Adenosine and arteriogenesis: promoter or suppressor?

Masatoshi Fujita*

Department of Cardiovascular Medicine, Uji Hospital, Uji, Kyoto, Japan

Online publish-ahead-of-print 9 November 2012

This editorial refers to ‘Lack of ecto-5′-nucleotidase (CD73) promotes arteriogenesis’ by Y.C. Böring et al., pp. 88-96, this issue.

The principal therapeutic approach to atherosclerotic obstructive disease is to provide a sufficient blood flow to the jeopardized area perfused by the severely narrowed or occluded artery, which is accomplished by bypass grafting surgery, percutaneous transluminal intervention, and angiogenic therapy. Angiogenesis has been clearly separated into arteriogenesis and angiogenesis in a narrow sense in a rabbit hindlimb ischaemia model.1 Using the experimental model, Schaper et al.2 established a conceptual framework of arteriogenesis.2 A pressure gradient across the collateral network increases the collateral blood flow, with resultant augmented fluid shear stress at the site of collateral vessels. Vascular endothelium activated by increased shear stress produces and releases monocyte chemotactic protein-1 (MCP-1) and adhesion molecules.3 Accumulated monocytes produce various angiogenic growth factors and proteases. These bioactive substances lead to arteriogenesis, together with tissue degradation.3 A number of pharmacological treatments have been attempted to enhance arteriogenesis. Heparin exercise treatment for patients with chronic effort angina accelerates and potentiates arteriogenesis.4 More recently, a variety of angiogenic growth factors and cytokines have been intensively investigated.5

In this issue, Böring et al.6 have focused on the relationship between adenosine and arteriogenesis. They have elegantly demonstrated, using sophisticated methods such as magnetic resonance angiography and magnetic resonance spectroscopy, that adenosine formed extracellularly by CD73 is an inhibitor of arteriogenesis on the basis of the evidence that the lack of ecto-5′-nucleotidase promotes arteriogenesis in hindlimb ischaemia of CD73−/− (CD73 knockout) mice. Although it is well known that adenosine dilates capillaries and potentiates angiogenesis,7 to my knowledge this is the first report demonstrating the effects of adenosine on arteriogenesis.

At first, one might assume that adenosine enhances collateral development (arteriogenesis), based on the observation that dipyridamole, a potentiatior of adenosine, acutely augments the collateral blood flow by reducing vascular resistance in the collateral-

development area8 in the Franklin’s 2-min repeated coronary occlusion model.9,10 Thus, augmented fluid shear stress by an increased collateral blood flow would lead to arteriogenesis. In contrast, Kerner et al.11 reported that vascular inflammation promotes collateral development in humans. Because adenosine has the potential to attenuate inflammation,12 it is likely that adenosine suppresses collateral development (arteriogenesis). As shown in Figure 1, arteriogenesis is triggered by increased shear stress resulting from an increased collateral blood flow. Up-regulated expression of vascular cell adhesion molecule 1 and MCP-1 in the endothelium leads to the accumulation of monocytes at the endothelium. Finally, monocytes produce and release various angiogenic growth factors and cytokines.2,3 Adenosine probably suppresses the expression of MCP-1 by attenuating inflammation and the proliferation of vascular smooth muscle cells, resulting in reduced arteriogenesis.

Adenosine possesses two contradictory actions on arteriogenesis, as mentioned above. Other agents also have both acute vasodilatory and anti-arteriogenic effects.13,14 Nitroglycerine acutely and directly...
dilates collateral vessels. In contrast, nitroglycerine suppresses the proliferation of vascular smooth muscle cells, which is a main component of arteriogenesis. It is uncertain whether the chronic administration of nitroglycerine promotes or suppresses arteriogenesis. A single oral administration of sarpogrelate augments the collateral blood flow, presumably due to dilation of collateral vessels. Because sarpogrelate also suppresses the proliferation of vascular smooth muscle cells, it remains unclear how the chronic administration of this drug affects arteriogenesis. Hirose et al. demonstrated that chronic sarpogrelate treatment enhances collateral development (arteriogenesis) in a rabbit hindlimb ischaemia model. Thus, since each vasoactive substance acts in opposing ways on some part of the cascade of arteriogenesis, the relative contribution to arteriogenesis may differ among them (Figure 1).

The present study provides an answer for the role of adenosine in arteriogenesis, suggesting that modulation by adenosine may lead to potentiation of arteriogenesis. However, pleiotropic actions of adenosine may limit the clinical application of adenosine suppression treatment for enhancing arteriogenesis.

Conflict of interest: none declared.

References
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