Title: NON-INVASIVE DETECTION OF MALIGNANT HYPERTHERMIA SUSCEPTIBILITY BY *IN VIVO* 31-P NMR

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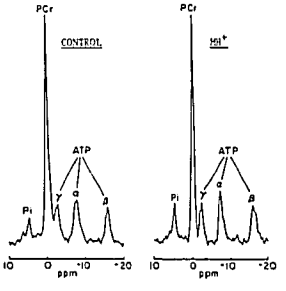
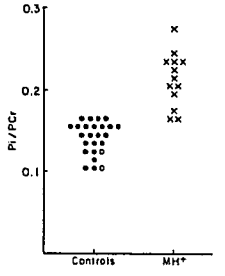
Introduction. Malignant hyperthermia (MH) is a genetic disorder characterized by a devastating reaction to many general anesthetics, most notably halothane. The reaction can be prevented if MH susceptibility is known pre-operatively. However, since the signs are usually present only during anesthesia, pre-anesthetic diagnosis is difficult. Suspicion of MH susceptibility is based upon either havings signs during anesthesia or being related to a known MH susceptible person. However, confirmation is made only be a contracture test on muscle biopsy. This is an invasive test with some risk to the patient. We employed the technique of *in vivo* phosphorus magnetic resonance spectroscopy (31-P NMR) to non-invasively determine the levels of phosphocreatine (PCr), inorganic phosphate (Pi) and ATP in muscles of MH susceptible patients, in the hopes of distinguishing this population from normals.

Methods. Thirteen MH susceptible subjects (shown to be so by halothane contracture tests[1]) were tested by 31-P NMR. Patients with concurrent muscle disease were excluded from the study. The 25 control subjects were normal, healthy, non-athlete individuals. Two of these controls were proven nonsusceptible to MH by halothane contracture tests. Informed consent and approval from the Human Research Committee were obtained prior to the study. The basic protocols for studying human arm muscle with *in vivo* 31-P NMR is described in previous publications.[2] The subject's arm was placed in a 30 cm bore magnet on a probe coupled to a Cybex ergometer and containing a surface radiofrequency coil. 31-P NMR spectra of the wrist flexor muscles were obtained at rest, steady-state graded exercise (at 20%, 40% and 60% of each subject's maximum force) and during post-exercise recovery. The spectra were analyzed by triangulation to obtain ratios of Pi/PCr. Wilcoxon's rank sum test was used to analyze population differences. Values are given as mean ± SEM.

Results. Typical 31-P NMR spectra at rest from an MH susceptible patient and a normal conrol are shown below.



There are similar peaks in both spectra. However, the Pi to PCr ratio is higher in the MH susceptible patient. The population distributions of Pi/PCr values obtained during rest in MH susceptible subects and controls are shown below. The open circles are those control subjects proven non-MH susceptible.



The resting Pi/PCr values from the MH susceptible population is significantly different from normal controls ($p<0.001$); the higher values being the MH susceptible subjects (0.215 ± 0.009) compared to normals (0.140 ± 0.004). A resting Pi/PCr of 0.175 or greater was seen in the affected persons only, while all persons with a resting Pi/PCr less than 0.160 were normal. In addition, a significantly ($p=0.01$) slower postexercise recovery rate (return of high energy phosphates to resting levels following exercise) was found in the MH susceptible group. An average recovery rate of 1.833 ± 0.245 PCr/Pi/min was obtained from the MH susceptible group and an average of 2.960 ± 0.227 PCr/Pi/min from controls. There was no significant difference found in the relation of work rate to Pi/PCr between the two groups during exercise.

Discussion. It is clear from our results that MH susceptible patients can be distinguished from normals with a simple 31-P NMR measurement of muscle Pi/PCr at rest. In addition, post-exercise recovery rates may aid in the interpretation of these resting data. These finding suggest the potential use of 31-P NMR for diagnosing MH susceptibility. The NMR test is non-invasive and painless, and can be accomplished in under 20 minutes. While these findings are encouraging, further studies are needed to confirm the usefullness of 31-P NMR in diagnosing MH susceptibility.

References.

1. Fletcher and Rosenberg: In vitro interaction between halothane and succinylcholine in human skeletal muscle. Anesthesiology 63:190-194, 1985

2. Chance, Eleff, Leigh, Sokolow and Sapega: Mitochondrial regulation of PCr/Pi ratios in exercising human muscle: A gated 31-P NMR study. Proc Natl Acad Sci 78:6714-6718, 1981