EDITORIAL COMMENT

Attenuated Coronary Collateral Function After Drug-Eluting Stent Implantation
A New Downside of Drug-Eluting Stents?*

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Caution has been, and should continue to be, the watchword for coronary artery stent implantation. Astute cardiologists should not be lulled to sleep in the face of the overwhelming everyday success of their expert interventional colleagues’ skill in the use of drug-eluting stents (DES). Despite its revolutionary advances, DES implantation has a downside. In addition to the rare complications known to occur during the implantation procedure (extensive dissection, emboli, perforation, side branch occlusion, early abrupt closure, and so on), DES are associated with late subacute thrombosis despite perfect implantation technique and concomitant antiplatelet therapy (1).

In this issue of the Journal, Meier et al. (2) identify a new downside to DES: the late attenuation of collateral function. Recall that the most important, if not the only, role of coronary collaterals is to protect the myocardium from ischemia. The rate and type of collateral recruitment with or without angiogenesis vary greatly and for reasons not completely understood (3). Acute recruitment of collateral flow can be demonstrated in some normal hearts without coronary artery disease (4). However, in most but not all patients with chronic ischemic heart disease, collaterals are recruited slowly, forming gradually over time. Responding to loss of distal coronary perfusion pressure and intermittent ischemia, angiogenic growth factors and other mediators are postulated to promote formation of new capillary pathways, thus improving perfusion to the challenged myocardial bed (5,6). In other patients, for example, some acute myocardial infarction (MI) patients, collaterals are acutely recruited, opening immediately during abrupt arterial occlusion and serving to limit what would otherwise be extensive MI.

It is also important to note that collateral function can change after coronary intervention. Opening a chronic totally occluded vessel with percutaneous angioplasty alters the microcirculatory responses (7,8). Abrupt occlusion of a newly recanalized chronic total coronary artery occlusion may result in an MI even though substantial preexisting collaterals protected the myocardium before opening the occlusion. The restored perfusion after percutaneous coronary intervention (PCI) changed the collateral bed responses for the worse (9).

Collateral function after stenting. Meier et al. (2) studied 120 patients undergoing repeat PCI 6 months after bare-metal stent (BMS, n = 60) and DES (n = 60) implantation, matching patients for clinical and angiographic features including the in-stent stenosis severity. The collateral flow index (CFI = coronary occlusion pressure/aortic pressure – central venous pressure) was measured during stent implantation using a pressure sensor angioplasty guidewire and invasively determined again at a follow-up catheterization. The functional impact of collaterals was also correlated to ischemic tolerance, as measured by intracoronary electrogram ST-segment elevation (\(\geq0.1\) mV) during ischemia induced by balloon coronary occlusion.

Despite similar clinical and angiographic characteristics with equal in-stent stenosis severity (46 ± 34% and 45 ± 36%) at follow-up (6.2 ±10 months and 6.5 ± 5 months), CFI was reduced in the DES group compared with the BMS group (0.154 ± 0.097 vs. 0.224 ± 0.142; \(p = 0.0049\)). Moreover, CFI failed to prevent ischemia (by intracoronary ECG), which occurred more frequently in the DES group (50 of 60) than in the BMS group (33 of 60, \(p = 0.001\)). This effect was less pronounced in sirolimus-DES than paclitaxel-DES.

This study points to a new downside of DES (applicable to both sirolimus and paclitaxel): late impairment of collateral function might contribute to an increased ischemic burden in the event of late subacute thrombosis, and this loss could lead to more serious cardiac events when abrupt coronary occlusion occurs.

Why would the drugs on DES have an influence on collateral function? Sirolimus (rapamycin) and tacrolimus (paclitaxil) are potent immunosuppressant and antiproliferative drugs. Tacrolimus reduces peptidyl-prolyl isomerase activity by binding to the immunophilin FKBP-12 (FK506-binding protein), creating a new complex (FKBP12-FK506) that interacts with and inhibits calcineurin, thus inhibiting both T-lymphocyte signal transduction and interleukin (IL)-2 transcription and production. In a similar, but not identical, way, sirolimus acts by...
binding to the cytosolic protein FK-binding protein 12 (FKBP12). However, the sirolimus–FKBP12 complex does not affect calcineurin but rather inhibits the mammalian target of rapamycin (mTOR) pathway through derepression of PP2A, inhibiting lymphocyte proliferation and responses to IL-2 as well as blocking the activation of T- and B-cells. Some of these mechanisms likely affect either the stimuli of or direct response to collateral angiogenesis (6,10).

**Stimuli to collateral development.** Few pathogenetic factors have been described that favorably or unfavorably influence collateral development and angiogenesis. The duration of myocardial ischemic symptoms and the severity in influence collateral development and angiogenesis. The factors have been described that favorably or unfavorably Stimuli to collateral development.

Some of these mechanisms likely affect either the stimuli of to IL-2 as well as blocking the activation of T- and B-cells. Does the inhibition of the associated carcinogenic angiogenic mechanisms play a role in collateral growth impairment? The answer is not known. However, the anti-angiogenic properties of rapamycin are linked to decreased production of vascular endothelial growth factor (VEGF) and an inhibited response of vascular endothelial cells to stimulation by VEGF. Peripheral blood mononuclear cells from healthy human volunteers were inhibited by sirolimus to outgrow to smooth muscle-like and endothelial cell-like cells (early neointimal hyperplasia) (13). Thus, although sirolimus acts against large-vessel restenosis, it is conceivable that its inhibitory effect on smooth-muscle progenitor cells affects re-endothelialization or distant angiogenesis. Interestingly, the adverse effects of DES on endothelialization and endothelial function have been shown only for sirolimus-eluting stents, but collateral function attenuation was seen for both sirolimus and paclitaxel in the study by Meier et al. (2). The important new findings that both sirolimus and paclitaxel elicit a negative effect on collateral function, and that the effect of sirolimus appears to be less pronounced than that of paclitaxel, require further exploration into mechanisms of collateral stimulation angiogenesis beyond our current understanding.

**Study limitations.** The limitations of the current study are few. The investigators have a long and distinguished track record of successful explorations in the subtleties of directly measured coronary physiologic responses in patients during cardiac catheterization. The technical feat of such data collection, coupled with ischemic quantification, should be acknowledged, and its limitations would be unlikely to yield spurious results. The need to study collateral function over time from the large data bank of BMS- and DES-treated patients did not permit randomization beforehand and limited intra- and intergroup comparisons. It is understandable why the limited applications of BMS precluded such study. Finally, concerns may exist regarding individual propensities to form collaterals that might skew the results. No clinical study can guarantee precise patient matching, but the statistical analysis appeared to discount this factor as an important influence on the results.

**Clinical implications.** This study highlights a previously unappreciated downside of DES. Although it is still of largely theoretical concern, should abrupt late occlusion occur after DES, the normal collateral protection would be impaired to some degree, with more ischemia potentially permitting a larger ischemic insult and higher mortality risk than would otherwise occur. No one would question the acceptance of this downside given the superior long-term restenosis results for the vast majority of our patients with DES. The observations from this study serve to focus our attention on how and why collaterals act to protect the heart and what the future might hold for pharmacologic manipulation of collateral function.