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Source: Journal of Wildlife Diseases, 26(2) : 219-224

Published By: Wildlife Disease Association

URL: <https://doi.org/10.7589/0090-3558-26.2.219>

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PHYSIOLOGICAL RESPONSES OF RED FOXES (*VULPES VULPES*) TO SURGERY

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ABSTRACT: Radio transmitters were surgically implanted into the abdomens of red foxes (*Vulpes vulpes*). Blood samples were taken before, immediately after, and 8 hr after surgery and analyzed for hormonal, biochemical, electrolyte and hematologic changes. Samples were taken at the same times from control foxes. Adrenocorticotropin increased after surgery ($P < 0.05$), but returned to pre-surgery values after 8 hr. Cortisol increased and remained elevated in the surgery group relative to pre-surgery values or to control values ($P < 0.05$); Triiodothyronine and thyroxine both decreased from post-surgery values 8 hr later ($P < 0.05$). Creatine kinase, total bilirubin and aspartate aminotransferase increased after 8 hr in both surgery and control groups ($P < 0.05$). Carbon dioxide increased under anesthesia in both groups, but returned to initial values after 8 hr ($P < 0.05$). The white blood cell count increased after 8 hr only in the surgery group ($P < 0.05$). There were no differences between the groups for any value obtained from the initial blood sample. These data indicate that abdominal surgery results in prolonged adrenocortical activity and decreased thyroid hormone levels, but otherwise has minimal systemic effects in red foxes.

Key words: Red foxes, *Vulpes vulpes*, endocrinology, serum chemistry, hematology, surgery, radio transmitter, physiological response.

INTRODUCTION

Surgical implantation of radio transmitters into the abdomen has been performed in many wild species (Amlaner and MacDonald, 1980). However, there are no studies that examine the physiological responses of wild animals to the stress and trauma of surgery. Such information could be important to determine if supplements, such as fluids, are necessary during surgery or to evaluate an animal's potential for recovery. We implanted radio transmitters into the abdomens of red foxes (*Vulpes vulpes*) to evaluate heart rate and body temperature in response to restraint (Kreeger et al., 1990a). In conjunction with these studies, we also examined the pathophysiological responses of foxes to the surgical procedure.

MATERIALS AND METHODS

This study was conducted from September 1988 through February 1989 in south central Minnesota (45°16'N, 92°55'W). In June 1988, 8- to 12-wk-old fox pups were obtained from natural rearing dens in North Dakota (47°10' to 47°20'N, 98°45' to 99°15'W), transported to Min-

nesota, and housed there by sibling groups in 1.8 × 3.1 m kennels equipped with den boxes. The foxes were fed frozen animal byproducts (Lang Packing, St. Cloud, Minnesota 56080, USA), provided water and vaccinated for rabies, canine distemper, canine parvovirus, infectious canine hepatitis, leptospira and parainfluenza (TechAmerica®, Fermenta Animal Health, Omaha, Nebraska 68134, USA). At 4 mo of age, unrelated males and females were paired and housed separately.

Ten pairs of foxes were used in this study. Every 2 wk beginning in September, two pairs of foxes were selected; one pair was surgically implanted with a heart rate and body temperature radio transmitter (Cedar Creek Bioelectronics Laboratory, East Bethel, Minnesota 55011, USA) while the other pair was treated similarly except for the surgery (controls). Once foxes were implanted with the radio transmitter, they were removed from the study. All control foxes eventually underwent surgery. Thus, with the exception of the first pair, foxes served as their own controls. The foxes were manually restrained and anesthetized with tiletamine and zolazepam (Telazol®, A. H. Robins, Richmond, Virginia 23220, USA) given intramuscularly (Kreeger et al; 1990b). One surgery fox and one control fox were anesthetized at the same time, brought indoors, weighed and initial 10-ml blood samples were taken from the jugular vein. Aseptic surgery consisted of a midline laparotomy with the transmitter placed in the abdomen

and electrodes exiting the anterior incision and placed subdermally on either side of the heart (Kreeger et al., 1989). The transmitter measured $85 \times 38 \times 25$ mm and weighed 105 g, representing about 2.0% of the body weight of a fox. At the completion of surgery, 10-ml blood samples were again taken from both foxes and both were given 20,000 IU/kg procaine penicillin G and benzathine penicillin G intramuscularly (Flocillin, Bristol Laboratories, Syracuse, New York 13221, USA). The foxes were then returned to their kennels, and the second surgery and control foxes anesthetized and handled as before. All surgeries were performed at approximately the same time in the morning. Eight hr after the second blood sample was taken, foxes were again immobilized with tiletamine and zolazepam and a third 10-ml blood sample taken. This third sample was taken to measure tissue responses to acute sterile trauma over time as well as to relate these responses to other restraint studies conducted for 8 hr time periods (Kreeger et al., 1990a).

Aliquots of blood were placed either in chilled (4 C) or non-chilled EDTA tubes or in clot tubes. Immediately after sampling, blood in the chilled EDTA tubes was centrifuged in a cold centrifuge, plasma drawn off, and the plasma centrifuged again to remove residual cells. Serum from the clot tubes was obtained later in the day. Non-chilled EDTA samples were used for hematologic analysis. All serum or plasma samples were stored at -20 C until endocrine or biochemical analyses were performed.

Adrenocorticotropin (ACTH) was determined in serum by double-antibody radioimmunoassay (RIA) (Diagnostic Products Corp., Los Angeles, California 90045, USA). The ACTH antiserum crossreacted with α -melanocyte stimulating hormone (α -MSH) at $<0.5\%$. Sensitivity was 7.0 pg/ml and the inter-assay coefficient of variation (CV) was 12.7%.

Beta-endorphin (β -END) was determined by competitive protein binding RIA utilizing specific anti-human beta-endorphin antibody (New England Nuclear, Boston, Massachusetts 20118, USA). Crossreactivity with β -lipotropin was 50.0% and $<0.01\%$ with α -endorphin, leu-enkephalin, met-enkephalin, and α -MSH. Sensitivity was 5.0 ng/ml.

Cortisol (CORT) was determined by competitive protein binding RIA after Murphy (1967) using commercial cortisol standards (#386698, Calbiochem-Behring, San Diego, California 92112, USA). Sensitivity was 1.0 μ g/dl and inter-assay CV was 12.8%.

Thyroxine (T4) and triiodothyronine (T3) were determined by solid-phase RIA (Diagnostic Products Corp., Los Angeles, California

90045, USA). The assays were highly specific with no significant crossreactivity with any other compounds. Sensitivity for T4 was 0.5 μ g/dl and for T3 was 7.0 ng/dl. Intra-assay CV for T4 was 11.3% and inter-assay CV was 18.2%. Intra-assay CV for T3 was 10.6% and inter-assay CV was 13.2%.

Insulin was determined by double antibody RIA (Bio-RIA, Montreal, Quebec, Canada H3M 3A2). Sensitivity was 3.0 international units (IU)/ml. Intra-assay CV 4.5% and inter-assay CV was 6.0%.

Serum chemical values were obtained from an autoanalyzer using bovine standards (SMAC II, Technicon, Inc., Tarrytown, New York 10591, USA). Creatine kinase (CK) was measured after the method of Nuttall and Wedin (1966). Blood cell counts were performed by an automatic counting device (Coulter Electronics, Hialeah, Florida 33012, USA) and hematological indices were calculated by standard mathematical formulae (Duncan and Prasse, 1978). Hemoglobin (Hgb) was analyzed using the cyanmethemoglobin method (Benjamin, 1979).

Statistical analyses were by one-way ANOVA at a significance level of $P < 0.05$. Means are reported with standard errors (SE).

RESULTS

All foxes survived the surgery. The time from the first to second blood sample was 58.8 ± 1.1 min. There was no difference between surgery and control foxes for any value obtained from the initial blood sample ($P > 0.05$). There also were no differences between surgery and control foxes or among times within the surgery or control groups for β -END (7.7 ± 0.1 ng/dl), insulin (15.3 ± 1.1 IU/ml), protein (5.4 ± 0.1 g/dl), albumin (3.4 ± 0.1 g/dl), gamma-glutamyl transpeptidase (4.1 ± 0.1 IU/liter), alkaline phosphatase (38.1 ± 1.0 IU/liter), lactate dehydrogenase (214.0 ± 11.9 IU/liter), uric acid (0.3 ± 0.1 mg/dl), sodium (151.0 ± 0.3 meq/liter), chloride (115.5 ± 0.3 meq/liter), potassium (4.7 ± 0.1 meq/liter), serum urea nitrogen (28.5 ± 1.0 mg/dl), creatinine (0.7 ± 0.1 mg/dl), glucose (121.0 ± 3.4 mg/dl), calcium (7.6 ± 0.1 mg/dl), phosphate (6.2 ± 0.1 mg/dl), cholesterol (173.9 ± 2.8 mg/dl), triglycerides (42.2 ± 2.6 mg/dl), red blood cell count ($11.6 \pm 0.1 \times 10^6/\mu$ l), hemoglobin (15.5 ± 0.2 g/dl), hematocrit (48.1

TABLE 1. Endocrine, biochemical and hematologic values for 20 red foxes before, immediately after and 8 hr after abdominal surgery. Control foxes received same treatment as surgery foxes except for laparotomy. Means reported with standard errors.

Index	Group	Pre-surgery	Post-surgery	8 hr post-surgery
Adrenocorticotropin (pg/ml)	Surgery	66.2 ± 4.8	104.4 ± 8.1 ^{a,c}	65.1 ± 8.5 ^b
	Control	66.3 ± 4.8	65.2 ± 5.8	72.4 ± 4.6
Cortisol (µg/dl)	Surgery	6.1 ± 0.5	9.5 ± 0.8 ^{a,c}	8.9 ± 1.6 ^a
	Control	6.6 ± 0.4	5.0 ± 0.8	7.3 ± 0.7
Triiodothyronine (ng/dl)	Surgery	60.8 ± 12.1	70.4 ± 11.2	29.8 ± 3.9 ^{a,b}
	Control	69.0 ± 9.1	72.5 ± 8.3	51.2 ± 4.9
Thyroxine (µg/dl)	Surgery	2.6 ± 0.3	2.9 ± 0.3	1.8 ± 0.2 ^{a,b}
	Control	2.8 ± 0.2	3.2 ± 0.2	2.5 ± 0.1
Creatine kinase (IU/liter)	Surgery	424.8 ± 98.0	641.0 ± 78.9	4,411.7 ± 665.4 ^{a,b}
	Control	454.4 ± 113.2	943.1 ± 191.4	5,885.2 ± 945.6 ^{a,b}
Total bilirubin (mg/dl)	Surgery	0.6 ± 0.1	0.5 ± 0.1	0.8 ± 0.1 ^b
	Control	0.5 ± 0.1	0.5 ± 0.1	0.8 ± 0.1 ^{a,b}
Aspartate aminotransferase (IU/liter)	Surgery	126.4 ± 21.0	110.6 ± 13.3	315.9 ± 30.3 ^{a,b}
	Control	97.5 ± 11.2	126.8 ± 17.4	320.2 ± 29.1 ^{a,b}
Carbon dioxide (meq/liter)	Surgery	20.3 ± 0.9	22.9 ± 0.8 ^a	20.7 ± 1.1
	Control	19.7 ± 1.1	22.9 ± 0.8 ^a	20.7 ± 1.1
Leukocyte Count (×10 ³)	Surgery	7.6 ± 0.6	7.0 ± 0.9	11.7 ± 0.7 ^{a,b}
	Control	8.3 ± 0.5	7.9 ± 0.6	9.0 ± 0.8

^a Significantly different from pre-surgery value ($P < 0.05$).

^b Significantly different from post-surgery value ($P < 0.05$).

^c Significantly different from comparable control value ($P < 0.05$).

± 0.4%), mean corpuscular volume (41.6 ± 0.2 fl), mean corpuscular hemoglobin concentration (32.2 ± 0.1 g/dl), and mean corpuscular hemoglobin (13.4 ± 0.1 pg).

Adrenocorticotropin increased after surgery, but returned to pre-surgery values after 8 hr ($P < 0.05$; Table 1). Cortisol increased and remained elevated in the surgery group relative to pre-surgery values or to control values ($P < 0.05$; Table 1). Triiodothyronine and T₄ both decreased from post-surgery values 8 hr later ($P < 0.05$; Table 1). Creatine kinase (CK), total bilirubin, and aspartate aminotransferase (AST) increased after 8 hr in both the surgery and control groups ($P < 0.05$; Table 1). Carbon dioxide increased in the second sample in both groups, but returned to initial values after 8 hr ($P < 0.05$; Table 1). The only hematologic index to change was the white blood cell count which increased after 8 hr in the surgery group ($P < 0.05$; Table 1).

DISCUSSION

Endocrinology

Cuthbertson (1942) recognized that the response to physical injury could be divided into an “ebb” and “flow” phase on the basis of metabolic rate. The ebb phase was considered to last up to 72 hr after the injury (Cuthbertson, 1976) and was characterized by depression of metabolic processes (Fleck, 1988). The neuroendocrine response to injury is largely a feature of the ebb phase (Barton, 1987). However, the responses of red foxes to surgery were a function of two systemic stressors, the stress of being caught and restrained for anesthesia and the physical trauma induced by surgery. At the time of the first blood sample, ACTH and cortisol values had increased ($P < 0.05$) over such values for unstressed foxes (Kreeger et al., 1990a). The increase in ACTH and cortisol reflected activation of the hypothalamic-pitu-

itary-adrenocortical axis (Moberg, 1985) and indicated that the initial handling process was perceived as a stressor by the foxes (Rosin, 1981).

Both ACTH and cortisol increased even further during surgery whereas they remained stable for the control animals (Table 1). This parallel rise reflects the release of cortisol in response to ACTH (Newsome and Rose, 1971) and is the most extensively documented endocrine effect of the trauma of surgery (Barton, 1987). Nociceptive afferents are probably the stimulus for this response since it is diminished when regional anesthesia is employed (Brandt et al., 1979).

Although β -END and ACTH are part of a common precursor molecule, proopiomelanocortin (Mains et al., 1977) and are secreted in parallel (Guillemin et al., 1977), no increase in β -END was noted for either group. Beta-endorphin also did not increase in dogs during anesthesia or surgery (Rees et al., 1983). Beta-endorphin does increase in foxes restrained for 8 hr (Kreeger et al., 1990a). The kinetics of β -END in red foxes are unknown, but differences in relative ACTH and β -END values may be a function of different metabolic and clearance rates.

Increased glucocorticoid activity caused by stress can decrease both T_3 and T_4 levels (Du Ruisseau et al., 1978). The decrease in T_3 and T_4 observed in this study is typical following surgery (Kirby et al., 1973). Lowered T_3 and T_4 concentrations depress metabolic processes which are characteristic of the ebb phase. Whereas total T_4 tends to be low after surgery, plasma T_3 falls more precipitously and can remain depressed for days (Barton, 1987).

Serum chemistries and electrolytes

Serum electrolytes remained unchanged throughout surgery and 8 hr thereafter indicating that hyperosmolarity or hypovolemia probably did not occur despite the removal of 30 ml of blood (representing approximately 9% of blood volume) during this period (Bright and Lantz, 1985). The consistent hematocrit also

supported euhydration. Hemorrhage due to surgery was minimal. Since osmolality was not measured, an accurate assessment of body fluid distribution could not be made. These relative findings suggest, though, that fluid therapy probably is not required in red foxes for these procedures.

The increases in CK, AST and total bilirubin noted in both groups after 8 hr were most likely a function of the physical exertion expended by the foxes during the restraint and immobilization process. Creatine kinase and AST commonly increase in humans after exercise (Fowler et al., 1968; Noakes, 1987) and reflect leakage due to muscle cell damage (Wolf et al., 1987). Bilirubin is primarily derived from hemoglobin which is liberated during hemolysis. Physical exertion can cause hemolysis and account for the increased bilirubin values (Eichner, 1985). Foxes trapped for 8 hr also had significant elevations of CK, AST, and bilirubin (Kreeger et al., 1990a). The increase in CO_2 measured in both groups at the second blood sample most likely reflects a respiratory acidosis induced by anesthesia (Tietz et al., 1986).

Hematology

The increased white blood cell count noted in the surgery group after 8 hr was most likely the result of a "stress neutrophilia" (Jain, 1986). This neutrophilia can be caused by two stress-induced factors; increased catecholamines from the adrenal medulla and increased glucocorticoids from the adrenal cortex (Jasper and Jain, 1965). The consistent, elevated cortisol values in the surgery group support this hypothesis. Foxes trapped for 8 hr also had a significant increase in white blood cell counts caused by an absolute neutrophilia (Kreeger et al., 1990a).

Conclusions

These data indicate that prolonged activation of the hypothalamic-pituitary-adrenal axis and decreased thyroid hormone levels due to surgical trauma were the ma-

for differences between the two groups of foxes. Both groups responded similarly to restraint stress and physical exertion. This study supports the contention in domestic animals that a noninfected, surgically-incised wound results in minimal systemic effects (Rosin, 1981).

ACKNOWLEDGMENTS

The authors wish to acknowledge the financial support of the Fur Institute of Canada. We are also indebted to N. Manning, M. Lewis, and S. Ruen of the Veteran's Administration Medical Center, Minneapolis, Minnesota; Edward D. Plotka, Marshfield Medical Foundation, Marshfield, Wisconsin; the North Dakota Department of Fish and Game; and the Minnesota Department of Natural Resources.

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Received for publication 29 August 1989.