Platelets and endothelium: Two key players in percutaneous coronary intervention

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Introduction

As a consequence of great advances in the pharmacological environment, in the devices used, and in refinements in technique, PCI has become the most common form of coronary revascularization. The main limitation of PCI is EST (i.e. within 30 days post PCI)—a rare (0.75—2\%) but deadly event. Investigations aimed at identifying biomarkers for these complications have focused on markers of platelet activation, as assessed by PR inhibition \cite{1}. In-stent restenosis, on the other hand, is a frequent complication of bare-metal stent implantation, occurring within 3 to 6 months after PCI and with a high morbidity. It is a complex phenomenon involving several players. Early regeneration of the injured endothelial monolayer is key to prevent in-stent restenosis \cite{2}. Since EPC were identified recently in the peripheral blood of adults, studies have demonstrated that their role is critical for the repair processes \cite{3}. Endothelial biomarkers reflecting injury and repair potential could therefore be of interest to identify patients at risk of in-stent restenosis.

Early stent thrombosis

Early stent thrombosis is a multifactorial process; factors responsible for this complication are related to the patient, the lesion and the procedure. The development of antiplatelet

Abbreviations: EPC, Endothelial Progenitor Cells; PCI, Percutaneous Coronary Intervention; PR, Platelet Reactivity; VASP, Vasodilator-Stimulated Phosphoprotein; EST, Early Stent Thrombosis.

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agents has been critical to reduce the rate of early stent thrombosis following PCI. The addition of thienopyridines to aspirin has dramatically reduced the rate of EST from 10 to 15% to less than 3% [4]. Iakovou et al. [5] observed a hazard ratio of 151 for stent thrombosis in the case of premature discontinuation of antiplatelet therapy, thus underlining the key role of these agents. However, investigators observed wide inter-individual variability in the biological efficacy of clopidogrel. This variability is related to several factors, including genetic, clinical and cellular elements. The biological efficacy of clopidogrel is therefore unpredictable. Several platelet assays have been developed to overcome the limitations of aggregometry, including technical requirements, lack of standardization and lack of specificity [6]. Since then, the literature has demonstrated that the biological variability in the response to clopidogrel is associated with the occurrence of recurrent thrombotic events and in particular early stent thrombosis. Although these studies were performed with various platelet assays, they consistently observed a strong association between high on-treatment PR and thrombotic events after PCI. In addition, investigators using identical assays have observed a similar optimal PR cut-off value to predict thrombotic events. These findings suggest a threshold of PR inhibition associated with thrombotic events. A consensus has therefore been proposed to define high on-treatment platelet reactivity based on clinical outcome [1]. Platelet reactivity is a validated biomarker of risk of early stent thrombosis.

Following the demonstration of a strong association between PR inhibition and outcome, investigators aimed to determine if PR was a marker of risk or a modifiable risk factor. The VASP studies were among the first to investigate the clinical impact of clopidogrel dose-adjustment according to PR monitoring in patients undergoing PCI. In these studies, a significant reduction in 1-month major adverse cardiac events was observed, driven largely by a reduction in early stent thrombosis in patients receiving a tailored antiplatelet therapy [7,8]. The gauging responsiveness with a verifinow assay-impact on thrombosis and safety (GRAVITAS) study did not confirm these preliminary findings [9]. There are several explanations for this disappointing result: the inclusion of a low-risk population, lack of power, insufficient therapeutic strategy in low responders, and a dose adjustment performed after PCI [9]. According to our findings of improved outcome with optimal PR inhibition, the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel—thrombolysis in myocardial infarction (TRITON—TIMI), 38 trial demonstrated a significant reduction in major adverse cardiac events with prasugrel compared with clopidogrel in patients with an acute coronary syndrome undergoing PCI. Prasugrel is a third-generation thienopyridine, with a faster and stronger biological efficacy compared with clopidogrel but similar active metabolites [10]. We recently observed that in patients receiving prasugrel, high on-treatment PR, as defined with the above-mentioned cut-off value, was associated with a poor outcome, further validating PR as a biomarker of thrombotic events following PCI [11]. The role of this biomarker to optimize therapy requires a large randomized trial adequately testing an early and efficient therapeutic strategy to overcome high on-treatment PR. Such trial is currently lacking.

Role of the endothelium in intimal hyperplasia

The development of in-stent restenosis is currently a major limitation of PCI using bare-metal stents. The primary event leading to intimal hyperplasia is loss of endothelial integrity induced by vascular injury. This endothelial damage initiates a cascade of events, including smooth muscle cell proliferation and migration, leading to intimal hyperplasia. Indeed, endothelial cells located at the interface between blood and tissues are plastic cells able to integrate signals from blood or surrounding tissues. By developing adaptive responses they critically participate in the maintenance of vascular homeostasis through their capacity to prevent activation of haemostasis, inflammatory responses and smooth muscle cell proliferation. Uncontrolled activation or loss of physical integrity of the endothelial monolayer leads to endothelial dysfunction or injury, which critically determines initiation and progression of vascular diseases. Although the pathophysiological importance of the endothelium is widely recognized, this organ has long been inaccessible for non-invasive exploration. Recently, improvement in understanding of the endothelial dynamics has led to the identification of endothelium-derived components in the peripheral blood, providing original biomarkers for the assessment of the endothelial integrity in clinical practice. As a result of activation or apoptotic processes, vessel wall endothelial cells shed microparticles or became detached, leading to the presence of circulating endothelial cells in the peripheral blood. Circulating endothelial cells can be enumerated using a standardized CD146-based immunomagnetic separation assay and constitute a reliable marker of endothelial injury with diagnosis and prognostic value in various cardiovascular settings. They can also behave as effective factors modulating vascular homeostasis due to their capacity to disseminate proinflammatory and procoagulant signals in the bloodstream [12]. More recently, the endothelial response to injury has been enlarged by the discovery of powerful repair mechanism involving bone-marrow-derived EPC. First described by Ashara et al. [3], these cells are identified among CD34+ circulating progenitors with respect to their ability to proliferate and differentiate in vitro into functional endothelial cells and to actively contribute to endothelial repair or growth when recruited at the sites of endothelial injury or ischemia in vivo. EPC are now recognized as a heterogeneous population of cells originating from various potential tissue reservoirs and differentiation lineage. This heterogeneity allows the main distinction of cells from myeloid lineage that supports angiogenesis through paracrine activities and ‘true’ angioblasts, of non-haematopoietic origin, which display specific ability to incorporate into healing or growing vessels. Although the exact phenotype of EPC is still a matter of debate, clinical studies have documented increased levels of circulating EPC following ischaemia or endothelial injury. By contrast, lower levels of EPC are representative of a compromised endothelial repair potential and may identify patients with a poor cardiovascular outcome [13]. In the specific
context of arterial injury, experimental models strongly support the contribution of bone-marrow-derived progenitors to early re-endothelialization. Moreover, infusion of exogenous EPC and mobilization of endogenous EPC are effective strategies for increasing EPC availability in the blood, resulting in early re-endothelialization, which translates into the prevention of vascular remodelling and neointimal formation [14]. However, despite these encouraging findings some controversies remain. Animal experiments have indicated that among progenitor cells mobilized from bone marrow after vascular injury, some have the capacity to differentiate into neointimal smooth muscle cells. In addition, the impact of mobilizing drugs is dependent on their selectivity for EPC. To date, human studies suggested that EPC deficiency may be associated with in-stent restenosis [15]. However the retrospective design of the studies and the heterogeneity in methods used for EPC assessment do not allow a definite conclusion. In our recent studies, we evidenced that circulating endothelial cells behave as a promising marker of PCI-induced endothelial injury, integrating not only the mechanical trauma associated with the procedure but also an individual susceptibility for vessel wall injury response [16]. Interestingly, among factors determining the extent of circulating endothelial cell increase following PCI, we identified the role of platelet reactivity. Indeed, an optimal control of clopidogrel-induced P2Y12 blockade (as evidenced by the VASP index) independently predicted reduced endothelial injury consistent with its endothelial protective impact [17]. Collectively, these data suggest that endothelial dynamics play a crucial role in the pathophysiology of angioplasty-associated vascular complications, including in-stent restenosis. In addition, the available literature regarding the role of EPC in early re-endothelialization of vascular injury and reduced neointimal hyperplasia formation in animal models suggests that EPC could be a biomarker of in-stent restenosis in humans. This hypothesis should be tested in a prospective trial.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References