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Focal In-Stent Restenosis Near Step-Up

Roles of Low and Oscillating Shear Stress?

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A 64-year-old man with exercise-induced chest pain underwent coronary angioplasty of his stenosed left anterior descending coronary artery (segments 6 and 7). We recanalized the artery and placed a 3.0×18-mm stent distally and a 3.0×28-mm stent proximally. The residual diameter stenosis at the proximal edge was 26% on quantitative coronary angiography (QCA). Intravascular ultrasound (IVUS) showed an in-stent lumen area of 7.5 mm^2, which exceeded that immediate proximal of the stent (5.6±0.8 mm^2) and caused a so-called "step-up" phenomenon (Figure 1A and 1B, open arrow). Although the stent was well apposed and deployed as indicated by IVUS, the patient presented with worsening anginal symptoms 4 months later; both the angiogram and IVUS showed focal in-stent restenosis at the proximal edge of the proximal stent (78% on QCA) and mild diffuse neointimal hyperplasia (NIH) through the entire length of the stent.

The mechanism of in-stent restenosis has not been fully elucidated, despite numerous animal and human investigations. Stent placement may cause changes in 3D geometry, coronary flow velocity profile, and, as a consequence, in shear stress (SS). It is known that low oscillating SS gives rise to the expression of several growth factors. No clinical evidence has been provided for the potential importance of oscillating SS and its localizing role in in-stent restenosis. Because this patient had been included in a prospective 6-month follow-up study to investigate the association between (oscillating) SS and NIH, angiography and IVUS (ANGUS) had been performed to 3-dimensionally reconstruct the lumen of the stented coronary artery (Figure 1B). Doppler flow (Figure 2B) and blood viscosity measurements were used as input conditions for application of computational fluid dynamics in this 3D reconstruction. The result of these calculations was the SS at the wall as a function of time over the cardiac cycle. The ANGUS procedure was repeated when the patient presented at 4 months, and NIH was determined from this 3D reconstruction (Figure 1F). As found previously, NIH was highest near the locations where average SS was low (Figure 1E, 1F, and 1G). Subsequently, the temporal SS pattern in the region of the step-up (Figure 1C) was evaluated. This analysis showed that the SS vectors were either permanently or temporarily retrogradely directed near the "corner" of the step-up. This indicates the existence of a region of flow separation (Figure 1D). In Figure 2C, locations showing retrograde axial velocities are presented in black at 5 time points as indicated in the Doppler recordings (Figure 2B). At locations that temporarily experience retrograde velocities, SS alters direction periodically. Interestingly, those locations of oscillating SS were nearest to the area of highest NIH (Figure 2A). Our findings warrant further studies to clarify the benefits of the step-up phenomenon.

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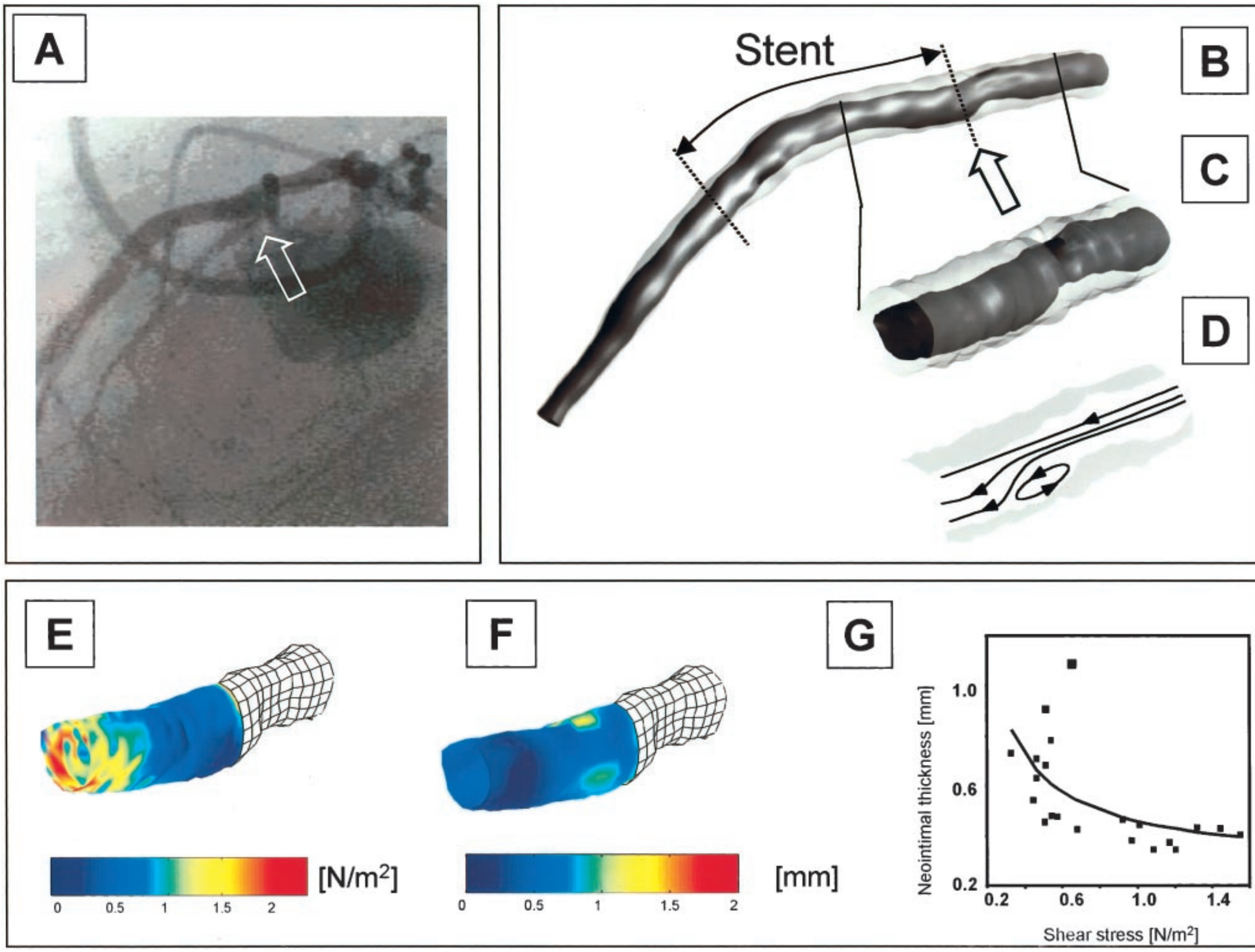

Figure 1. A, Lateral angiographic view of the left anterior descending coronary artery after stent placement. Open arrow indicates location of step-up. B, 3D (ANGUS) reconstruction of the coronary artery shown in A, clearly showing the step-up phenomenon at the proximal edge of the stent (open arrow). C, Segment in which detailed analysis of the temporal shear stress variations is performed. D, Cartoon showing the existence of a region with retrograde velocities and flow separation. E, Averaged shear stress over the cardiac cycle color-coded at the surface of the stented region of the 3D reconstruction. F, Neointimal thickness color coded at the lumen surface of the stented region. G, In-stent average neointimal thickness per cross section versus the shear stress averaged over the cardiac cycle and per cross section showing a non-linear inverse relationship (NIH=$0.3+0.2\times SS^{-1}$ [mm]; $r^2=0.34$, $P<0.01$).

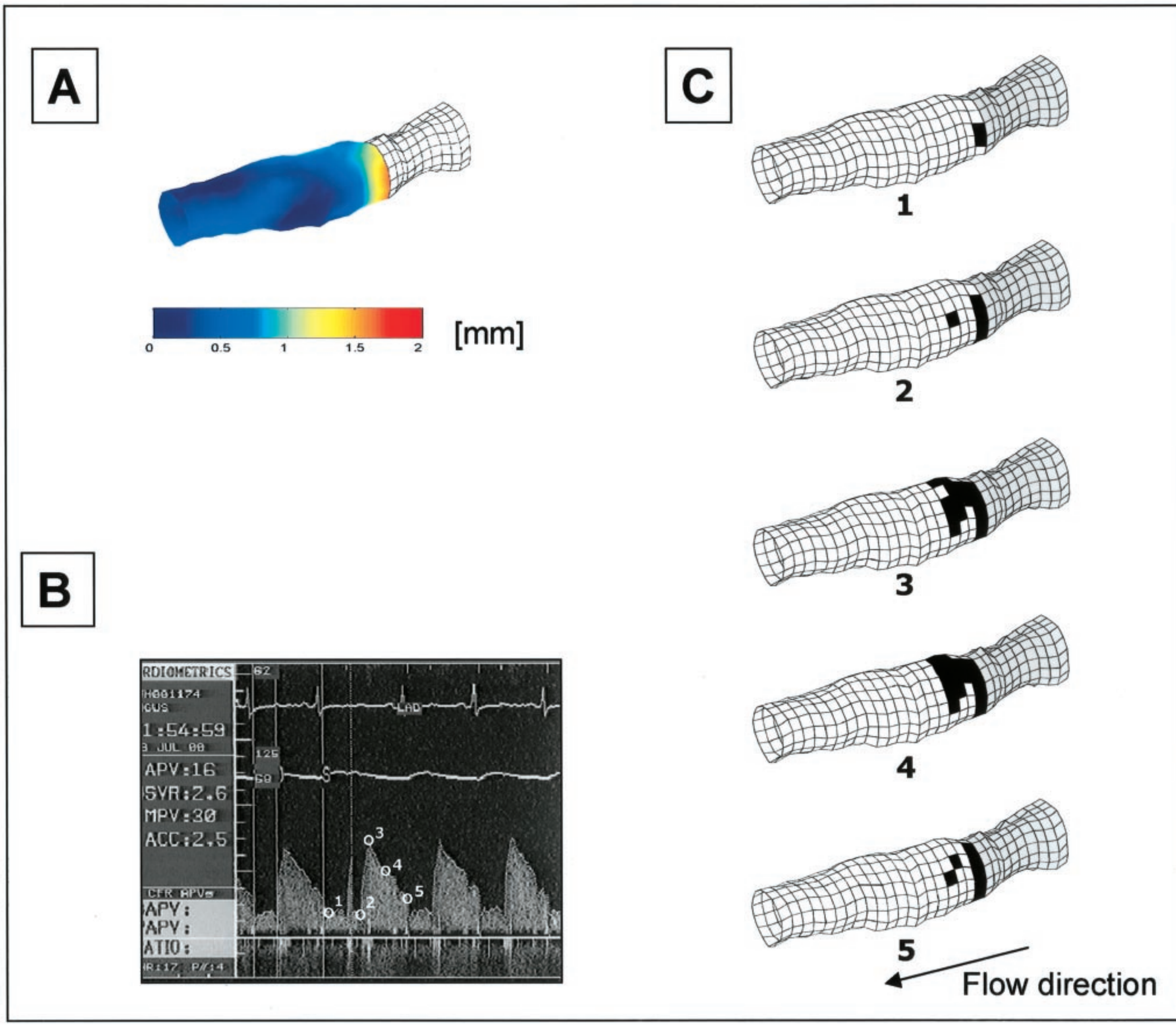

Figure 2. A, Neointimal hyperplasia, which is color-coded at the 3-dimensionally reconstructed lumen at baseline. The perspective view of Figure 2A and 2C differs from Figure 1. B, Doppler measurements used for the time-dependent flow calculations. C, In black, locations in the stent that periodically experience retrograde axial velocities at 5 time points during the cardiac cycle. As can be seen in this view, the size of this area periodically changes, which implies that locations with temporary retrograde velocity experience oscillating shear stress.