Anatomic Considerations in Therapeutic Arteriogenesis for Cerebral Ischemia

To the Editor:

The pioneering efforts in the development of therapeutic arteriogenesis for cerebral ischemia reported by Buschmann et al.1 herald a new era in the field of stroke therapy. The role of collaterals in maintaining perfusion beyond the site of a proximal arterial occlusion has long been appreciated as a critical factor in reducing ischemic injury in the brain.2 analogous to observations in the coronary and peripheral circulation. Despite recent advances in therapeutic arteriogenesis of coronary and peripheral collaterals, studies of the cerebral collateral circulation have been limited.

Anatomic considerations are paramount in the study of the cerebral collateral circulation. The anatomy of the cerebral collateral circulation is strikingly dissimilar to that of the coronary or peripheral circulation. Proximal collateral routes at the circle of Willis recruited at the onset of ischemia may be easily assessed with various modalities, yet the influential distal leptomeningeal collaterals that determine stroke outcome require multivessel angiography for evaluation.3,4 These proximal and distal collateral arteries or arterioles have numerous anatomic differences that influence hemodynamics and ultimately, cerebral perfusion. The hemodynamic characteristics of arterograde collateral blood flow from an adjacent proximal cerebral artery to supply distal anastomoses are also different from the hemodynamics of retrograde collateral blood flow in distal aspects of an occluded artery.

Several anatomic details have been omitted in the recent report by Buschmann et al.1 Occlusion of the left carotid and bilateral vertebral arteries was used to demonstrate therapeutic arteriogenesis in the left posterior cerebral artery, yet there are no data on the contralateral posterior cerebral artery or posterior communicating arteries that supply the left posterior cerebral artery via the circle of Willis. Other “collateralyzed” vessels such as the anterior and middle cerebral arteries ipsilateral to the occluded carotid artery were also not described. Therapeutic arteriogenesis with granulocyte-macrophage colony-stimulating factor was demonstrated in the left posterior cerebral artery, a relatively large conductance vessel, yet arteriogenesis was not demonstrated in the distal anastomoses. These distal anastomoses are pre-existing collateral arterioles that have previously been described as “the substrates of arteriogenesis.”5 Why should arteriogenesis occur in the large conductance artery and not in the pre-existing collateral arterioles?

Future studies of the cerebral collateral circulation and arteriogenesis must account for all of the specific anatomic routes that supply collateral blood flow. Each experimental model of cerebral ischemia, such as the three-vessel occlusion method, elicits collaterals with a particular anatomic configuration. Selective description of collateral recruitment leaves far more questions unanswered.

David S. Liebeskind, MD
Departments of Neurology and Radiology
University of Pennsylvania
Philadelphia, Pa
davidliebeskind@yahoo.com


Response

We very much appreciate Dr Liebeskind’s letter. We fully agree that the collateral circulation in the brain is far more complex than in the peripheral vasculature. Indeed, in the first part of our study, we carefully characterized the response of the circle of Willis to 3-vessel occlusion (3-VO, ipsilateral carotid and bilateral vertebral artery ligation) both short term (1-week survival) and long term (3-week survival). These data were published before our investigation on the therapeutic effects of granulocyte-macrophage colony-stimulating factor and actually deal with the questions raised by Dr Liebeskind.

We examined the diameter of the anterior and middle cerebral arteries, the internal carotid artery, and Heubner’s dorsal leptomeningeal anastomoses after 1 and 3 weeks of 3-VO. We expected that arteriogenic growth would also take place in regions of smaller arteriolar connections, as described by Wei and coworkers in rats after stroke. However, after 1 week, the only significant difference in vessel diameter was observed in the ipsilateral anterior cerebral artery and the contralateral PCA. After 3 weeks, a significant increase in vessel size was also detected in the ipsilateral anterior cerebral artery and the contralateral PCA. At this time, the diameter of the ipsilateral PCA had increased significantly from 187 ± 27 to 322 ± 50 μm (plus 72%), that of the contralateral PCA from 196 ± 29 to 261 ± 38 μm (plus 33%), and that of the ipsilateral anterior cerebral artery from 251 ± 37 to 322 ± 42 μm (plus 28%). Other supplying arteries did not change in diameter during the observation period. Heubner’s leptomeningeal anastomoses did not change either; in control animals, the mean diameter was ipsi- and contralateral 37 ± 4 μm; after 3-VO, it was 38 ± 2 μm on the ipsilateral and 37 ± 3 μm on the contralateral side; and after granulocyte-macrophage colony-stimulating factor treatment, it insignificantly changed on the ipsilateral side to 39 ± 6 μm and on the contralateral side to 36 ± 4 μm.

In summary, our study demonstrates that the basal cerebral arteries respond more to 3-VO than Heubner’s dorsal leptomeningeal anastomoses, but this effect may be adequate to protect the brain against ischemia arising from vascular stenosis. Collateral growth is closely linked to the location of blood pressure gradients within the vascular system. Thus, any experimental brain ligation model can only partially reflect the complex pattern of brain arteriogenesis.

Ivo R. Buschmann, MD
Hans-Joerg Busch, MD
Max-Planck-Institute for Neurological Research
Cologne, Germany

Konstantin-Alexander Hossmann, MD
Department of Experimental Neurology
Max-Planck-Institute for Neurological Research
Cologne, Germany

Albert Ludwigs University Freiburg
University Hospital
Department of Internal Medicine III
Research Group for Experimental and Clinical Arteriogenesis
Freiburg im Breisgau, Germany
buschmann@med1.ukl.uni-freiburg.de

Günter Mies, MD
Albert Ludwigs University Freiburg
University Hospital
Department of Internal Medicine III
Research Group for Experimental and Clinical Arteriogenesis
Freiburg im Breisgau, Germany

1. Buschmann I, Busch HJ, Mies G, et al. Arteriogenesis for cerebral ischemia reported by Buschmann et al.1 hernia a new era in the field of stroke therapy. The role of collaterals in maintaining perfusion beyond the site of a proximal arterial occlusion has long been appreciated as a critical factor in reducing ischemic injury in the brain.2 analogous to observations in the coronary and peripheral circulation. Despite recent advances in therapeutic arteriogenesis of coronary and peripheral collaterals, studies of the cerebral collateral circulation have been limited.

2. Wei L, Erinjeri JP, Rovainen CM, et al. Collateral growth is closely linked to the location of blood pressure gradients within the vascular system. Thus, any experimental brain ligation model can only partially reflect the complex pattern of brain arteriogenesis.
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