Therapeutic Arteriogenesis Has Arrived

Wolfgang Schaper, MD

The report by Seiler et al on a clinical trial using granulocyte-macrophage colony-stimulating factor (GM-CSF) to stimulate the growth of coronary collateral vessels is the temporary culminating point of a long history of research that started in the early 1940s with the observation that the pressure measured in the distal stump of an occluded canine coronary (or femoral or carotid) artery rose as a function of time and was caused by the development of a collateral circulation. Strandness and Schoop and Jahn were probably the first to measure the pressure in the coronary arterial system that was later refined by Scheel. By that time, the pioneering work of the animal physiologists was already forgotten. Most cardiologists continued to rely on angiography. The study of pressure-flow relationships in diseased coronary arteries was more or less regarded as an academic exercise. This opinion may soon change, because the time has come to stimulate the collateral circulation with recombinant angiogenic and arteriogenic growth factors or their genes. This would require a detailed study of the collateral circulation. This was tried before with fibroblast growth factor and vascular endothelial growth factor (VEGF), but the studies were confounded by conceptual and technical limitations. The conceptual limitation was that growth factors were studied that act mainly on endothelial cells (VEGF), and the technical limitation was that methods were used that relied on surrogate end points and did not directly measure collateral pressure and flow.

The present study by Seiler et al overcomes both of these limitations: they studied a growth factor that stimulates arteriogenesis, and they used methods that are directly related to the status of the collateral circulation. Furthermore, they applied a new paradigm, arteriogenesis, that differs from that of angiogenesis in that it tries to substitute the occluded artery with arterial collaterals. It is finally recognized that an occluded epicardial coronary artery cannot be replaced by capillaries, regardless of numbers. Only arterial collaterals come somewhat close to replacing the conductance of a coronary artery.

In a canine heart with a progressive coronary stenosis leading to complete chronic coronary occlusion but not to infarction due to the synchronous growth of collateral channels, the PCP usually reaches 80% of the aortic perfusion pressure under conditions of rest (anesthesia). The ratio of PCP over aortic pressure falls with coronary vasodilatation and remains, ≈6 weeks after chronic occlusion, at 40% of aortic perfusion pressure. This is an indication that collateral growth has not completely restored the conductance of the occluded artery to preocclusive values but rather to only ≈35% (ie, the collateral vessels offer finite resistance). The flow they can deliver is sufficient to avoid ischemia under normal ambulatory conditions but would become limiting under physical exertion. It is presently unknown why the process of arteriogenesis stops prematurely before the optimal adaptation is reached. One explanation could be that the 2 forces which had initiated the growth process, ie, fluid shear stress and tangential wall stress, become normal again soon.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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Dr Schaper’s employer is a holder of a GM-CSF user patent.

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after the growth starts. It would therefore be desirable to prolong the period of growth or to restart it. The discovery of the arteriogenic potency of circulating monocytes offers such a possibility. Monocytes produce a host of different growth factors, and when they attach to a transforming vessel, a mixture of factors is released. This may be superior to monotherapy. Arras et al reported that increasing the attraction of monocytes to the endothelium of collateral vessels by an infusion of monocyte chemoattractant protein-1 increases the speed of growth.

By increasing the life cycle of monocytes with the stem cell factor GM-CSF, the speed of development and the level of adaptation could be increased in experimental animals.

Seiler et al are very circumspect about the effects of GM-CSF on atherosclerosis. It is known that GM-CSF lowers cholesterol levels; this is also what Seiler et al observed in their treated patients. However, they are cautious not to overestimate this effect because LDL cholesterol remained unchanged. However, experiments in relevant animal models (Watanabe rabbits) have shown that GM-CSF reduces the plaque surface, and it is not unreasonable to assume that this may also occur in patients. GM-CSF is thus far the only growth factor that has not been accused of being negatively associated with atherosclerosis. Most of the other angiogenic or arteriogenic factors are prothrombic, upregulate tissue angiogenesis and arteriogenesis.

References


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