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Evaluation for Malignant Hyperthermia Susceptibility in Black-tailed Deer

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ABSTRACT: To investigate a possible link of malignant hyperthermia to capture myopathy, between June 1990 and July 1993 we anesthetized four black-tailed deer (*Odocoileus hemionus columbianus*) and challenged them with halothane and succinylcholine. Halothane had no significant effect on oxygen consumption. Succinylcholine significantly ($P < 0.05$) increased cardiac output (mean \pm SD), from 2.94 ± 1.05 l/min to 5.26 ± 1.79 l/min, and oxygen consumption, from 5.5 ± 2.1 ml/kg/min to 10.1 ± 2.9 ml/kg/min. Muscle biopsy specimens tested for malignant hyperthermia susceptibility responded normally to halothane and caffeine. We conclude that these deer did not experience malignant hyperthermia, suggesting no link to capture myopathy.

Key words: Capture myopathy, malignant hyperthermia, black-tailed deer, *Odocoileus hemionus columbianus*.

Capture myopathy occurs in some animals as the result of maximum exertion to avoid capture (Bartsch et al., 1977). The capture myopathy syndrome includes acidosis, rhabdomyolysis and death (Bartsch et al., 1977). It is physiologically similar to malignant hyperthermia (MH), an inherited hypermetabolic disorder of skeletal muscle involving abnormal calcium flux that occurs upon exposure to triggering anesthetic agents such as halothane and succinylcholine (Gronert, 1980). Whether MH and capture myopathy are closely related or linked is unclear. Capture myopathy has occurred in white-tailed deer (*Odocoileus virginianus*, Kocan et al., 1980) but no one has yet examined the relationship between capture myopathy and MH in this or any other genus of deer. Thus, we determined the response of black-tailed deer (*Odocoileus hemionus columbianus*) to halothane and succinylcholine. We also performed muscle biopsy, and halothane and caffeine contracture testing, to determine MH susceptibility.

This study, approved by the Animal Care and Use Committee, University of California, Davis, California (USA), was conducted between June 1990 and July 1993. Four adult black-tailed deer (two female, two male), weighing 37 ± 4 kg (mean \pm SD) were studied. The deer were part of a group maintained at the University of California, Davis, or were captured near Placerville, California ($120^{\circ} 49'W$, $38^{\circ} 43'N$). The deer were anesthetized with 0.8 to 2 mg/kg intramuscular xylazine (Miles, Inc., West Haven, Connecticut, USA) and 1.1-2 mg/kg ketamine (Parke-Davis, Morris Plain, New Jersey, USA), an endotracheal tube was placed and the lungs mechanically ventilated. A peripheral intravenous catheter was inserted, and anesthesia was maintained with 50 to 70% nitrous oxide (Puritan-Bennett, Lenexa, Kansas, USA) and intravenous thiamylal as needed with incremental doses of 25 mg, to a maximum of 4.5 mg/kg (Parke-Davis). A catheter was inserted into the ear or femoral artery to obtain arterial blood gases and to measure arterial pressure. A pulmonary artery catheter (Baxter Inc., Irvine, California) was inserted aseptically via an external jugular vein. Core temperature was monitored with the pulmonary artery catheter and maintained at 37 to 39 C with heating pads and a heating lamp. Heart rate was monitored with an electrocardiogram (Tektronix, Inc., Beaverton, Oregon, USA) and cardiac output was determined by averaging triplicate thermal dilution values. Oxygen consumption ($\dot{V}O_2$) was calculated using the Fick equation: $\dot{V}O_2 = \dot{Q} \cdot (a - vO_2)$, where \dot{Q} = cardiac output and $a - vO_2$ = the arterial-venous oxygen content difference. After the animal was stabilized, pre-exposure levels of these parameters

TABLE 1. Oxygen consumption ($\dot{V}O_2$), cardiac output (\dot{Q}) and temperature among four black-tailed deer, 1990 to 1993.

	Control	1% halothane (1st exposure)	2% halothane	3% halothane	1% halothane (2nd exposure)	Succinylcholine
$\dot{V}O_2$ (ml/kg/min)	3.9 \pm 1.1 ^a	6.4 \pm 2.6	5.2 \pm 1.2	4.4 \pm 1.3	5.5 \pm 2.1	10.1 \pm 2.8 ^b
\dot{Q} (l/min)	3.77 \pm 0.60	4.83 \pm 1.77	3.82 \pm 1.18	2.39 \pm 1.37 ^c	2.94 \pm 1.05	5.26 \pm 1.79 ^d
Temperature (C)	38.4 \pm 0.8	38.5 \pm 1.0	38.5 \pm 1.0	38.5 \pm 1.0	38.5 \pm 1.0	38.6 \pm 1.1

^a Mean \pm SD.

^b $P < 0.05$ compared to first 1% halothane value.

^c $P < 0.05$ compared to all preceding values.

^d $P < 0.05$ compared to 3% value and second 1% value.

were obtained and the deer were exposed to 1% halothane (Halocarbon Laboratories, River Edge, New Jersey). After a 10 min exposure, \dot{Q} and $\dot{V}O_2$ were determined. The halothane concentration was increased to 2% and 3% and the measurements repeated 10 to 15 min after each increase. Following the 3% exposure, halothane was decreased to 1% and the measurements repeated. We then injected 0.1 mg/kg succinylcholine (Burroughs Wellcome, Research Triangle Park, North Carolina, USA) intravenously and 10 min later \dot{Q} and $\dot{V}O_2$ were repeated. The succinylcholine dose was chosen because, in pilot studies, it resulted in 15 to 20 min of neuromuscular blockade. The anesthetic was discontinued and the animals awakened.

Prior to the introduction of halothane and succinylcholine, a semi-tendinosis (semi-membranosis in one deer) muscle biopsy was performed for halothane-caffeine contracture testing (Melton et al., 1989). The specimen, taken from the mid-portion of the muscle, was dissected into bundles approximately 3 \pm 1 cm (mean \pm SD) long weighing 133 \pm 75 mg. Silk ties were placed at the ends and each bundle was attached to a fixed hook on one end and a force transducer (Grass, Inc., Quincy, Massachusetts, USA) on the other, in individual tissue baths containing Krebs solution (Melton et al., 1989). Temperature was maintained at 37 C and 95% O₂/5% CO₂ was bubbled through the bath. Tension was recorded with a pen recorder. The bundles were electrically stimulated using two flat platinum field elec-

trodes placed on either side of the muscle bundle. Bundles were considered viable when they responded with a mechanical twitch. Optimal length was determined at supramaximal stimulating voltage. The stimulation rate was 0.1 Hz, duration 2 milliseconds. In general, three bundles from each animal were exposed to incremental concentrations of caffeine (0.5, 1, 2, 4, 8 and 32 mM). The response following each concentration was observed for at least 4 min. If a contracture occurred, the next concentration of caffeine was not added until the peak had occurred. Two or three bundles from each animal were exposed to 3% halothane, which was bubbled through the Krebs solution via a vaporizer in line with the O₂/CO₂ gas. Abnormal responses include a contracture \geq 0.7 g on exposure to 3% halothane and a \geq 0.2 gm contracture on exposure to 2 mM caffeine or less (Larach, 1989). In three animals, histological examination was performed on the muscle specimens. Stains included hemotoxylin and eosin (H&E), modified trichrome, esterase, alkaline Pase, acid Pase, and Oil Red-O (Gronert et al., 1992).

Data are presented as mean \pm standard deviation and were compared using analysis of variance with repeated measures (InStat, GraphPad, Inc., San Diego, California); $P < 0.05$ was considered significant (Fisher, 1990).

There was a dose-dependent effect of halothane on cardiac output with a decrease in cardiac output at 3% halothane (Table 1). Oxygen consumption was in the

TABLE 2. Blood gas analysis among four black-tailed deer, 1990 to 1993.

	Control	1% halothane (1st exposure)	2% halothane	3% halothane	1% halothane (2nd exposure)	Succinylcholine
Arterial						
pH	7.44 ± 0.05 ^a	7.45 ± 0.07	7.45 ± 0.08	7.45 ± 0.09	7.41 ± 0.07	7.30 ± 0.04 ^b
P _a CO ₂ ^c	41 ± 6	41 ± 7	40 ± 7	40 ± 8	43 ± 6	55 ± 2 ^b
P _a O ₂ ^d	144 ± 24	162 ± 66	167 ± 71	144 ± 86	173 ± 66	161 ± 64
Venous						
pH	7.40 ± 0.05	7.41 ± 0.06	7.40 ± 0.08	7.38 ± 0.08	7.35 ± 0.06	7.26 ± 0.04 ^b
P _v CO ₂ ^e	49 ± 5	47 ± 5	46 ± 6	49 ± 6	51 ± 5	64 ± 4 ^b
P _v O ₂ ^f	42 ± 8	40 ± 4	40 ± 6	32 ± 13	35 ± 8	36 ± 6

^a Mean ± SD.

^b $P < 0.05$ compared to 1%, 2%, 3% and second 1% halothane values.

^c P_aCO₂ (arterial partial pressure of carbon dioxide, mmHg).

^d P_aO₂ (arterial partial pressure of oxygen, mmHg).

^e P_vCO₂ (mixed venous partial pressure of carbon dioxide, mmHg).

^f P_vO₂ (mixed venous partial pressure of oxygen, mmHg).

physiologic range with no statistically significant change upon exposure to halothane. Succinylcholine nearly doubled the oxygen consumption and increased cardiac output. There were no significant temperature changes. No animal had other signs of MH such as arrhythmias or rigidity. Halothane had no effect on arterial or venous blood gases; succinylcholine decreased pH and increased CO₂ in arterial and mixed venous blood (Table 2). In the muscle contracture studies, no animal had a contracture in response to 3% halothane and the thresholds for caffeine were all greater than 2 mM, indicating non-susceptibility to MH. In histological studies, there were no overt abnormalities. In two animals there were a few scattered hypercontracted type 2 fibers.

Malignant hypothermia is a sub-clinical abnormality of skeletal muscle calcium homeostasis, wherein control of calcium release by sarcoplasmic reticulum is impaired, resulting in contractures induced by high intracellular calcium concentrations (Gronert, 1980). The muscle dramatically increases its metabolism in an attempt to normalize calcium gradients, and there is increased release of end-products of metabolism, such as carbon dioxide, hydrogen ions, and heat (Gronert, 1980).

These four black-tailed deer had no ev-

idence of MH susceptibility. Halothane and succinylcholine are potent MH triggers (Gronert, 1980) and the halothane-caffeine contracture test is considered to be the valid test for evaluation of MH susceptibility in horses, dogs, pigs and humans (Gronert, 1980; Larach, 1993). Thus, because of the normal findings and the absence of other signs of MH, we conclude that these black-tailed deer were not MH-susceptible. The increased VO₂ after succinylcholine may have been related to muscle fasciculations and ion-pumping. The increased VO₂ that follows exposure to succinylcholine in MH susceptible swine is different in that it is accompanied by other indices of MH, including tachycardia, metabolic acidosis, and markedly increased mixed venous P_vCO₂ (Gronert et al., 1976), none of which occurred in our animals.

Capture myopathy has been reported in white-tailed deer (Kocan et al., 1980). This syndrome consists of increased creatine kinase, increased body temperature, and muscle breakdown (Bartsch et al., 1977). The physiologic process directly responsible is unknown, but MH secondary to stress now appears unlikely. Wolff et al. (1965) reported nine mule deer (*Odocoileus hemionus*) that were anesthetized 48 times with chloral hydrate-halothane-ni-

trous oxide. Of note, two of these deer died for unknown reasons, but "heat-related" causes were suspected. Malignant hyperthermia has been reported in other species including dogs (McGrath et al., 1982), cats (DeJong et al., 1974) and horses (Hildebrand et al., 1990), but the link to MH in these animals is also unclear. There is controversy as regards MH in these species and some observed phenomena may represent exercised-induced heat stress, and not true MH. In a previous study we demonstrated that a group of greyhounds were not susceptible to MH, despite reports that these animals developed post-exercise hyperthermia (Cosgrove et al., 1992).

We conclude that, in these black-tailed deer, there was no evidence of MH susceptibility. If there is widespread pre-disposition to capture myopathy in deer, it is unlikely to be related to MH. Thus, capture myopathy might represent the end result of prolonged desperation exertion in normal animals.

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