Coronary stent healing, endothelialisation and the role of co-medication

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Since the second half of 2006 percutaneous coronary revascularisation using drug-eluting stents (DES) has come under the scrutiny of the general cardiology community. The initial favourable reports and publications on the merits of DES suddenly changed due to more or less qualified new data on complications such as late stent thrombosis. It seems that the commotion about late stent thrombosis has been over-emphasised, considering the publications that followed from the randomised controlled trials published together in one issue of the *New England Journal of Medicine* earlier this year.¹ The main message from these publications was that indeed late stent thrombosis occurred, but also in the bare metal stent (BMS) groups. However, the debate was further fuelled by data showing that in pathological specimens from autopsy studies more fibrinoid and less endothelialisation could be demonstrated in DES.² Furthermore, in atherectomy specimens from patients with DES restenosis we were able to show delayed healing in DES compared with BMS.³ In addition, in DES patients without restenosis, Togni et al.⁴ and Hofma et al.⁵ demonstrated that the coronary segments

adjacent to the DES had a dysfunctional endothelium. Taken together these data should convince us that the current generation of BMS, because of restenosis, but also DES, because of vascular healing problems, are still imperfect and should be improved. The problems to be solved seem obvious: restenosis, endothelialisation and healing, but this may be an oversimplification.

Re-endothelialisation

There is a common notion that DES inhibit re-endothelialisation, because of toxicity of the currently used drugs, such as sirolimus or paclitaxel, towards endothelial cells.⁶ In our view, it is not certain whether this is a valid hypothesis. Data on re-endothelialisation have thus far been obtained by late pathological studies² or early angiography observations.⁷ However, it is far from certain that later pathological studies are appropriate to retrospectively give insight into earlier processes. In addition, angiography is a macroscopic technique that inherently does not allow discriminating between a bare stent and a stent with only a few cell layers of covering.

Pooled data from real-world registries or controlled, clinical trials show that the 30-day stent thrombosis rates of BMS and DES are similar.^{1,8} This underscores the hypothesis that DES are not more thrombogenic (or in other words less endothelialised) than BMS in the short term. Alternatively, differences occur later, when the toxicity of permanent polymer are not counteracted by a sufficient dose of anti-inflammatory drug. In particular, it is common knowledge, but maybe less well remembered, that about 90% of the paclitaxel dose in the Taxus stent is retained on the stent almost permanently, and this while the SIBS polymer on the same stents continues to exert its chronic irritating effect. It seems, therefore, that drugs eluting from a biodegradable polymer and released in parallel to the polymer degradation products may be more effective. For instance, we showed that parallel release of the limus analogue, tacrolimus, blended in a degradable PLGA polymer, did not reduce early endothelialisation or induce late toxicity.⁹ In about 90 days, both the effects of the drug as well as the polymer proved to be minimised and at 180 days no late catch-up of inflammation or neointimal build-up could be observed (figure 1).

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Figure 1. Histology at 90 days (left) and 180 days (right) shows the similarity between the two time points and the lack of late neointimal growth after complete drug elution. H&E stain, Bar = 1mm.

The healing of vascular injury by circulating progenitor cells has been a topic that caused enthusiasm in the interventional community. Although favourable reports have been published the true potential of this hypothesis still has to be demonstrated. A stent engineered with a coating that contains antibodies directed towards binding sites on EPCs is already in clinical use, although its efficacy has not yet been proven. A potential disadvantage of the recruitment of circulating progenitor cells is that certain patient groups have been identified to possess less active progenitor cells, such as patients with advanced atherosclerosis, diabetics and the elderly. In addition, certain pharmacological agents widely used in cardiovascular diseases may potentially reduce the activity of endothelial progenitor cells. In particular, agents interfering with the renin-angiotensin system (RAS) such as ACE-I or ARBs may theoretically inactivate progenitor cells.

In ICIN project 59 we performed a pilot study investigating this interference of RAS-modulating agents with endothelial progenitor cells (EPCs).¹⁰ Firstly, we standardised the experimental conditions in both labs (Groningen and Rotterdam). Subsequently, we evaluated effects of different RAS interventions on survival and proliferation toward endothelial progenitor cells in vitro. Preliminary results from in vitro studies indicate that the angiotensin heptapeptide Ang-(1-7) enhanced the proliferation of bone marrow and blood mononuclear cells and increased the fraction of EPCs within this cell population. Thirdly, we validated the quantitative methodologies for measuring the network-forming capacity of EPCs (figure 2), in order to examine the quality of the cells after culture. In addition, preliminary data showed that the angiogenic activity of the EPCs, assessed as network

forming capacity, appeared not to be modified. In contrast, angiotensin II type I receptor blockade by losartan depressed EPCs. In the light of the ubiquitous use of ACE-I and ARB, these observations warrant more comprehensive examination of the role of RAS components in EPC function. ■

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Figure 2. Top panel: Phase-contrast microphotograph 50x. Left: Rat bone marrow derived endothelial progenitor cells (EPCs) network forming capabilities without drug. Middle: Rat bone marrow EPCs with 10⁻⁷M angiotensin (1-7) shows decreased activity. Right: Rat bone marrow EPCs with 10⁻⁸M Ang(1-7) shows enhanced activity. Bottom panel: Phase-contrast microphotograph 100x. Left: Rat bone marrow EPCs with 10⁻⁸M Ang (1-7). Right: Identical picture to left with greyscale contrast optimisation and Clemex matrix tools superimposed for quantitative data analysis.