Correlation of Cerebral Metabolites With Clinical Outcome Among Patients With Severe Congestive Heart Failure

Craig R. Malloy, MD

Patients with severe congestive heart failure have deranged cognition, and their ability to manage everyday problems is impaired. Cardiovascular reflexes, as well as autonomic and endocrine functions that may involve the central nervous system, are also profoundly disrupted. It is therefore of the utmost importance to understand the consequences of severe congestive heart failure for brain function and metabolism. In vivo proton magnetic resonance spectroscopy (\(^1\)H MRS) is generating interest for 2 reasons. First, \(^1\)H MRS provides a new probe of cerebral function that measures important brain metabolites by detecting the hydrogen nuclei in these molecules. Furthermore, this examination is becoming widely available, and the patient’s experience is virtually identical to that with conventional MRI.

A large number of biochemical intermediates, neurotransmitters, peptides, and structural molecules could, in principle, be detected by MRS; however, biological factors and current limitations on the MRS experiment limit the number of different signals that may be observed in routine clinical examinations. For example, the concentration of the metabolite must be high, which means that important neurotransmitters (such as dopamine or serotonin) and low-concentration metabolites cannot be observed. Another factor is the molecular weight and physical environment of the compound: ideally, the molecular weight is low and the molecule is freely diffusing in aqueous solution. Large molecules, such as relatively immobile membrane lipids or proteins, do not contribute discrete resonances in the clinical \(^1\)H magnetic resonance spectrum. Another factor is the chemical structure itself. Organic molecules contain many hydrogen nuclei in different positions that interact with one another through spin-spin coupling. This effect is exploited for structure analysis by MR spectroscopists, but the phenomenon reduces the height of any single resonance from that molecule. Therefore, hydrogen nuclei in simple chemical groups (such as methyl hydrogens) are more easily detected. For all of these reasons, the \(^1\)H MR spectrum of the human brain is (superficially) relatively uncomplicated.

The resonance (or peak) assigned to N-acetyl aspartate (NAA) is composed of signals from several N-acetylated compounds. NAA is synthesized by an enzyme located in the mitochondria, aspartate acetyltransferase. NAA itself is thought to be present only in viable and mature neurons but not in glia. Although NAA is usually the dominant resonance in \(^1\)H MRS studies of the normal brain, its role in brain metabolism is poorly understood. The choline resonance results from a handful of molecules with a choline moiety, such as phosphorylcholine and glycerophosphorylcholine. Other choline-containing compounds are present in high concentrations in the brain, but they are immobilized in membrane structures and are hence difficult to detect by MRS. The total concentration of choline-containing compounds varies with the anatomical structures of the brain and parallels the density of myelinated tissue. As a rule, the choline signal is thought to reflect membrane synthesis and degradation. The creatine resonance is the sum of creatine and phosphocreatine. Because these 2 molecules are not separately detected in the \(^1\)H spectrum, a direct measure of energy state (the ratio of phosphocreatine to creatine) is unfortunately not possible by \(^1\)H MRS. The myoinositol resonance is generally low amplitude, and it may be a marker of glia. Finally, the nuclei of the methyl hydrogens of lactate are typically not detected in the normal brain, although lactate evolves in the brain during anoxia or other severe injury.

Although the analysis is currently restricted to myoinositol, creatine, choline, and NAA, useful insights have emerged. To take just one example: because NAA is localized to neurons, it is perhaps not surprising to find that NAA levels increase during maturation. Conversely, processes that disrupt neuronal integrity are associated with a loss of NAA. \(^1\)H MRS of cortical white matter among patients with multiple sclerosis and other white matter disorders have shown decreases in NAA. It is important to appreciate that these changes are observed in both white matter lesions and in regions of the brain that are apparently normal on conventional MRI. These observations have been widely confirmed. Other abnormalities in \(^1\)H MRS spectra have been reported among patients with cancer, psychiatric disorders, stroke, \(10,11\) hepatic encephalopathy, \(12\) and epilepsy. \(13\)

Previous applications of \(^1\)H MRS have focused on disorders that primarily involve the brain. Lee and colleagues used \(^1\)H MRS to measure the concentration of choline, creatine, myoinositol, and NAA in the parietal white matter and occipital gray matter among patients with congestive heart failure and severely depressed left ventricular systolic function. The authors concluded that reduced NAA levels in both the occipital gray matter and parietal white matter are associated with poor outcome among these patients. This
study complements and is supported by an earlier report from the same group,15 which found that metabolic abnormalities are to some extent reversible after heart transplantation.

The biological mechanism of the apparent decrease in the concentration of NAA is not known, but it is worth considering 2 elements underlying this calculation.14 1H MRS determines the absolute concentration of NAA (or other metabolites) by relating the amplitude of the 1H resonance of NAA to the 1H resonance of water in the same region of the brain. Therefore, the estimated concentration of NAA will be influenced by the factors controlling the water signal: water concentration (either intracellular or extracellular) and T1 or T2 relaxation times. Any effect of heart failure on the relaxation times of 1H in NAA will similarly distort the calculated concentration of NAA. Because all patients underwent the same MRS examination, these analytical issues are important for understanding the mechanism of decreased calculated NAA concentration, but presumably, they should not explain the differences in MRS observations that correlate with clinical outcome.

How are the pathophysiological events responsible for long-term morbidity and mortality in heart failure related to the abnormal 1H NMR spectrum? Of course that question cannot be answered in a single study, but the question suggests investigations in 4 areas. First, our interpretation of these abnormalities in cerebral neurochemistry requires correlation with other hemodynamic indices of prognosis, including cardiac output, and particularly with direct measurements of brain perfusion. MRI methods for brain perfusion are available, which suggests that a single integrated examination of both perfusion and metabolite concentrations could be informative. Second, this study should stimulate analysis of the relations between metabolite levels and cognitive function in heart failure. Again, the flexibility of MRI methods may contribute to these investigations. Functional MRI, the single most exciting application of MR since the introduction of MRI, allows anatomical localization of regional brain activation during various tasks ranging in complexity from simple voluntary motor activity to sophisticated language and cognitive responses. Third, the relation between drug therapy and abnormal metabolite levels is not known. These results, although interesting, may be less useful to clinicians if subsequent studies show that the abnormalities only occur among patients who require intermittent inotropic/vasodilator therapy. Finally, postmortem correlation studies and more advanced MRS methods will undoubtedly prove valuable in understanding these results.

For example, magnetic resonance spectroscopic imaging permits the measurement of these metabolites in every region of the brain, not just 2 voxels. Higher-field MR instruments are becoming available and offer improved spectral quality.5,6 The report by Lee and colleagues14 is an interesting application of 1H MRS to an ever-expanding population of patients. It represents a first step toward determining if serial proton MR spectroscopy of the brain is a clinically relevant monitor of the evolution of congestive heart failure.

References

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