Prediction and prevention by progenitors? Stent thrombosis and EPCs

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This editorial refers to ‘Circulating endothelial progenitor cell levels and function in patients who experienced late coronary stent thrombosis’, by E.I. Lev et al., on page 2625

During the late 1980s balloon-expandable vascular stents were developed to prevent abrupt closure and restenosis after angioplasty.\(^1\) Their initial success was hampered by an overwhelming rate of early stent thrombosis. Introduction of P2Y-receptor antagonists (i.e. ticlopidine and clopidogrel) for platelet inhibition in combination with acetylsalicylic acid greatly reduced this often fatal complication. Long-term clinical studies, however, identified in-stent restenosis as an additional hindrance of sustained success. New drug-eluting stents (DES) promised to inhibit the pathological vascular smooth muscle cell migration and proliferation and proteoglycan deposition responsible for restenosis. To the dismay of all of us, the reduced risk of restenosis with DES was accompanied by an increased stent thrombosis rate. Unlike stent thrombosis after implantation of a bare metal stent, which generally occurs within the first 2 weeks, late (>30 days) and very late (>1 months) stent thrombosis is not infrequent after implantation of a DES.\(^2\)

The main contributors leading to stent thrombosis include procedure-related factors such as stent diameter and length, apposition or expansion, patient-related factors including reduced ejection fraction, diabetes mellitus, or advanced age, antiplatelet-related factors comprising different drugs and individual responsiveness, stent thrombogenicity-related factors incorporating strut thickness, polymer type, and polymer thickness, and, most importantly, local and systemic factors influencing endothelial integrity, activation, and re-endothelialization.\(^3\) In in-stent thrombus formation, the initial tethering of platelets is activated by free stent struts and extracellular matrix proteins. It is mediated by the glycoprotein Ib/V/IX receptor complex and its major ligand von Willebrand factor.\(^4\) After the initial platelet adhesion, autocrine and paracrine mediators, including adenosine diphosphate (ADP), thrombin, epinephrine, and thromboxane A2, amplify and sustain the platelet response by recruit circulating platelets from the flowing blood to form a growing haemostatic plug. An intact and healthy endothelium, however, supports normal blood flow by separating platelets for the extracellular matrix. Furthermore, endothelial cells release nitric oxide and prostacyclin, two powerful soluble inhibitors of platelet activation, and express high levels of CD39 which rapidly metabolizes ADP.

Thus, the common problem on the cellular level responsible for complications with angioplasty, stent implantation, and cytotoxic agents in DES seems to be a destruction or prolonged repair of the protective endothelial layer. Recent research is therefore focusing on protecting this natural vascular defence shield and improving endothelial regeneration.

Endothelial function is essential for vascular integrity. The endothelium possesses antiplatelet and antithrombotic properties, provides a barrier from the underlying matrix, regulates vascular tension, and is involved in angiogenesis. Shear stress, cholesterol crystals, inflammation, and other factors are constantly damaging individual endothelial cells, but angioplasty and stent implantation rip apart and destroy large endothelial segments. These damaged endothelial cells are renewed by healthy adjacent cells and/or by circulating progenitor cells. Endothelial progenitor cells (EPCs) potentially derive from the bone marrow and are defined by surface antigens and in vitro culture protocols. Early EPCs (early outgrowth EPCs) are important for re-endothelialization and neoangiogenesis through paracrine activity but, unlike late EPCs (late outgrowth EPCs), most probably do not differentiate into endothelial cells. Not only are the number and function of circulating EPCs associated with the cardiovascular outcome of patients with coronary artery disease,\(^5\) but increasing the number of circulating EPCs by direct injection,\(^6\) pharmacological stimulation,\(^7,8\) or exercise\(^9\) facilitates endothelial repair and thereby impairs neointima formation, which is the cellular basis of in-stent restenosis (Figure 1).

Lev and colleagues have presented data from a case–control study analysing the number and function of EPCs in patients that suffered late stent thrombosis. They demonstrate that the...
The number of circulating VEGFR-2⁺, CD133⁺, and CD34⁺ cells is significantly reduced in patients >3 months after late stent thrombosis. The number of EPC colony-forming units (EPC CFU) was also decreased in patients with stent thrombosis, verifying FACS (fluorescence-activated cell sorting) analysis data. In concert with this finding, the viability of circulating EPCs assessed by MTT assays and migration behaviour was reduced in EPCs of stent thrombosis patients. Patients that developed stent thrombosis had higher platelet aggregation in response to ADP than the matched controls, even though antiplatelet therapy was similar. Wenaweser and Buonamici have reported comparable findings. Lev et al. are certainly to be congratulated for their work, but some limitations, as already stated by the authors, deserve attention. Due to the retrospective design, no assumptions on the predictive and possibly protective role of EPC numbers in stent thrombosis can be made. Nor can we speculate on the stability and reproducibility of EPC numbers at other times. EPC number and function just before or during stent thrombosis may differ from the time point 10 months after the event. In this context, it would be crucial to ensure that medical treatment and lifestyle were comparable at the time immediately before stent thrombosis compared with the sample drawing period 10 months later. Physical exercise, statins, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), hormone replacement, kidney function, diabetes, etc. readily influence circulating EPC numbers and may lead to uncontrollable variations of this biomarker over time. Antiplatelet treatment just prior to stent thrombosis was heterogeneous and may have been a major factor contributing to stent thrombosis, especially since discontinuation of antiplatelet therapy is a strong predictor of stent thrombosis. Furthermore, as acknowledged in the Discussion, DES use and incidence of myocardial infarction, issues which may well trigger the appearance of stent thrombosis, were also different between the groups. Late stent thrombosis was defined as occurring >30 days after stent implantation. On average, stent thrombosis occurred 16.9 ± 10 months following the index procedure and was most prevalent in patients with a DES (80%). Notably, only patients who were still alive were to be allocated to the stent thrombosis group in this retrospective analysis. Considering the lethal nature of stent thrombosis, this
leaves the evaluation with a substantial risk of survival bias. Lastly, it would have been nice to compare other circulating inflammatory and progenitor cells for control purposes in order to provide some more mechanistical clues. Nevertheless, if these initial data are supported by prospective studies, one could postulate some hypotheses and envisage potential clinical implications.

As stated above, stent thrombosis is a multifactorial event dependent on procedural/technical/device issues, antplatelet therapy, and systemic conditions. High pressure implantation, intravascular ultrasound, optical coherence tomography, novel stent platforms, thinner stent struts, abluminal device drug reservoirs, abandonment or variation of the drug-eluting polymer, drug modification, and degradable stent material are just a few of the large joint efforts to upgrade the technical and interventional side of the problem. We are witnessing a rapid progress in the development of antplatelet drugs, and recent studies suggest that the frequency of stent thrombosis can be reduced with novel compounds such as prasugrel or ticagrelor. However, even with confidence in technical and pharmaceutical development, due to the high mortality rates, even infrequent stent thrombosis will remain a relevant issue. In addition, antplatelet therapy prevents stent thrombosis at the cost of an increased and also potentially fatal bleeding risk. Therefore, this treatment should last as short a time as possible and should be applied only if unequivocally required. This is an area of high uncertainty, since reliable studies on the duration of antplatelet therapy after stent deployment are lacking.

This leads us to these curious systemic conditions. Obviously, diseases such as heart failure, renal insufficiency, or diabetes, which all predispose to stent thrombosis, are not instantaneously curable and appear in a broad array of severity and combinations. Therefore, it will be important to identify the risk of stent thrombosis by easy and reliable assessment of biomarkers in order to tailor individual strategies which could influence the choice of stent type and duration of antplatelet therapy. Since repair of the endothelial monolayer is the central cellular event which governs thrombogenicity of the stented vessel area, markers which inform about the status of the formerly disrupted endothelium would be extremely helpful. Circulating EPCs are supposedly involved in re-endothelialization processes and may serve as a predictor of cardiovascular outcome. It is therefore an intriguing speculation that measurement of these progenitors may help to develop an individualized therapy after stent implantation. Besides device and antplatelet treatment, this could affect treatment with, for example, statins, which are known to enhance circulating numbers of EPCs, although missing statin therapy has not been identified as a predictor for stent thrombosis. One could think of various selective treatment options to enhance EPCs [e.g. erythropoietin, vascular endothelial growth factor (VEGF), and antiinflammatory and antihypertensive drugs] and supplement the basis of a guideline-driven treatment in coronary artery disease. Whether the so-called EPC-capturing stents are able to solve these clinical problems is an open issue, since the scientific evidence is still preliminary.

Sometimes answers to complicated questions or solutions to challenging problems are simple. Physical activity helps to improve diabetes and hypertension, leads to weight loss, supports positive affect, and therefore ultimately reduces cardiovascular events. Above all, exercising increases the number of circulating EPCs. Enthusiastic supporters of exercise state that sports could even prevent the need for stent implantation. Wouldn’t it be a nice compromise to embark on physical exercise programmes at least after a coronary intervention?

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References