Can Raising Cerebral Blood Flow Improve Outcome After Acute Cerebral Infarction?

James C. Grotta

Cerebral blood flow correlates poorly with outcome after stroke, and most therapies aimed at increasing cerebral perfusion have not succeeded in predictably reducing neurological deficit. Newer approaches such as hemodilution and thrombolysis may prove to be more effective but might be most advantageous if combined with efforts to correct postischemic disturbances in cellular metabolism. (Stroke 1987;18:264-267)

Since cerebral infarction (CI) is most often due to arterial occlusion by thrombus, embolus, or vasospasm, it is logical to assume that cerebral blood flow (CBF) will be low in infarcted brain regions and that increasing CBF will be therapeutically effective. However, quantitative measures of CBF may be disappointing due to the correlation of clinical stroke severity with extent of extracranial arterial stenosis. Furthermore, regions of low, normal, or even increased flow can be seen for several days after CI probably because of variability from patient to patient in reperfusion through collateral channels, breakup of emboli, and compensatory vasodilation.

Combining CBF with measures of brain metabolism using positron emission tomography (PET) has demonstrated regions of low-flow, preserved oxygen metabolism and, consequently, increased oxygen extraction suggesting that hyperperfusion persists for 24-72 hours after stroke in regions of threatened but viable tissue. This interpretation of PET data may be too simplistic since many different ratios of CBF to cerebral metabolic rate for O\textsubscript{2} (CMRO\textsubscript{2}) have been found after infarct and correction of abnormal CBF/CMRO\textsubscript{2} ratios does not always occur after successful reperfusion.

In addition to doubts raised by the poor correlation of CBF and clinical state, therapeutic trials aimed at improving CBF in the acute stage of CI have been inconclusive. Possible reasons include the following: The therapeutic technique might not increase CBF to vulnerable brain regions; treatment was begun too late; patient selection was poor; or outcome measures were not sufficiently sensitive to detect clinical benefit. Finally, however, it must be considered possible either that raising CBF is not effective (i.e., "the horse is already out the barn door") or that reperfusion must be coupled with therapy that rectifies delayed events triggered by ischemia.

Therapies for raising CBF have been based on the well known Hagen-Poiseuille equation, \[ Q = \frac{(\Delta P \pi r^4)}{(8L \eta)} \], where Q is blood flow, \( \Delta P \) is pressure gradient, r is vessel radius, L is vessel length, and \( \eta \) is blood viscosity. Flow can be increased by raising perfusion pressure or lowering cerebrovascular resistance:

1. Increasing CBF by raising perfusion pressure
   a. raising mean arterial blood pressure
   b. surgical reperfusion

2. Increasing CBF by lowering cerebrovascular resistance
   a. vasodilators
   b. removing arterial obstruction (thrombolysis)
   c. lowering viscosity

Raising perfusion pressure by induced hypertension and surgical reperfusion by carotid endarterectomy (CEA) or extracranial-to-intracranial bypass attempt to capitalize on the passive nature of the cerebral vasculature after cerebral injury. Autoregulatory mechanisms that normally maintain constant CBF despite fluctuations in mean arterial blood pressure (MABP) are lost for several weeks after CI, and CBF can be increased in regions correlating with clinical signs after raising MABP or after surgical reperfusion. Unfortunately, these therapies have not resulted in clinical benefit and, in fact, except in carefully selected patients, are avoided because they are associated with increased risk of cerebral edema and hemorrhage. Patients with cerebrovascular occlusive complications of angiography or surgery may benefit from immediate induced hypertension, and patients with minimal deficit and high-grade carotid stenosis may benefit from CEA. Further studies in these subpopulations are needed.

Cerebrovascular resistance can be lowered by increasing vessel radius (vasodilation), removing arterial obstruction (thrombolysis), or lowering whole blood viscosity. Many vasodilators can raise hemispheric CBF, and they include papaverine, prostacyclin, and carbon dioxide. However, in ischemic brain regions responsiveness to carbon dioxide is lost, and vasodilator drugs often fail to raise CBF perhaps because vessels are already maximally dilated in dam-
Aged brain due to accumulation of hydrogen ion, adenine, or other local vasoactive agents. The end result of therapy, then, may be dilation of the normal vascular bed “stealing” blood from unresponsive ischemic regions. Most clinical studies of vasodilators have been negative but these studies were flawed by delay in therapy and poor patient selection. Two recent studies of prostacyclin, one of the most potent vaso dilators known, insured maximal therapy within 24 hours of proven cerebral infarction. Nevertheless, both studies were negative, but hypotension caused by prostacyclin may have prevented upward titration of the drug to a dose sufficient to achieve cerebral vasodilation. While not yet discarded, vasodilator therapy has been disappointing as a therapeutic approach to CI.

Thrombolytic agents can lower cerebrovascular resistance by removing arterial obstruction by thrombosis or embolism, though CBF measurements have not been reported after this form of therapy. Pilot studies with streptokinase demonstrated an unacceptably high incidence of cerebral hemorrhage caused by systemic fibrinolysis. The development of tissue plasminogen activator (tPA) by recombinant genetic techniques has renewed interest in thrombolytic therapy since tPA, normally synthesized in the vessel wall, is clot specific and its activity is limited to fibrin and fresh thrombus in situ. Demonstrated benefit in coronary artery disease, anecdotal reports of safety and efficacy in basilar artery occlusion, and animal stroke studies have generated enthusiasm; and pilot studies of tPA in CI are now planned or underway. Initiation of therapy in the first few minutes after vascular occlusion and before tissue necrosis occurs will probably be necessary to maximize benefit and reduce the likelihood of hemorrhagic transformation of the infarct.

Blood viscosity has been lowered clinically by lowering hematocrit (by hemodilution) or fibrinogen (with Ancrod), and by increasing red blood cell deformability (with pentoxifylline). Such maneuvers increase CBF in ischemic regions and improve physiologic measures in animal and human studies, but the jury is still out regarding clinical benefit. Hemodilution in acute stroke patients was clearly beneficial in one recent study though not when extended to community hospitals where accomplishment of effective hemodilution was sometimes delayed several days. Two studies are presently underway in the United States. Ancrod was associated with clinical benefit after CI even though fibrinogen is a relatively weak determinant of blood viscosity. This therapy may be useful in the subset of patients with very high fibrinogen at the time of CI. Pentoxifylline did not reduce morbidity or mortality after acute stroke in a recent study though some transient effect on motor function and level of consciousness was seen.

Even if ongoing studies prove positive, CBF augmentation, while seductive in simplicity and logic, is unlikely by itself to dramatically reverse morbidity after CI. An understanding of CBF in CI has taught us that an inadvertent drop in CBF caused by hypoten-
8. Baron JC, Rougemont D, Bousser MG, Lebrun-Grandpe, Iba-Zizen MT, Chiras J: Local CBF, oxygen extraction fraction (OEF), and CMRO2: Prognostic value in recent supratentorial infarction in humans (abstract). J Cereb Blood Flow Metab 1983;3(suppl 1):S1


40. Hoechst-Roussel Pharmaceutical Inc. files.


42. Tindall GT: Augmentation of cerebral blood flow induced by — A randomized multicenter trial (abstract). Stroke 1986;17:143


Can raising cerebral blood flow improve outcome after acute cerebral infarction?

J C Grotta

Stroke. 1987;18:264-267
doi: 10.1161/01.STR.18.1.264
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/18/1/264