Title : MALIGNANT AND EXERCISE HYPERTHERMIA : INVESTIGATION OF 73 SUBJECTS BY CONTRACTURE TESTS AND P31 NMR SPECTROSCOPY

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Introduction. Malignant Hyperthermia (MH) is an acute syndrome occuring in genetically predisposed subjects. Exercise Hyperthermia (EH), often called "heat stroke" is an hyperthermic state induced by sustained muscular exercise beyond the subject's capability. These syndromes can often be lethal or leave invalidating sequelae. A method able to detect non invasively this potential risk would thus allow prevention and be wellcome. The changes in the concentration of phosphorylated compounds, at rest, during exercise and recovery, may provide useful information whether the muscle function is normal or not. P31 NMR-S allows to follow the time course of concentration changes of the main phosphorylated metabolites such as creatine phosphate (CP) inorganic phosphate (Pi), ATP, as well as intracellular pH (pHi). The possibility that metabolic disturbances will be linked to contraction abnormalities led us to investigate MH and EH subjects by P31 NMR-S.

Methods. Seventy three subjects underwent both muscle biopsies and P31 NMR-S : 60 had a personal or family history of MH and 13 had developped a severe episode of EH. 10 healthy volunteers were investigated as control subjects.

Contracture tests. The sample of "quadriceps femoris" muscle taken under local anaesthesia was divided in 6 bundles. Caffeine and halothane contracture tests were performed on the first 4 ones, according to the EMHG. One bundle was submitted to a halothane + caffeine test according to the Rosenberg protocol.

The contracture tests allowed to classify the subjects as MHS (18), MHE(h) (5), MHE(c) (5) and MHN (45).

Exercise protocol. The 6 minute exercise consisted in finger flexions (4 kg weight lifting) repeated every 2 seconds. The work done during non ischemic exercise was chosen in order to get about 50 % decrease in CP for each subject. The same protocol was applied in both normal and ischemic conditions, which were produced by arm compression with a cuff. Normal circulatory conditions were restored at the end of exercise. It was verified that a 6 minute ischemia without exercise neither affected the phosphate metabolites nor the pH.

NMR spectroscopy. NMR spectra were obtained in a home-built 2 Tesla, 53 cm bore, superconducting magnet operating at 34.8 MHz for P31. Free induction decays (FIDs) were acquired at 1.5 s intervals with a 3 cm diameter surface coil (90° flip angle at the coil's center). The coil was positionned over the muscles of the flexor compartment of the forearm. Sixty FIDs (90 sec) were summed for each spectrum at rest, during exercise and recovery and 40 FIDs (60 sec) during the first 5 minutes of recovery. Relative concentration of metabolites were measured from the respective peak areas. pHi was calculated from the chemical shift of the main Pi peak relative to that of CP peak.

Results. Whereas, at rest, no difference was observed among patients and normal subjects, MH and EH patients developped an abnormal P31 spectral configuration during exercise and recovery. No differences appeared between control and MHN subjects. The value for CP (CP/CP+Pi ratio) and pHi obtained at rest, at the end of the 4 kg non ischemic and ischemic exercises, and at the 3rd and 8th minute of the recovery are given in the table. The main difference between MHN and MHS subjects was a faster and deeper decrease in pHi and a slower return to resting value during recovery. This drop in pHi was still accentuated by ischemia. Similar but weaker abnormalities were observed in MHE (h or c) as in MHS subjects. In that case, pHi decreased more during exercise than in normal subjects but less than in MHS patients. EH patients exhibited no alteration during exercise except when muscle blood perfusion was restricted.

Discussion.The results indicate a perturbed energy metabolism and most probably an increased anaerobic glycolysis in EH and MH during exercise. The presence of metabolic alterations is not surprising in MH since its suspected mechanism is an excess release of Ca2+ which are known to activate glycolysis and muscle fiber contraction. But the results show that metabolic abnormalities are also present during the recovery after an ischemic exercise when the blood flow is largely increased and then O2 supply abondant. This can indicate defects in the oxydative pathway leading to a prevalent glycolytic metabolism. Metabolic disturbances are observed at distance from the heat stroke episode (up to 4 years in one subject).

Conclusion. Acidosis and disturbances of energetic metabolism are observed in MH (MHS and MHE) as well as in EH subjects even in the absence of crisis. P31 NMR-S may be used as a first step in the diagnosis of these two groups of acute rhabdomyolysis.

Table

		Controls		MHN	
		E	IE	E	IE
Rest	CP	0.80±0.01	0.80±0.03	0.83±0.05	0.80±0.04
	pHi	7.04±0.02	7.04±0.01	7.05±0.04	7.02±0.07
Ex 6'	CP	0.60±0.05	0.48±0.04	0.57±0.06	0.50±0.05
	pHi	6.72±0.06	6.67±0.04	6.75±0.10	6.68±0.11
Rec 3'	CP	0.72±0.04	0.77±0.03	0.77±0.05	0.82±0.04
	pHi	6.87±0.11	6.82±0.04	6.90±0.07	6.79±0.09
8'	CP	0.77±0.02	0.80±0.01	0.83±0.03	0.80±0.05
	pHi	6.91±0.05	6.94±0.05	6.93±0.05	7.00±0.05
		MHS		EH	
Rest	CP	0.82±0.04	0.82±0.03	0.81±0.02	0.80±0.01
	pHi	7.00±0.05	6.98±0.06	7.05±0.02	7.02±0.01
Ex 6'	CP	0.51±0.10	0.42±0.12	0.52±0.03	0.41±0.02
	pHi	6.47±0.09	6.23±0.07	6.36±0.04	6.13±0.04
Rec 3'	CP	0.77±0.06	0.75±0.09	0.74±0.01	0.70±0.02
	pHi	6.55±0.08	6.40±0.08	6.72±0.11	6.33±0.03
8'	CP	0.81±0.05	0.78±0.08	0.82±0.02	0.77±0.01
	pHi	6.79±0.07	6.77±0.06	6.94±0.05	6.70±0.07

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