TITLE: Two Facets of Shear Stress Post Drug-Coating Balloon: Angiography versus Optical Coherence Tomography Fusion Approach

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A 58-year-old patient with hypertension, dyslipidaemia and typical angina symptoms was referred for a coronary angiogram following a computed tomography coronary angiogram showing a significant stenosis in the left circumflex artery (**Figure 1A**). This demonstrated moderate stenosis with a minimum lumen diameter (MLD) of 1.2 mm, diameter stenosis of 51% and a Quantitative Flow Ratio (QFR, Medis Imaging, Leiden, Netherlands) assessment of 0.80 indicating a flow-limiting stenosis (**Figure 1B**). The patient was enrolled in the randomised TRANSFORM-I trial (1), comparing the novel Magic Touch^{TM} sirolimus-coated (SCB, Concept Medical, Surat, India) to the SeQuentPlease Neo^{TM} paclitaxel-coated balloon (PCB, B.Braun, Berlin, Germany) in small vessels. The patient received treatment with a 2.5×30 mm SeQuent PCB. The balloon was inflated for 60 seconds, resulting in an acute gain of 0.60 mm (MLD pre-procedure *versus* MLD post-procedure: 1.20 *versus* 1.80 mm) and an improved post-procedure QFR of 0.91 (**Figure 1C** and **1D**). The patient underwent optical coherence tomography (OCT) imaging post-procedure, which showed a minimum lumen area of 2.36 mm^2 and an area stenosis of 46%, respectively. In addition, OCT revealed a non-flow limiting dissection 12.6 mm in length (**Figure 1E** and **1F**) that extended to the media with a maximum dissection arc of 153°, and a large dissection volume of 13.8 mm^3 (**Video S1**).

The angiographic and OCT imaging data were used to reconstruct the treated vessel and the generated geometry was processed with computational fluid dynamics (CFD) techniques (2,3). Two types of reconstruction were performed: the first was based on the angiographic images post-procedure using dedicated three-dimensional quantitative coronary angiography software (3D-QCA, Medis Imaging, Leiden, Netherlands) and the second on the fusion of OCT and angiographic images using an established and well-validated method (3). CFD analysis was performed assuming a pulsatile coronary flow and a non-Newtonian blood behaviour, and the wall shear stress (WSS) was computed.

In the 3D-QCA model, the WSS had a homogenous distribution with normal WSS values (**Figure 2A**), oscillatory shear index (OSI) and transverse shear stress (transSS) values close to 0, signalling smooth unidirectional blood flow in the model. Results were different in the OCT-based model (**Figure 2B**). Low WSS was found proximally to the dissection, at the dissection and the distal end of the vessel. OSI was high in the proximal dissection segment and the transSS was low to moderate in the dissection site but high proximally and distally to the dissection. In the segment with the high OSI, there was a mild luminal stenosis at 6 months (**Figure 2C,** white asterisks) but overall MLD increased by 0.12 mm (**Figure 2C**) and the QFR was estimated at 0.93 (**Figure 2D**). The oscillatory and multi-directional flow patterns and the consequent local increase in blood viscosity detected only in the OCT-based fusion models (**Figure 3, Video S2**), but not in the 3D-QCA model, might provide additional insights into late anatomical changes and vessel wall healing and remodelling at the 6-month follow-up.

This case provides novel insights into the implications of the local hemodynamic milieu on vessel wall healing following SeQuent PCB therapy, potentially contributing to the recent observation of late lumen gain in a large dissection over a 6-month period (1). In this case, a "flap" type dissection extending into the media was observed post-procedure with a maximum dissection arc of 153° and a large dissection volume of 13.8 mm^3 (**Figure 1E** and **1F**). These important dissection measurements would not be accessible without the optional OCT pullback and a fly-through 3D OCT reconstruction (**Video S1**) that provides a greater understanding of the disrupted and complex endoluminal lining of the vessel.

Furthermore, although a QFR > 0.91 post-procedure predicts a favourable vessel-oriented composite endpoint (**Figure 1D**), for the first time we underscored another limitation of QCA-based reconstruction in assessing coronary physiology after DCB therapy. This limitation, in addition to a number of QCA acquisition-related requirements, stems from the inherent inability of QCA-based reconstruction to provide a detailed evaluation of the 3D dissection volume and the effect of dissection on the local haemodynamic distribution (**Figure 2A**). This emphasises the need for the fusion of advanced intravascular imaging data to coronary angiography for a comprehensive haemodynamics assessment (4).

In this setting, the fusion of OCT and angiography seems to be the preferred modality as OCT is superior to angiography and intravascular ultrasound in assessing vessel wall dissections enabling realistic reconstruction of lumen architecture (**Figure 2B**). CFD analysis in this complex geometry provided unique mechanistic insights about the vessel wall response following DCB therapy. It revealed low and multidirectional WSS (**Figure 2B**), flow stagnation in the dissected segment and a raised blood viscosity (**Figure 3, Video S2**) that may promote a regional thrombosis – also regulated by the dual antiplatelet therapy – and controlled by the antiproliferative drug intimal proliferation, vessel wall remodelling and healing without compromising lumen dimensions (MLD improved from 1.8 to 1.92 mm in 6 months [**Figure 1C** and **2C**]) and physiology (QFR from 0.91 to 0.93 [**Figure 1D** and **2D**]).

Further research is needed towards this direction to better understand the implications of the local haemodynamic milieu and elevated blood viscosity on procedural results. Our work incorporating high-fidelity OCT imaging and novel CFD algorithms demonstrates the exciting potential to improve our understanding of DCB treatments and adds to the already existing data highlighting the benefits of QFR methodologies. This exciting potential can help guide clinicians in formulating a personalised treatment approach that may prove beneficial for specific patient subsets encountering large, non-flow-limiting dissections in small vessels undergoing DCB therapy without the need for permanent stent implants long-term.

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Figures and Figure Legends

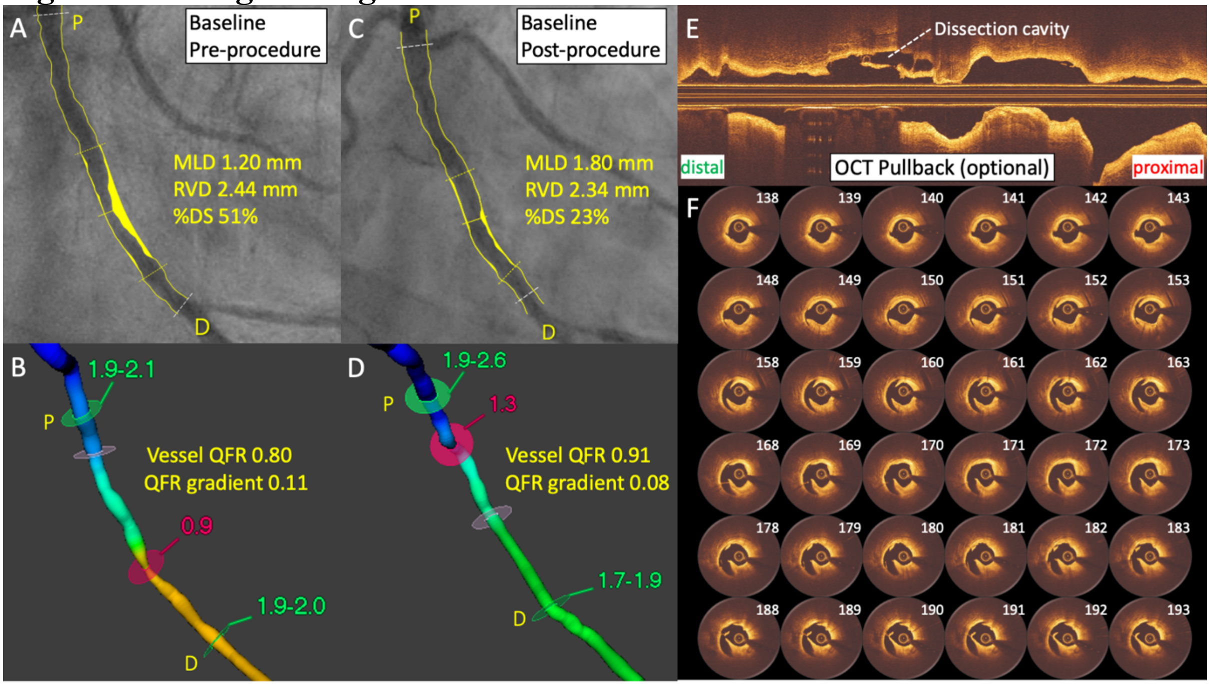

Figure 1 Multi-modality imaging analysis and quantitative flow ratio (QFR). Coronary angiography shows a moderate *de-novo* stenosis in mid-LCx with a minimum lumen diameter (MLD) of 1.20, reference vessel diameter (RVD) of 2.44 mm, a diameter stenosis (DS) of 51% and a QFR of 0.80 (**A** and **C**). Post-DCB therapy, the MLD increased by 0.60 mm with a reduction in DS to 23% and QFR improved to 0.91 (**B** and **D**). OCT revealed a non-flow limiting dissection extending up to the media (**E** and **F**) with a length of 12.6 mm, a maximum arc of 153°, and a total dissection volume of 13.8 mm^3.

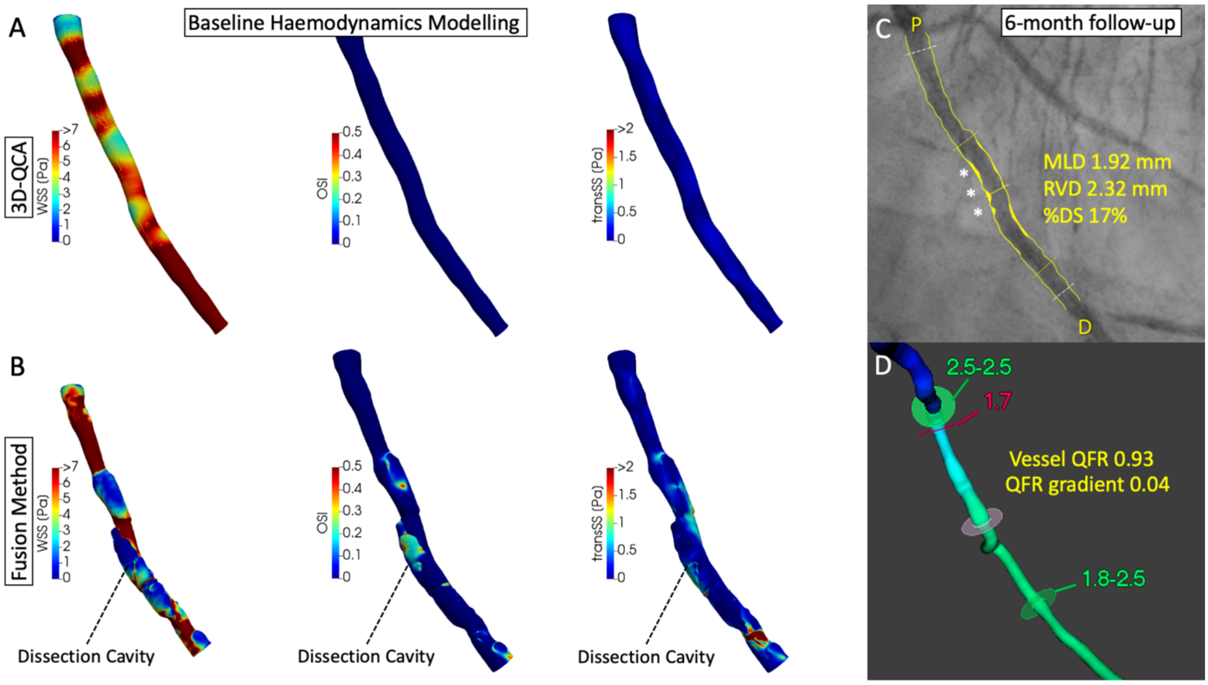

Figure 2 Baseline CFD analyses and the corresponding QCA and QFR results at 6-month follow-up. Two 3D arterial models were created to assess flow patterns in the treated segment. The 3D-QCA model was generated from two angiographic images (>25° apart) assuming that the lumen has elliptical cross-sections (**A**). The smooth vessel geometry resulted in a relatively homogeneous wall shear stress (WSS) pattern with minimal multi-directional flow (i.e., oscillatory shear index [OSI] ≈ 0; transverse shear stress [transSS] ≈ 0 Pa). The second reconstruction relied on the placement of the OCT images (**Figure 1E** and **1F**) that enable detailed evaluation of lumen geometry onto the vessel centreline extracted from two angiographic projections (**B**). In this model, the WSS was greatly heterogeneous, particularly across the dissection cavity with increasing OSI and transSS at the dissection area. The abnormal shear stress patterns at baseline co-localised with the mild lumen stenosis at 6-month follow-up – marked by white asterisks (**C**). However, at that time point there was an increase in the MLD (1.80 *vs*. 1.92 mm) and QFR (0.91 *vs*. 0.93) (**C** and **D**).

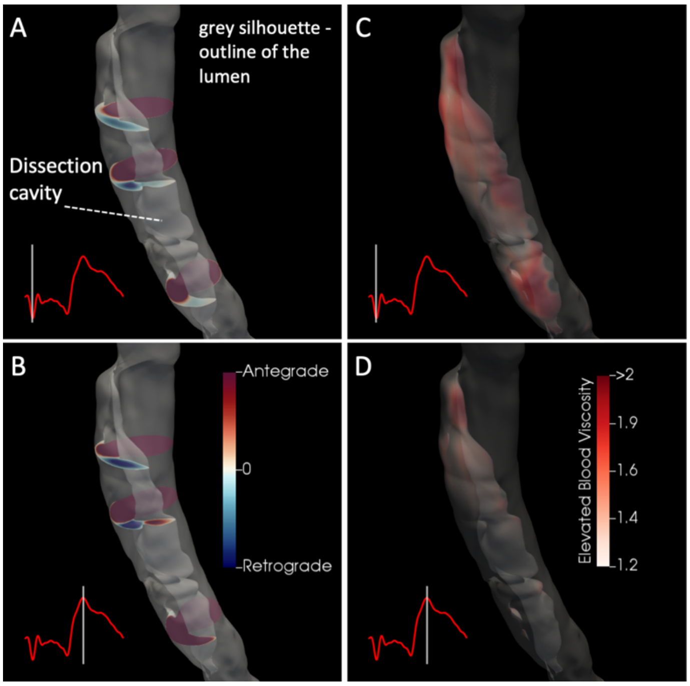

Figure 3 Blood flow patterns and viscosity within the dissection reconstructed by the fusion of OCT and angiographic data. Antegrade blood flow (red) was observed along the main lumen throughout a cardiac cycle (**A** and **B**). Conversely, the flow oscillates within the dissected region. Retrograde flow largely occupied the dissected lumen area at systole (**A**). Blood flow in the distal dissection renormalised and became antegrade again at peak diastole (**B**), leaving only a small amount of retrograde flow within the proximal dissection segment. The slow retrograde blood flow led to a local elevation in blood viscosity (as the ratio of the local blood viscosity to the infinite shear viscosity, μ/μ_∞) in the dissected area. A high elevated blood viscosity (EBV) value is hypothesised to reflect a long-term residency time known for promoting neointima hyperplasia. High EBV was predominantly found in the proximal dissected segment (**C** and **D**), while the EBV was high in the distal dissected segment, only very transiently at early systole (**C**).

Disclosures:

All authors have no relationship with the industry relevant to the contents of this paper.

Supplementary Materials:

Video S1 Offline fly-through of the OCT pullback revealing the large non-flow limiting dissection in 3D.

Video S2 Temporal evolution of elevated blood viscosity in the dissected region of the OCT-based model.