Contribution of mechanical and fluid response to in-stent restenosis

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Introduction

Despite the improved success rates of stent implantation for revascularisation of an occlusive atherosclerotic lesion, acute inflammation of the vessel wall and resultant in-stent restenosis still prevail in 10% of all bare metal stent cases. The formation of neointimal hyperplasia (NIH) within the stented region has been suggested to be linked to both the solid mechanics of the vascular wall and the modification of the fluid dynamic environment within the vessel post-stenting. Thus, consideration of both components within stented vessels may provide insights into the processes of initiation and progression of NIH. The pathogenesis of in-stent restenosis (ISR) has been recognised as a wound healing response and arises from four identified phases: thrombosis, inflammation, proliferation, and remodeling [1]. Following the partial denudation of the endothelial cells lining the arterial wall, and exposure of the underlying tissue to intralumenal haemodynamic forces, such as low wall shear stress values (<0.5 Pa), and promotion of shear induced inflammatory cell aggregation, further intimal thickening may result. In addition, the sustained compression on the medial tissue layer following stent deployment may result in local injury of the extracellular matrix and cell death, promoting smooth muscle cell modulation and proliferation [1].

Whilst computational studies are becoming increasingly sophisticated, using patient-specific images for construction of the structural and/or fluid domains, the relative roles of solid and fluid mechanics in the process of ISR remains undetermined. Combined characterisation of the localisation of stimuli arising from vascular solid and fluid mechanics under consistent conditions should therefore be investigated. This paper describes a methodology to study the localisation of both structural and fluid dynamic stresses in a stented vessel, using the finite element method (FEM) and computational fluid dynamics (CFD), respectively. The use of stent geometry from a porcine model of ISR allows comparison between the numerical results and the level of ISR observed in histological sections of the stented vessel.

Materials and Methods

We have previously reported the methodology for the study of stainless steel, balloon expandable stents implanted into a porcine coronary artery [2]. In summary, stents were deployed with a balloon; artery ratio of 1.4:1 to induce sufficient injury to encourage neointimal growth, without causing tissue laceration. The stents were then explanted at specified time-points, imaged with high resolution micro-CT, and reconstructed in 3D. Following micro-CT, the stented vessels were embedded, sectioned and submitted for histology and histomorphometric evaluation. In the work reported here numerical analysis was performed using a stent geometry deployed in the right coronary artery (RCA) and explanted at 14 days; further time-points are currently under investigation. This single stent and arterial wall domain were used for both the solid mechanics and fluid dynamics model.

FEM model. A coronary artery model was created within ANSYS Mechanical APDL (v12.0) with the following geometry: an initial radius of 1.4 mm (as measured from angiography before stenting), wall

thickness of 0.1 mm and a length of 36 mm, thus longer than the stent length of 18 mm. The arterial wall was described by a third-order incompressible isotropic hyperelastic material model. The reconstructed stent geometry was imported and positioned in the same coordinate system as the vessel. The contact between the inner surface of the vessel and external surface of the stent was controlled by expansion and release of the vessel onto the stent surface elements. The stress generated within the vessel wall during contact with the stent is reported for comparison with the fluid dynamics results and with the histology data.

CFD model. To perform fluid dynamics simulations on the deformed state of the stented artery, the final FEM configuration of both the stent and vessel surface was used to define the boundary for a fluid volume mesh created using ANSYS ICEM CFD (v13.0). Following definition of the fluid domain along the entire 36mm region, including the central 18mm stented section, steady state simulations were performed using the finite-volume ANSYS FLUENT solver (v13.0). A parabolic flow profile was applied at the inlet using a porcine RCA velocity waveform. The wall shear stress (WSS) magnitude along the stented vessel model was evaluated for comparison with the corresponding histology and stress analysis.

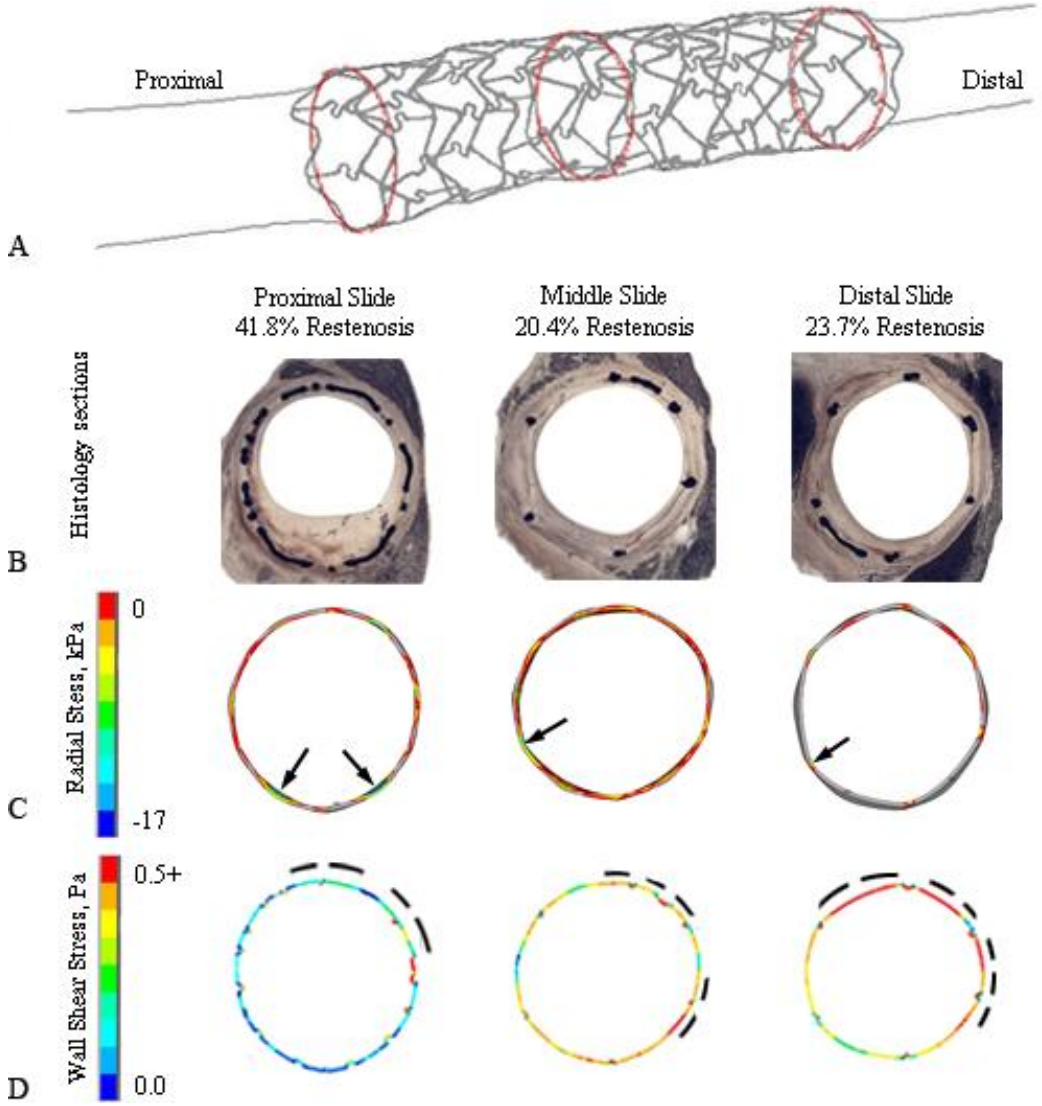

Figure 1: A. Stented domain for numerical (FEM and CFD) simulations. Locations of proximal, middle and distal circumferential histological sections are shown in red; B. Histology cross-sections with measured histomorphometric percentage restenosis; C. FEM radial compressive stress (blue for higher values, indicated by arrows); D. CFD results- dashed line indicates areas with relatively high arterial WSS magnitude and lower NIH.

Results

Figure 1a illustrates the model geometry and identifies three locations (proximal, middle, and distal) along the axial direction for which corresponding histology and numerical data is available. Figure 1b-d shows the compressive radial stress (up to 17 kPa, computed from the FEM model), the wall shear stress magnitude (clipped at 0.5 Pa, computed from the CFD model) and the histological cross-section at each of these locations. Three locations were chosen for analysis in order to investigate the variation in the mechanical and fluid dynamic stimuli and the corresponding NIH response along the length of the vessel.

Discussion

FEM simulations. The simulations showed the peak stresses, in terms of radial compression, corresponded to the locations of the stent struts. The greatest distributions of high compressive stress were associated with areas of maximal neointimal growth seen from histology (Fig.1c) This correlates with the reaction to a deeper injury and is also consistent with the hypothesis that vasculature adapts to changes in the mechanical environment in an attempt to re-establish the homeostatic levels of wall stress [3, 4].

CFD simulations. Fluid dynamic simulations revealed that higher values of WSS (>0.3 Pa along the circumference of the data plot) corresponded to less neointimal growth (Fig. 1d). The influence of the stent on the local flow field increases the propensity for regions of stagnant flow at the wall, or particularly low wall shear stress values [1, 2].

Conclusion

This computational study considers the structural and fluid dynamic stimuli acting on a stented coronary artery in the post-deployment configuration using a combined FEM and CFD approach. The availability of corresponding histological data provides insight into the relationship between these factors and the degree of NIH. Extension of the methodology to consider the changes in structural and fluid stimuli during the development of NIH could provide insight into dynamic changes in these stimuli during the growth of neointimal tissue.

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