Chapter 29

Potential Application of $^{17}$O MRI to Human Ischemic Stroke

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Abstract In cerebral ischemia, measurement of cerebral blood flow (CBF) alone is not a sensitive or specific predictor of tissue survival. Measurements of oxygen metabolism, which are directly related to cellular energy metabolism, are better predictors of tissue survival and the best of these is the “oxygen extraction fraction” (OEF). Elevation of OEF in Stage 2 hemodynamic failure, or “misery” perfusion, indicates that prolongation of this state or further reduction in blood flow will lead to failure of oxygen metabolism and cellular necrosis, making it a sensitive and specific biomarker for the “ischemic penumbra” and a predictor of impending cerebral infarction. The methods now used to measure in vivo human cerebral metabolic rate of oxygen (CMRO$_2$) and OEF include $^{15}$O-PET and MRI deoxyhemoglobin sensitive techniques (Blood Oxygen Level Dependent, BOLD methods). These methods have practical and fundamental limitations for use in the clinical stroke setting. $^{17}$O-MRI is a method of imaging oxygen metabolism by detecting the tissue water (H$_2^{17}$O) produced by oxidative metabolism of $^{17}$O$_2$ gas that can be performed on conventional, clinical MRI scanners using a chemically stable, non-radioactive, MR-detectable isotope of oxygen. It is more logistically applicable to clinical stroke than $^{15}$O-PET and more directly quantitative than BOLD MRI. $^{17}$O-MRI promises to provide a direct, quantitative, widely available and clinically practical method for assessing CMRO$_2$ and OEF for evaluation of human cerebral ischemia.
29.1 Limitations of Hemodynamic Imaging of Cerebral Ischemia

When reduced tissue perfusion pressure produces cerebral hemodynamic compromise, reflex autoregulatory vasodilation occurs in order to maintain blood flow by reducing arteriolar vascular resistance and increasing vascular blood volume (CBF=CBV/MTT). This compensatory mechanism can maintain normal or minimally reduced levels of cerebral blood flow (CBF) in regions of cerebral ischemia and mask hemodynamically compromised tissue from methods that measure CBF alone. Methods that also measure the increase in cerebral blood volume (CBV) and prolongation of the mean transit time (MTT) are more sensitive to hemodynamic compromise. However, vascular flow methods do not directly reflect the metabolic or morphological integrity of cerebral tissue and are relatively insensitive predictors of ischemic energy failure and cellular necrosis. A wide, overlapping range of severity and duration of hemodynamic changes may be seen with cerebral tissue that is either reversibly ischemic or irreversibly injured (1).

MRI methods that combine hemodynamic parameters with water diffusion imaging (perfusion-diffusion or PWI-DWI imaging) have improved the predictive value of blood flow methods by using diffusion restriction as a marker for the ischemic infarct “core” and reduced flow without diffusion restriction as a marker for ischemic but viable tissue. These methods typically use gadolinium bolus dynamic susceptibility contrast (DSC) MR perfusion weighted imaging (PWI) to measure tissue blood flow parameters (CBF, CBV, MTT and TTP) which are compared to the volume of presumed infarcted tissue indicated by restricted water diffusion (reduced ADC on DWI). When the low blood flow volume is larger than the restricted diffusion volume by 20% or more, a perfusion-diffusion (PWI-DWI) “mismatch” is said to exist. A key limitation of the MRI mismatch approach is that it may overestimate the true “ischemic penumbra” and not specifically identify tissue at risk of infarction. The low blood flow in the mismatch zone may include both underperfused but metabolically stable “oligemic” tissue which is likely to survive at the existing perfusion level as well as unstable “penumbral” tissue that is likely to become infarcted if reperfusion therapy is delayed or ineffective. In addition, all regions of diffusion restriction may not indicate completed infarction but may include recoverable “penumbral” tissue (2,3).

29.2 Hemodynamic Failure and Oxygen Metabolism in Cerebral Ischemia

Because the brain is an obligate aerobic tissue (oxygen is essential for preservation of energy metabolism) measurements of oxygen metabolism are directly related to cellular energy metabolism and are better predictors of ischemic tissue survival than blood flow measurements alone. Although delivery of oxygen decreases with decreasing blood flow, brain tissue can increase the relative amount of oxygen it