Final Technical Report

Project Title: Consortium to develop the medical uses of NMR Imaging, NMR Spectroscopy, and Positron Emission Tomography.

Project Director: Gerald M. Pohost, M.D.

Recipient: University of Alabama at Birmingham

SubProject Title: CARBON-13 GLYCOGEN ASSESSMENT OF SKELETAL MUSCLE IN PATIENTS WITH DISEASE OF THE PERIPHERAL VASCULATURE

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A. Specific Aims.

The overall aim of the present proposal is to perform clinically relevant studies using a new whole-body 4.1 T NMR imaging spectrometer. Initially, we will develop an approach for the assessment of the severity of skeletal muscle involvement in ischemic peripheral vascular disease. Another reason for studying skeletal muscle is to compliment the UTK work (see below). The specific aims of the present proposal are:

- 1) to test the hypothesis that, a) in patients with resting ischemia the extent and severity of vascular disease corresponds to the resting glycogen level, and b) in patients with exercise induced ischemia, the extent of vascular disease is related to the level of residual glycogen at the end of exercise stress;
- 2) to test the hypothesis that a) patients with resting ischemia exhibit elevated lactate levels that corresponds to the degree of disease, b) patients with exercise induced ischemia have elevated lactate after exercise and c) patients adapt to chronic vascular insufficiency by increasing their muscle buffering capacity;
- 3) to determine the relationship between resting glycogen content, lactate, high energy phosphate levels, and pH;
- 4) to determine the significance of alterations in glycogen depletion and synthesis rates after exercise in patients with disease involving the peripheral vascular supply to the leg.

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Significance:

Glycogen provides a source for the fueling of skeletal muscle energy metabolism during severe exercise. In patients with disease involving the peripheral vascular supply to the skeletal muscles of the legs, glycogen stores may be reduced or totally depleted, depending on the severity of the disease. Furthermore, lactate at rest and with exercise may result from inadequate oxygenation (i.e., a mismatch between glycolysis and oxidation) and inadequate clearance by the reduced blood supply. ^{13}C NMR and ^1H spectroscopy provide means of *in-vivo* monitoring of skeletal muscle glycogen and lactate. As such, spectroscopy may provide a mechanism for the evaluation of the severity of ischemic skeletal muscle disease. The purpose of the present study is to utilize a 4.1 T whole-body imaging spectroscopy system to evaluate 1) skeletal muscle glycogen stores and 2) lactate accumulation in control patients and in patients with varying degrees of peripheral vascular disease. In addition to monitoring the basal levels of glycogen and lactate, the patients will undergo an exercise protocol to determine the rate of residual glycogen depletion and lactate accumulation. Glycogen synthesis and lactate clearance will then be monitored by serial ^{13}C and ^1H NMR *in-vivo* spectroscopy over a one-hour interval during recovery.

Peripheral vascular disease resulting from arterial stenosis is relatively common occurrence in the adult population. For these patients even minor physical exertion can result in fatigue and pain. The detailed origin of the onset of pain is not known. In order to determine the possible metabolic origin of this phenomenon, studies investigating substrate availability, lactate accumulation and changes in energy metabolism need to be addressed. Substrate availability can be visualized by monitoring the natural abundance ^{13}C glycogen (1) level. In order to achieve adequate time resolution (2.48 min), due to the low sensitivity of the ^{13}C nucleus, the glycogen studies should be optimally performed with a high field (4.1T in our case) whole body system. Measurements of lactate and high energy phosphates will take advantage of the increased S/N and chemical shift dispersion available at 4.1T.

Summary:

Although modest funding was granted for this project (\$47K/yr) significant scientific advancement was made. Results demonstrated the feasibility of performing natural abundance ^{13}C glycogen measurements in muscles with time resolution sufficient to resolve energetic changes as observed by ^{31}P NMR. This approach has allowed us to assess both the interaction of substrate availability at the glycogen level and energetic failure. Further, these results suggest the onset of pain and decline in the PCr content of muscle in patients with peripheral vascular disease is not due to a limitation in glycogen. Finally, higher

time resolution can be obtained by the use of ^1H decoupling or polarization transfer methods. In addition, these preliminary studies were pivotal to the application and successful funding of a NIH National Center of Research Resources grant at the UAB. This Center now serves a multidisciplinary research team of faculty, clinicians, and staff.

Direct and Related Publications Resulting from this Research

Hetherington HP, Fasbender T, Wieland J, Maas R, Bomsdorf H, Pohost G. C^{13} glycogen studies at 4T in patients with peripheral vascular disease and ^{31}P studies at 1.5T. SMRM, 1990.

Newcomer BR, Hetherington HP, Pan JW, Mantil J, Pohost GM, Boska MD. Evaluation of initial PCr breakdown and resynthesis kinetics in human gastrocnemius/soleus using high time resolution ^{31}P MRS. SMRM, 1994.

Boska MD, Newcomer BR, Hetherington, HP, Pan JW, Mantil J, Pohost GM. Obtaining non- P_i buffer capacity of human gastrocnemius/soleus using high time resolution ^{31}P MRS. SMRM, 1994

Mason GF, Pan JW, Chu W-J, Zhang YT, Khazaeli K, Williams R, Newcomer BD, Orr R, Conger K, Pohost GM, Hetherington HP. TCA cycle rate measurement in human brain by indirect C^{13} Detection with a volume coil. SMR, 1996.