinsic discrete nature, as systems of cells.[30,31] They are convenient in a multiscale optic since they replicate complex systems' behavior that directly emerges from (i) agent individual dynamics, (ii) interactions among agents, and (iii) environmental conditions. ABMs easily incorporate stochasticity, consistently with the real observations of the phenomena of interest. Additionally, they capture spatial-related aspects as tissue heterogeneity and composition, and can integrate phenomena at different scales within a multiscale framework. These integrated frameworks have a twofold advantage: (i) they can augment the knowledge we have on complex systems, thanks to their bottom-up structure, and (ii) they can act as a therapy/intervention outcome predictor, since they are able to track the propagation of perturbation (therapy/intervention) across the multiscale network and quantify its effect at tissue/organ level.

Agent-based multiscale frameworks have been largely adopted to describe the complexity of vascular pathologies (*e.g.* atherosclerosis[32,33]) and depict the driving mechanisms of response to endovascular procedures or surgical interventions, from stenting (*e.g.*[11,12]) to vein graft bypass (*e.g.*[34,35]). In the specific arena of ISR, several studies have been presented until now, even though none of them has been applied to femoral arteries. Hoekstra's research group proposed a multiscale framework to dissect the hemodynamic and mechanical effects of stenting on the pathological process of ISR and the benefit of eluting antiproliferative drugs to reduce neointimal growth.[11,13,16–18,36] The following four modules were integrated: (i) a Lattice-Boltzman-based module for hemodynamic computation, (ii) a finite difference scheme to solve the set of partial differential equations of drug transport, (iii) an ABM of tissue mechanics to compute the stress and strain state within arterial wall, and (iv) an ABM of cellular dynamics to replicate cellular activities. The stent deployment acted as a perturbation from the model equilibrium and propagated to the other sub-modules, driving the system towards its adaptation. In the last improvements of the framework, the ECM was included and a validation against data from porcine coronary arteries was conducted.[11] On a different perspective, an Irish research group focused on the arterial wall damage induced by PTA and stenting.[12,37–39] The triggering action on cellular proliferation employed by arterial injury was studied by means of an agent-based multiscale framework characterized by three modules: (i) a finite element method module of stent deployment, (ii) a module based on the solution of ordinary differential equations to compute inflammatory cues, and (iii) an ABM of cellular dynamics.

Multiscale model of in-stent restenosis of femoral arteries: an example of agent-based computational framework

Our research group is currently developing a patient-specific multiscale computational framework of ISR of femoral arteries able to integrate the effects of hemodynamics and monocyte gene expression on the cellular dynamics (Figure 4). The framework is characterized by the integration of the following two modules: (i) a hemodynamic module computing the WSS along the stented region of the vessel coupled with (ii) an ABM of cellular dynamics replicating arterial wall remodeling in response to local WSS and gene expression inputs.

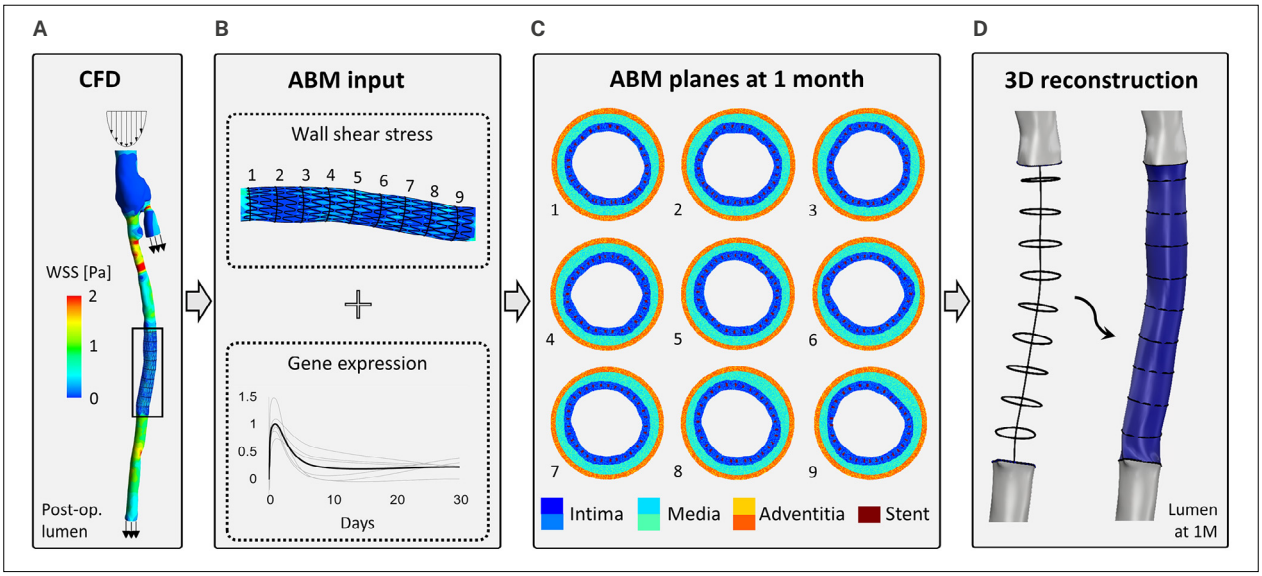

Figure 4: Workflow of a multiscale agent-based computational framework of in-stent restenosis in superficial femoral arteries, able to link hemodynamics, monocyte gene expression and cellular dynamics.

A) A computational fluid dynamics simulation (CFD) of a patient-specific stented superficial femoral artery is performed to compute the wall shear stress (WSS) along the stented segment.

B) The WSS profile for each selected cross-sectional plane within the stented region as well as monocyte gene expression data are used to initialize two-dimensional agent-based models (ABMs) simulating the arterial wall remodeling after stent implantation.

C) ABM-simulated intimal regrowth at 1-month follow-up. All cross-sectional planes are characterized by increased intima thickness with coverage of the stent struts, caused by perturbed cell and extracellular matrix activities, while media and adventitia preserve their initial areas.

D) The ABMs are stopped. The vessel geometry is updated by reconstructing the lumen from the ABM outputs at 1-month follow-up. Then, a new CFD analysis can be performed considering the updated vessel geometry and the entire cycle can be repeated for simulating the time period of interest.

To develop the framework, the CT images (at 1 week and 1 month after the intervention) and monocyte gene expression (measured at 1 hour before, and 2 hours, 1, 7 and 28 days after intervention) of one case of diseased SFA treated with self-expanding stent at the Malcom Randall VA Medical Center (Gainesville, FL, USA) were considered. The study was conducted in accordance with the ethical standards of the local institutional review board, and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from the patient. A 3D stented SFA geometry was reconstructed from the CT images using a validated reconstruction algorithm[21] and the stent was deployed with morphing procedure. A steady-state CFD simulation was performed with Fluent (Ansys Inc., USA) to compute the average hemodynamics along the stented area (Figure 4A), extracting the WSS at specific equally-spaced vessel

cross-sections (Figure 4B). A two-dimensional ABM simulating the arterial wall remodeling by replicating cell and ECM dynamics was implemented in Matlab (MathWorks, USA) for each cross-section (Figure 4C). Each ABM was generated on a hexagonal grid and filled with smooth muscle cells, fibroblasts, ECM, and stent strut agents. The behavior of cell and ECM agents was simulated by assigning probabilistic rules to the following events: cell mitosis/apoptosis and ECM production/degradation. Constant activities were set in the media and adventitia layers to preserve homeostasis.[33] Cell mitosis and ECM production in the intima depended on the local WSS and patient-specific gene expression. Specifically, only those genes for which a statistically significant correlation was found with the intervention outcome were used as input of the ABM.[40,41] The process of intimal growth was preliminary simulated for a time period of 1 month (Figure 4C). After that period, the ABM simulations were stopped and an updated vessel geometry was reconstructed by smoothly connecting the ABM lumen contours at 1 month (Figure 4D). Potentially, new CFD simulations can be performed and the cycle can be then repeated to simulate the arterial wall remodeling for longer time periods.

Despite the work being preliminary and a validation of the model is still ongoing, the proposed framework was able to capture the process of intimal growth in a patient-specific stented region at 1-month follow-up in response to different stimuli (Figure 4C-D). In perspective, the application of such a framework to other patient-specific cases will enable elucidating the role and the interdependence of the different factors promoting ISR in femoral arteries.

Conclusions and future perspectives

This chapter reviewed the recent CFD studies that have sought to establish a direct link between the post-stenting altered hemodynamics and ISR in femoral arteries. Furthermore, it provided an overview about multiscale computational approaches that could allow elucidating the underlying pathological mechanisms, by integrating biological and biomechanical stimuli at different spatiotemporal scales.

The number of patient-specific hemodynamic studies in the context of femoral arteries is still limited. In addition to the studies reported in Table 1, it is worth mentioning those by Conti *et al.*[42] and Ferrarini *et al.*[43]. However, here the focus was on the relationship between hemodynamics and thrombus formation after stent-graft placement rather than hemodynamics and ISR. Moreover, the clinical dataset analyzed in each study was small (20 lesions in Gokgol *et al.*[19] and 10 lesions in Colombo *et al.*[20,22]). Thus, further investigations on larger datasets are strongly required to confirm the present findings.

Further experimental research, in tandem with computational multiscale modeling, is required to better understand the hemodynamic-driven mechanisms leading to ISR of femoral arteries. Future experimental and modeling work should seek to address some of the limitations highlighted here by considering the analysis of interactions, cause-effect relationships, feedback mechanisms and cascade signaling pathways across different spatial and temporal scales. Ideally, to assess the credibility of the computational models, future experimental protocols should allow quantitative comparison with the simulation outputs. In this way, it will be possible to confirm the potential of computational models as a tool able to (i) elucidate the mechanistic link between hemodynamic disturbances and clinical outcomes after femoral artery stenting, (ii) provide patient-specific predictions of the risk of ISR, and (iii) support the design, optimization and evaluation of femoral artery stents.

Acknowledgements

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