MR Perfusion Imaging in Acute Ischemic Stroke

William A. Copen, MD[a,b,*], Pamela W. Schaefer, MD[a,c], Ona Wu, PhD[b,c]

KEYWORDS

• Stroke • Brain ischemia • Magnetic resonance imaging
• Cerebrovascular circulation

When magnetic resonance (MR) imaging–based techniques for studying brain perfusion were developed in the 1980s and 1990s,[1] one of the first pathologic conditions to which they were applied was ischemic stroke, a disease that is caused fundamentally by impaired perfusion. Like the positron emission tomography (PET) and single-photon emission computed tomography (SPECT)-based methods that preceded it, MR perfusion imaging of acute stroke patients offered a window into a rapidly evolving disease process, in which changes in tissue perfusion may have dramatic effects on patient outcomes. MR-based perfusion-weighted imaging allowed perfusion measurements to be obtained more quickly than with PET or SPECT, and with scanners that were more widely available.

Interest in imaging perfusion rapidly was spurred by the US Food and Drug Administration's 1996 approval of intravenous tissue plasminogen activator (tPA), a thrombolytic drug whose purpose is restore brain perfusion, but which was approved for use only in those very few acute stroke patients who can be treated within 3 hours of symptom onset. Because tPA offers both the potential for life-saving rescue of underperfused tissue and the risk of catastrophic intracranial hemorrhage, the most active focus of research on MR perfusion imaging in acute stroke has been its potential application in refining the selection of patients for thrombolysis. However, perfusion imaging also has other potential roles in ischemic cerebrovascular disease, including establishing diagnosis, predicting prognosis, and guiding nonthrombolytic therapies designed to maintain cerebral perfusion.

Before addressing MR perfusion imaging's potential uses in these roles, this review first discusses the ways in which the various perfusion parameters that can be measured by perfusion imaging vary under different hemodynamic conditions. The following section presents the computational techniques that are used to create the various kinds of clinically used MR perfusion images. Although the details of these techniques and the artifacts that they may create are often overlooked in discussions of perfusion imaging, understanding them is essential to integrating the results of past research on MR perfusion imaging, and to using perfusion imaging in patient care.

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[a] Department of Radiology, Division of Neuroradiology, Massachusetts General Hospital, GRB-273A, 55 Fruit Street, Boston, MA 02114, USA
[b] MGH/MIT/HMS Athinoula A. Martinos Center for Biomedical Imaging, 149 Thirteenth Street, Suite 2301, Charlestown, MA 02129, USA
[c] Department of Radiology, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA
* Corresponding author. Department of Radiology, Division of Neuroradiology, Massachusetts General Hospital, GRB-273A, 55 Fruit Street, Boston, MA 02114.
E-mail address: wcopen@partners.org

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THE HEMODYNAMICS OF ISCHEMIC STROKE

The changes in perfusion that occur in acute stroke are driven fundamentally by global and/or regional changes in cerebral perfusion pressure (CPP).[2] CPP is the difference between mean arterial pressure and venous pressure, the latter of which is usually equal to intracranial pressure. The cerebral vasculature responds to small reductions in CPP by dilating small arteries, thereby reducing cerebrovascular resistance, and successfully maintaining normal cerebral blood flow (CBF) over a wide range of perfusion pressures.[3] This vasodilatory response results in an increase in cerebral blood volume (CBV),[4] which is the volume of the intravascular space within a particular volume of brain tissue, such as that within a single image voxel. The increase in CBV may be subtle and difficult to detect in MR perfusion images. Vasodilation also results in an increase in mean transit time (MTT), which is the average amount of time that red blood cells spend within a particular volume of tissue. CBF, CBV, and MTT are related via the central volume theorem[5]:

$$MTT = \frac{CBV}{CBF}$$

When CPP drops below the threshold at which the brain maintains autoregulation, the compensatory vasodilatory response is overwhelmed. CBF begins to decrease, and becomes pressure-dependent, that is, further reductions in CPP lead to worsening decreases in CBF. Although this reflects a decrease in the rate of oxygen delivery to the capillary bed, metabolic compromise can be avoided if CBF is only mildly reduced, because of the effect of MTT prolongation on oxygen extraction. When MTT is increased, red blood cells spend a longer time within oxygen-permeable capillaries, and this allows for an increase in the proportion of the available oxygen that can be extracted from the blood by the brain (oxygen extraction fraction, or OEF). If the CBF reduction is mild, the increase in OEF is sufficient to maintain oxygen metabolism (cerebral metabolic rate of oxygen consumption, $CMRO_2$), and neither the brain's electrical function nor its viability is threatened.[6] This level of hypoperfusion has been called "benign oligemia,"[7] although that term has also been used to refer less specifically to any underperfused state that does not threaten tissue viability, regardless of whether electrical function is preserved.[8]

With even further reductions in CPP, CBF falls so low that increased oxygen extraction is unable to maintain normal oxygen metabolism, and $CMRO_2$ falls. With a sufficient reduction in $CMRO_2$, neurons cease their electrical transmission, and the patient may experience a neurologic deficit. If the $CMRO_2$ reduction is mild enough, the survival of the tissue is not threatened, despite its electrical silence, and this situation can persist indefinitely without permanent damage. If there is an even more severe reduction in CPP, and therefore an even greater reduction in CBF, $CMRO_2$ falls to such a low level that the survival of the affected tissue is threatened. One of the most important principles of ischemic pathophysiology is that the time that it takes for ischemic damage to become irreversible is inversely related to the severity of the ischemia.[9] Brain tissue dies after just a few minutes without any blood flow, but moderately ischemic tissue may remain potentially viable for hours before becoming irreversibly injured. A primary goal of perfusion imaging in acute stroke is the identification of tissue that may be a target for thrombolytic therapy, in that it is threatened by ischemia, but still may be potentially salvageable. Tissue that is still structurally intact and hence viable but electrically dysfunctional has been called the "ischemic penumbra,"[10] with the word "penumbra" chosen because the mildly ischemic tissue sometimes forms a ring-like shape, surrounding a central area ("infarct core") where more severe ischemia has resulted in irreversible injury. It has been suggested that the term can be more usefully redefined to describe tissue that is potentially therapeutically treatable.[11]

It has been proposed[2] that, in conditions of extremely low CPP, low CBV may occur despite maximal vascular relaxation, perhaps because perfusion pressure is so low that the patency of blood vessels cannot be maintained. However, the early studies on which current understanding of cerebral hemodynamics is based offer little direct evidence of the occurrence of decreased CBV. These studies focused more often on the CBV/CBF ratio (ie, MTT), rather than CBV itself.[2] When early studies did measure CBV within infarcts, they often found that CBV was elevated, although these measurements were usually made in subacute infarcts that were days to weeks in age.[12–14] One study found that in an experimental model, macrovascular and microvascular CBV became uncoupled in response to severe hypotension, with macrovascular CBV increasing in some anatomic regions while microvascular CBV decreased.[15]

If the arterial lesion that caused ischemia resolves, either spontaneously or as a result of treatment, the affected tissue is reperfused. Reperfusion can occur in both viable and nonviable tissue, and therefore the absence of any apparent hypoperfusion does not preclude the existence of completed infarction. Reperfusion is the goal of thrombolytic therapy, and it also has been seen spontaneously within