

Title : E-C COUPLING STUDIES IN MALIGNANT HYPERTHERMIA PIG MUSCLE
 Authors : T.E. Nelson, Ph.D. and E.H. Flewollen, M.D.
 Affiliation: Department of Anesthesiology, University of Texas Medical Branch, Galveston, Texas 77550

Introduction. A variety of biochemical and physiological aberrations in skeletal muscle from malignant hyperthermia susceptible (MHS) man and pigs have been reported. Clinically, MH has been triggered by a pharmacologically heterogeneous group of agents; most of which produce abnormal contracture responses when exposed to MHS muscle *in vitro*. It has been proposed that a lesion of the electromechanical coupling system in MHS muscle may represent an etiologic pathway common to agents which trigger or prevent MH.¹ The excitation-contraction (E-C) coupling hypothesis for MHS is primarily based on *in vitro* contraction studies.² In the present study we have developed a method to measure the time interval between excitation (muscle membrane depolarization) and contraction (the first measurable tension change). The E-C coupling time interval was compared between MHS and control pig skeletal muscle both *in vivo* and *in vitro*.

Methods. The E-C coupling time interval was measured in 4 MHS and 4 control pigs as follows. Toe contractions were indirectly evoked and quantitated in pentothal anesthetized pigs as previously described.³ Each animal was allowed to breathe 100% oxygen spontaneously. Monitored end tidal CO₂ and rectal temperature did not differ significantly among animals tested. A compound muscle action potential (MAP) was obtained from surface electrodes and amplified into a voltage comparator. When the MAP voltage reached a predetermined threshold, a data storage and retrieval system was triggered to initiate tension measurements. Subsequently, the tension measurements could be displayed or printed such that the time to initiation of contraction could be determined within 0.1 msec. The interval of time between the MAP threshold voltage and the initiation of tension is considered to be an estimate of the E-C coupling time. Similar measurements were performed on biopsied muscle strips *in vitro*, except that stimulus voltage, rather than MAP, triggered the tension data storage and retrieval system. Collection of several hundred tension values during a single contraction provided data from which contraction kinetics (ie dT/dt) could be evaluated.

Results. The average E-C coupling times were longer for skeletal muscle from MHS pigs compared with controls ($p < 0.001$). When measured *in vivo*, the E-C coupling time averaged $6.04 \pm .46$ msec for MHS muscle and $5.20 \pm .28$ msec for controls. The E-C coupling times measured *in vitro* were unexpectedly longer than those measured *in vivo*

for both MHS and control muscle. The E-C coupling times *in vitro* were 9.49 ± 1.04 msec for MHS and $7.71 \pm .34$ msec for controls. When the kinetics of contraction were evaluated as dT/dt, differences were apparent between MHS and controls. The time to peak of contraction (maximum tension) was 10 msec longer for MHS muscle compared to controls. The slower time to maximum tension for MHS muscle was a function of the slower, later stages of tension development, rather than the initial rapid phase.

Discussion. Results of the present study provide additional support for the hypothesis that an abnormality exists in electromechanical coupling of MHS skeletal muscle. The E-C coupling time interval measured involves several steps involving time required for: (1) formation and propagation of MAP; (2) transfer of MAP signal from transverse tubule to the sarcoplasmic reticulum; (3) release and reuptake of Ca²⁺ by the sarcoplasmic reticulum; and (4) Ca²⁺ activation of contractile elements. The method used in this study cannot differentiate among these possible steps, but contraction kinetic data suggest that steps (2) and (3) above may be involved.

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References.

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