Editorial

A role for endothelin receptor blockade in improving the endothelial function of coronary artery grafts?

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See article by Verma et al. [4] (pages 146–151) in this issue.

Since the experiments of Furchgott and Zawadzki [1] at the end-seventies, there is an increased number of research projects on the endothelium and the endothelial function in vascular regulation. The experimental data produced then has reached tremendous quantities. Now we know that the endothelium plays a role as an autocrine and paracrine producer of vascular active substances [2], either with a constricting or a dilating effect of blood vessels, either directly or indirectly acting. Irregularities in this balance could be responsible for increased tone in vascular smooth muscle cells, altered reactivity and vasomotion, and over a longer period to changes in structure and geometry and to enhanced platelet aggregation.

One of the most potent vasoactive agents found to be produced in the vascular endothelium, are the so-called endothelins (ET). This group of vasoactive polypeptides contains different subgroups with subsequent different receptor subtypes. Two receptor subtypes have been cloned in blood vessels, namely, the ETA receptor, which preferentially binds ET-1 and the ETB receptor, which equally binds ET-1 and ET-3 [3].

The manuscript of Verma et al. in this issue [4] describes experiments on isolated segments (in vitro) of the human internal mammary arteries (IMA) used in coronary bypass surgery. It has been showed before that endothelin antagonists inhibit ET-1 mediated constriction of the IMA [3], but it was unknown whether these endothelin antagonists can improve the endothelial function. Therefore the authors examined the effects of specific and non-specific ET-receptor antagonists on the endothelial function, as assessed by using acetylcholine-induced vasodilatation in IMA. Isometric dose-response relations of vascular segments to acetylcholine and sodium nitroprusside were measured, in the presence or absence of ET A/B antagonist bosentan, the ET A antagonist BQ-123 or the ET B antagonist BQ-788. After blocking the ET receptor, the endothelium-mediated relaxation by acetylcholine was significantly augmented, independent of the type of ET-antagonist.

Based on these findings the conclusion has been made that improving the endothelial function of coronary artery grafts by ET-receptor blocking, may promote thromboresistance, decrease peri-perative vasospasm and impede IMA atherosclerosis [4].

A few restrictions have to be made in interpretation of the results of the study mentioned above. First, the population of patients undergoing bypass surgery showed to have a clustering of coronary artery disease risk factors and is a normal representation of the patient population undergoing bypass surgery. Hence to find patients with only one risk factor like diabetes, hypertension, smoking, obesity or a familiar hyperlipidemia, is extremely difficult and would need huge patient populations. Therefore, the results as presented in the paper could be mixed up with different influences to the endothelium and therefore possibly associated with different levels of endothelins in the blood. Thus no differentiation can be made between the relative roles of each individual risk factor in endothelial dysfunction.

A second heterogeneity can be found in the medication as used by the patients. Especially the ACE-1 and calcium channel blockers can have long lasting effects on endothelial receptors and therefore interfere with the found results.

Despite these restrictions in extrapolating the results from the in-vitro situation of the laboratory to a clinical conclusion, there is an important finding: it has been shown for the first time, that ET-receptor blockade improves endothelial dilating function in human IMA.

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The IMA is the conduit of choice for coronary revascularization, because of its long term patency [5] and thrombo-resistance as compared to saphenous veins or other arteries. However, it does have a small diameter, leading to high blood velocities which maybe is the cause of peri-operative vasospasm. The latter is a critical factor in postoperative infarction and mortality following CABG surgery, as recently shown again in a case report [6] where 3 patients were described with severe postoperative coronary artery spasm resulting in severe complications or death. Studying the phenomenon has led to several hypotheses and solutions to solve this problem. Improved drug therapy for arterial spasm is now available (nitroprusside, nifedipine). Using radial arteries instead of IMA is studied also, but seems not to be an alternative with a spasm frequency of 5–10% [7]. Optimization of the quality of the grafts or prevention of (endothelial or vascular smooth muscle) damage during coronary artery surgery are therefore the best options in this aspect.

It has been shown recently by Petrossian et al. [8] in a lamb model that plasma endothelin-1 levels increase significantly after hypothermic cardiopulmonary bypass operation. In respect to this finding, it is a logical step to examine the role of the constricting effects of endothelin onto the grafts and a possible role of ET-receptor antagonists in this process.

Further experiments with selected patient groups with single risk factor and/or single medical treatment have to be done to clarify possible interactions with current findings. More animal studies have to be done also to examine whether there is a possibility to implement present findings of Verma et al. [4] into clinical use of these endothelin receptor blockers.

References