

Final Report

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Detection and Assessment Using Positron Emission Tomography of Genetically Determined Defects in Myocardial Fatty Acid Utilization

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We have no objection from a patent standpoint to the publication or dissemination of this material.

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The aim of this project was to determine whether abnormalities in myocardial fatty acid metabolism could be delineated using positron emission tomography (PET) imaging in children with inherited diseases of enzymes involved in the metabolism of fatty acids. Deficiencies in these enzymes, specifically long-chain acyl-CoA dehydrogenase or carnitine transport deficiency can result in cardiomyopathy and sudden cardiac death in children. We determined that children with long-chain acyl-CoA dehydrogenase deficiency or carnitine deficiency showed specific abnormalities in fatty acid metabolism detectable by PET, and demonstrated the utility of this approach for the diagnosis of such defects.

We demonstrated that by use of a long-chain fatty acid labeled with carbon-11 (^{11}C), specifically ^{11}C -palmitate, we could track myocardial fatty acid metabolism. Utilization of long-chain fatty acid metabolism was compared with an estimate of mitochondrial turnover using ^{11}C -acetate, a 2-carbon fatty acid that is readily utilized by the myocardium and oxidized nearly exclusively in the mitochondria. Children with inherited defects had a decreased ability to use long-chain fatty acids as compared with the short-chain fatty acids, and differences between subjects with long-chain acyl-CoA dehydrogenase deficiency and those with carnitine deficiency could be identified.

In addition, we demonstrated that some patients with acquired forms of cardiomyopathy (such as alcohol, viral, or idiopathic cardiomyopathy) also had defects in myocardial long-chain fatty acid utilization. We demonstrated that, in subjects with acquired cardiomyopathy, the incorporation of long-chain fatty acids into the slow turnover pool (representing predominantly triglycerides and phospholipids) was a progenitor of sudden cardiac death or the need for urgent cardiac transplantation.

Thus, we demonstrated the ability to diagnose specific genetic defects in patients with abnormality of fatty acid metabolism and the utility of PET for this approach. In addition, the approach appears to be useful also for identifying patients with acquired cardiomyopathy who are at high risk for cardiac events.

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The Principal Investigator moved from Washington University where this award was originally performed to Columbia University in New York. This project has been continued under DOE contract #DE-FG02-97ER62433. The work is continuing in subjects with both inherited as well as acquired forms of cardiomyopathy.

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