Haemodynamic findings after drug-eluting stenting: expected, provocative, or challenging?

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This editorial refers to ‘Evaluation of the haemodynamic characteristics of drug-eluting stents at implantation and at follow-up’ by M. van’t Veer et al., on page 1811

In this article van’t Veer et al. present a comprehensive and detailed study comparing the haemodynamic characteristics of drug-eluting stents (DES) with those obtained by conventional bare metal stents (BMS). After DES, long-term physiological parameters including fractional flow reserve (FFR), hyperaemic gradient, and wall shear stress (WSS) were superior to those found in equivalent BMS implanted in the same patients. Although these findings are of major interest, most of the new information provided could be perceived as well expected considering the large body of evidence demonstrating the superb late results after DES implantation. Nevertheless, as will be highlighted in this editorial, some study findings and their potential implications are rather provocative. Furthermore, on the basis of their results, these investigators from the Catharina Hospital (Eindhoven) dare to challenge some widely accepted strategies in the management of patients with diffuse coronary artery disease (CAD).

Coronary physiology after DES

Previous land-mark studies from the same group have unequivocally established the superiority of FFR over conventional angiography to assess the functional severity of coronary stenosis. Even intravascular ultrasound (IVUS), able to provide a thorough anatomic coronary assessment, can only be used as a surrogate of lesion physiology. Large-scale serial morphological studies have consistently demonstrated the unique ability of DES to prevent restenosis and to inhibit neointimal proliferation. However, functional studies after DES implantation using direct haemodynamic assessment are scarce.

The elegant study of van’t Veer et al., assessing FFR, stent-induced gradients, Doppler-derived intracoronary velocities, and WSS, fills the gap in our understanding of DES influence on coronary physiology. The study design, randomly allocating in pairs DES and BMS in well-selected matched lesions of patients with two-vessel disease, circumvents the potential confounding influence of systemic and anatomic factors on outcome measures. This sound methodology enables to obtain meaningful haemodynamic information from a relatively small patient cohort, which, in turn, is critical when relatively sophisticated diagnostic procedures are performed during coronary interventions. Likewise, excluding unstable lesions, infarct-related vessels, and selecting the intravenous approach to adminster adenosine minimizes potential pitfalls in physiological measurements.

A previous study demonstrated that FFR immediately after BMS was able to predict long-term clinical outcome. Intuitively, it is difficult to anticipate a similar application for this parameter after DES, considering their low restenosis rate. Likewise, DES thrombosis is exceedingly rare (although occurred in one patient of the present series). Therefore, the routine assessment of haemodynamic factors is not justified. However, from an academic standpoint, the excellent long-term haemodynamic findings obtained after DES are re-assuring.

WSS in atherogenesis and neointimal proliferation

Atherogenesis

WSS is the tangential drag (frictional) force produced by flowing blood on the endothelial surface. WSS is probably the most important local factor influencing atherogenesis. It has been suggested that atherosclerosis predominantly develops at segments with low WSS. Low WSS induces endothelial dysfunction, inflammation, and smooth muscle cell proliferation. Atherosclerosis frequently has an eccentric distribution and preferentially occurs in the proximal coronary segments, at bifurcations, and in the inner curve of the artery. Typically, all these locations have low WSS. In particular, at the ‘hips’ of the bifurcation (walls opposite to the flow divider), low WSS values are systematically detected. According to the Hagen–Poiseuille’s law, WSS is inversely proportional to the cube of the radius explaining its dramatic relation with the lumen size. Although some investigators have hypothesized that a threshold level of
WSS is required to affect atherogenesis, the boundary between atheroprotective and atherogenic effects remains as yet undefined. Moreover, the contribution of WSS to atherogenesis appears clear in low-risk individuals, but its effects might be masked in high-risk subjects or in mature lesions. For precise ‘local’ WSS calculations, the non-linear, incompressible fluid, three-dimensional Navier–Stokes equations (governing the conservation of mass, energy, and momentum) need to be solved. This form of detailed virtual analysis (computational fluid dynamics) is now reasonably practical using specialized programs for the discretization of flow using finite-element methods. A mesh is generated and adequate boundary conditions are defined. Local WSS is a sophisticated parameter that may be calculated only after a comprehensive anatomical and physiological assessment. This requires a true three-dimensional anatomical reconstruction of the vessel in relation to the distribution of intravascular velocity profiles. In previous studies, biplane angiography combined with IVUS was used for accurate volumetric lumen reconstruction. Alternatively, WSS may also be measured using a ‘global analysis’ at different coronary segments, as in the study of van’t Veer et al. This provides a valid approximation to WSS at selected vessel positions highly attractive in the clinical setting.

Neointimal proliferation

Neointimal thickness distribution after BMS is related to local factors including extent of vascular injury, inflammation, and WSS. Neointimal tissue tends to proliferate in areas with low WSS, whereas the stent remains free of cell proliferation in areas with high WSS. Of interest, stent design and deployment techniques influence WSS. Experimentally, increasing WSS using a flow divider within BMS, has been accompanied by local reductions in neointimal hyperplasia, inflammation, and wall injury. Although evidence suggests that WSS influences neointima proliferation after BMS, its exact role remains controversial.

Preliminary data of WSS after DES are particularly intriguing. In the study of Gijsen et al., biplane angiography and IVUS were used to determine volumetric lumen geometry 6 months after DES. Flow velocities were directly recorded within the stent, and WSS was obtained from computational fluid dynamics. A significant inverse relation was found between WSS and DES neointimal thickness. More recently, Carter et al. conducted serial analysis of ‘segmental’ WSS after oversized BMS and DES implantation in a porcine model. Relatively low WSS was induced after deployment with both stents. However, at 30 days, IVUS-derived lumen areas were larger and normalized WSS was lower after DES. A negative correlation was found between WSS immediately after BMS and the subsequent neointimal formation. Unexpectedly, post-DES WSS had a positive correlation with the neointimal proliferation.

The study of van’t Veer et al. demonstrated that WSS at follow-up is higher in patients treated with BMS than in those treated with DES. Although such findings might be expected because of the poorer angiographic results of the former group, this concept deserves further attention. In particular, the ability of DES to inhibit neointimal proliferation critically depends on their initial pharmacological action. Later on, when the drug effect has vanished, an excellent haemodynamic profile, with physiological WSS patterns, may further prevent cell proliferation. However, in this study, the mean in-stent WSS after DES was $1.9 \pm 0.8 \text{ Pa}$ but only $1.6 \pm 0.7 \text{ Pa}$ at follow-up. Therefore, at least in some patients, relatively low late WSS values were found. Whether low WSS 6 months after DES could promote a delayed neointimal response remains speculative. Conversely, one may also suggest that a negative feedback control loop may occur after BMS. In this scenario, cell proliferation and the resulting lumen narrowing significantly increase WSS which, at least on theoretical grounds, might prevent further neointimal growth. The potential contribution of high WSS to ‘reduce’ the extent of late neointimal obstruction is also largely speculative. In the present study, however, the potential long-term implications of the haemodynamic parameters seen immediately after stenting were not analysed.

To the best of our knowledge, the attractive methodology used in this study has not been previously validated in human coronary arteries; therefore, reproducibility data might have been of interest. In contrast, the correlation of these measurements with those found using the classical approach to determine ‘local’ WSS warrants further studies. Finally, most WSS analyses currently neglect flow pulsatility, coronary motion, and wall distensibility. Eventually, the challenge remains to develop a robust and well-validated tool to readily assess the WSS in the clinical setting.

Implications for the management of diffuse CAD

Some of the authors’ conclusions in this regard are rather provocative. The virtual absence of measurable gradients along the entire stent length at late follow-up opens the Pandora’s box of the treatment of diffuse CAD. Currently, interventions on diffuse disease are only advocated when angiographically significant narrowings are identified, ideally associated with evidence of ischaemia. Otherwise, angiographically mild lesions on diffusely diseased long segments are usually left untreated despite their ability to generate gradients under maximum hyperaemia. Considering that significant gradients may be observed at follow-up after BMS implantation (despite persistence of good angiographic results), the full-metal-jacket approach does not provide an attractive solution for this elusive form of angiographically mild, but haemodynamically significant, disease. Thus, BMS ‘spot’ stenting after angiographic, IVUS, or FFR guidance has been proposed in this vexing scenario.

Current data from the Eindhoven group suggest that treatment of diffuse coronary segments with long or multiple DES might solve this situation. The absence of significant gradients at follow-up suggests that this approach could be used in selected patients. However, we should keep in mind that the risk of thrombosis after DES implantation is related to stent length. Accordingly, before this critical step is contemplated, more information is eagerly required. Only adequately designed trials, with well-established clinical and angiographic endpoints, will help to elucidate the potential clinical benefit of this provocative
and challenging strategy in selected patients with diffuse disease.

Conflict of interest: none declared.

References


**Clinical vignette**

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*In vivo* demonstration of lipomatous metaplasia in left ventricular scar following myocardial infarction

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A 65-year-old man with history of anterior myocardial infarction 6 years before was admitted for congestive heart failure. Echocardiography revealed a markedly dilated left ventricle with severe systolic dysfunction (EF 32%), apical aneurysm, and diffuse hypokinesis of the other segments. Cardiac catheterization showed three-vessel disease. Gadolinium-enhanced cardiac magnetic resonance (CMR) was performed to assess myocardial viability. Functional CMR with steady-state free precession imaging confirmed echocardiographic findings. Abnormal intramural lineal hyperintense area was detected in thinned anteroseptal mid-ventricular and apical segments. T1-weighted turbo spin-echo sequence also showed intramural lineal hyperintense area in the same segments suggesting myocardial fatty replacement (Panel A) that was confirmed with a fat suppression pulse (Panel B). Transmural gadolinium-enhanced CMR demonstrated non-viable myocardium in the anteroseptal and apical segments and patient underwent surgical coronary revascularization with left ventricular aneurysmectomy (Dor procedure). Histological analysis of specimen revealed fatty metaplasia of scar (Panels C and D) that confirmed CMR findings.

Panel (A) Anatomic CMR sequence showing intramural lineal hyperintense area in anteroseptal mid-ventricular and apical segments (arrow). (B) T1-weighted turbo-spin echo with fat suppression that nulls intramural hyperintense area. (C) Histologic specimen from aneurysmectomy (haematoxylin-eosin). (D) (200×). e, endocardium; f, fibrosis; m, myocytes; F, fatty tissue.