Collateral vessels reduce mortality

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This editorial refers to ‘The impact of the coronary collateral circulation on mortality: a meta-analysis’, by P. Meier et al., on page 614

Christian Seiler, Pascal Meier, and their co-workers of the University Hospital in Bern, Switzerland, well known for their pioneering clinical work on the collateral circulation of the heart, have described a meta-analysis of 12 studies involving 6529 patients of the role played by the collateral circulation in mortality. The authors come to the conclusion that the ‘coronary collateralization has a relevant protective effect’. Mortality is reduced by 36% in patients with, compared with those without, demonstrable collaterals.

This is a very important statement about a situation that most cardiologists believed that they knew from anecdotal evidence: patients with all three epicardial arteries occluded but without infarctions, in some cases even without typical ischaemic symptoms, die from an unrelated cause and with the post-mortem finding of long-standing major coronary artery disease, again without sign of infarction. However, the relevance of such observations was sometimes disputed: since collaterals develop in response to arterial stenoses and occlusions, it is quite clear that more collaterals can often be demonstrated in hearts with more advanced coronary artery disease, and indeed the conclusion was put forward that collaterals are the harbingers of a worsening course of the disease. Only a few but prominent clinicians clung to this view, but this is now roundly refuted.

Backed by their analysis, Seiler and his co-workers state, that ‘the results of this study highlight the importance of finding new means to induce collateral growth’. With the evidence of the life-prolonging effects of collaterals at hand, it is time to make a giant leap forward and increase efforts to prolong the lives also of the have-nots. This is a timely reminder for the pharmaceutical industry to increase activities in this direction, which have so far been virtually absent. Two reasons may be put forward for this: the disaster which occurred with the industry’s brief love affair with angiogenesis, which early on showed promise for patients and profits but which ended in disappointment and huge losses in investments. Secondly, the industry is reluctant to stimulate vascular growth because of its potentially cancerogenic effect. However, since the molecular pathways of arteriogenesis are now sufficiently well known (Figure 1), this should facilitate industrial development of very specifically acting new drugs.

The questions arising from that are: how feasible is the task of arteriogenic stimulation, are these vessels stimulatable at all, and will they stay enlarged after cessation of therapy? A further question is why is it that in so many patients collaterals do not develop?

To answer the first question: yes, collaterals can be stimulated to grow and to develop. Collaterals develop best when two conditions are met: increased fluid shear stress plus attraction of bone marrow-derived mononuclear cells that attach to stressed endothelium but also enter the adventitial space from leaky small veins. Stimulation of these cells by peptide hormones was shown to be successful in patients. Stimulation by increased fluid shear stress is probably the strongest stimulus for vascular growth. The fate of forced growth will finally depend on the tissue’s need for oxygen and nutrients. All excess will be trimmed. Another essential factor is the presence of proteases necessary for outward remodelling. Without proteases all new growth will clog the lumen. Peptide growth factors, mitogens for endothelial and smooth muscle cells, are probably not the answer because clinical studies were generally disappointing and animal experiments by the group of Keshet have shown that cardiac endothelial overexpression of vascular endothelial growth factor leads to overproduction of shed endothelial cells that clog the arteries and cause tissue ischaemia, i.e. the opposite of the intended result. It was shown that inhibition of the nitric oxide (NO)-producing enzymes inhibits arteriogenesis, but we showed that one relatively recently developed NO donor (detaNONOate) indeed stimulated collateral development in the vascular periphery.

Several reasons can be discussed to explain why collaterals do not develop in a number of patients.
In many cases coronary occlusions occur suddenly and sometimes by thrombi on plaques that by themselves did not constitute a relevant stenosis, necessary for early development of collaterals. This leads to infarctions that strongly reduce the need for blood and oxygen and hence reduce the stimulus for collateral growth, which needs time for development. This time (at least 3 days) is too long to guarantee the survival of the ischaemic myocardium, which, under favourable circumstances, already dies \( \approx 60 \) min after occlusion. The time course of collateral growth is well known from animal studies and is determined by immutable facts: the duration of the cell cycle (18–24 h) and the migration of new cells and their assembly to form and enlarge the pre-existing collateral into a functional bulk flow conductor.

Several other hypotheses have been put forward, i.e. genetic predispositions, insufficient activation of the innate immune system (i.e. the inability to recruit bone marrow-derived mononuclear cells), the absence of pre-existing collaterals, which are the remnants of the incomplete terminal differentiation of the embryonic capillary network, and, finally, the presence of growth inhibitors in the bloodstream. The latter hypothesis gains acceptance since it became known that a false substrate (and hence inhibitor) for endothelial nitric oxide synthase (eNOS; which plays a key role in arteriogenesis), i.e. asymmetric dimethyl arginine (ADMA), a known risk factor for atherosclerosis, is present in plasma of patients with reduced kidney function. Evidence from animal experiments showed significant reduction of collateral development after ADMA administration.

What if we finally find a way to stimulate collateral growth? Apart from the fact that the right moment has to be found (definitely before infarction occurs!), the result must be superior to that achieved by placement of stents, a steep order. If the calculations by Seiler and his group prove to be correct (there is no doubt about this) and collaterals are superior in outcome with regard to hard endpoints (mortality) compared with surgical bypasses, then the assumption that they will also be superior to stents in the long run has a definitive chance of being shown to be the case.

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**References**