Remember what I told you about therapeutic arteriogenesis, 11 years ago?

EXPERT’S PERSPECTIVE

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This editorial refers to an article by I.E. Hoefer et al. published in Cardiovascular Research in 2001. It is accompanied by a retrospective editorial by two authors of that original article, I.E. Hoefer and W. Schaper, pp. 154–156, this issue, as part of this Spotlight on Landmark Papers in Cardiovascular Research.

‘It remains to be demonstrated if the gain in time is of sufficient relevance in a clinical setting where often the time of occlusion is either not known or has occurred some time ago.’ With this insightful remark, the paper by Hoefer et al. ends after it had unequivocally demonstrated that there is only a short-time window for pro-arteriogenic therapy such as MCP-1 to establish its efficacy.

Onward from the early 1970s, the Schaper group has worked and published >80 papers on the molecular mechanisms underlying collateral formation and can without doubt be considered the single most influential authority on collateral formation. In addition, numerous trainees of the laboratory have spread out and continued academic arteriogenesis research as group leaders. One of the reasons why the Schaper group has stayed on top of the field is that the methodologies developed in their laboratory are of the highest standard and are based on sound physiological reasoning. The paper by Hoefer et al. in 2001 in Cardiovascular Research is a prime example. In earlier studies, the Schaper group had set the stage for conductance measurements to assess the capacity of the local circulation to absorb increasing flow demand. This is not only physiologically more meaningful than just measuring flow at a given pressure and contraction state of the arteriolar system, but also more accurately describes the anatomy of the collateral growth. In this study, they extended that technology to in vivo measurement of the regional flow at various pressures by six different fluorescent microspheres. Because they are labour intensive and technically challenging, none of these techniques has made it into the mainstream of arteriogenesis studies. For any novel diagnostic method to measure collateral capacity, such as contrast-enhanced ultrasound, physiological assessment of collateral capacity as described in the Hoefer paper should be the gold standard. From the difference in time course between the number of collaterals and conductance, it was inferred that arteriogenesis starts with numerous small contributing arteries and later develop in a limited number of large collaterals through pruning of the smaller or non-functional ones. This was confirmed by independent studies, one of which appeared in the same issue of Cardiovascular Research by Hershey et al.

As happens so often with successful agents in preclinical research, MCP-1 never really made it into the clinic. In the case of MCP-1, this was not the result of a lack of efficacy in patients but because the chemokine stimulated atherogenesis at the same time. To date, the notion that the innate inflammatory mechanisms leading to collateral formation are very similar if not equal to those that stimulate atherosclerotic plaque formation drives the direction of research into humoral or cellular mechanisms that are selective for arteriogenesis. Such selectivity has proved to be very difficult to define.

The closing remark in the Hoefer paper has gained significance over the last decade. First, it suggests that the natural tendency to grow collaterals after an acute occlusion in young healthy animals develops quite effectively, and the best that can be done is to speed up the process. Since then, it has become clear that collateral growth is hampered or delayed in diseases such as diabetes, hypercholesterolaemia, and in ageing. It is therefore important to define standardized disease or ageing models for preclinical testing of pro-arteriogenic agents, whose mechanism of action theoretically should restore the underlying deficiency. With MCP-1 that is clearly not the case as the chemokine is now seriously being considered as a marker of atherosclerosis, illustrating its abundant presence.

Secondly, it is equally evident that flow recovery through collateral formation may restore resting blood flow, but the flow reserve that is required for flow adaptations to exercise is still limited in the first weeks of follow-up. It was again the Schaper group that extended follow-up to 6 months after MCP-1 treatment in hyperlipidaemic disease.
rabbits and showed only 60% recovery and no difference with controls. Apparently, in the absence of systematic physical exercise, the natural course of full adaptive flow recovery in the peripheral arterial bed is protracted and late recovery is not affected by current therapies. This observation in animal models is paralleled by results from clinical trials, where results of either gene or cell therapies in the first month are typically favourable but efficacy seems to dwindle at later follow-up.10

The Hoefer study is an exemplary study that has stood the test of time and in retrospect offers explanations for every clinical observation in therapeutic arteriogenesis that has been made since. Excellent methodical preclinical studies based on sound pharmacological and pathophysiological reasoning should therefore continue to be the cornerstone of biological therapy design and testing.

Conflict of interest: none declared.

References


