Successful management of a dog that had severe rhabdomyolysis with myocardial and respiratory failure

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A 6-year-old castrated male Llewelyn Setter that weighed 32.4 kg (71.3 lb) was examined at the Veterinary Teaching Hospital at Colorado State University because of an acute onset of signs of pain with a nonspecific origin and respiratory distress. The medical history revealed that the dog had previously performed intense hunting activity 3 months prior to the acute onset of clinical signs. Three days prior to admission at our facility, the dog ingested beef rib bones that it had scavenged from the garbage. The referring veterinarian diagnosed gastroenteritis with bone-density foreign material in the pyloric outflow bage. The referring veterinarian treated by IV administration of a crystalloid solution for 15 hours; the referring veterinarian detected by the referring veterinarian, and the dog was treated by IV administration of a crystalloid solution (2.5 mL/kg/h [1.14 mL/lb/h]) for 15 hours; the referring veterinarian was treated by IV administration of a crystalloid solution were detected by the referring veterinarian, and the dog was treated by IV administration of a crystalloid solution.

Clinical Findings—Physical examination revealed a stiff stilted gait, swollen muscles that appeared to cause signs of pain, panting, and ptism. The dog had a decrease in palpebral reflexes bilaterally and a decrease in myotatic reflexes in all 4 limbs. The panniculus reflex was indistinct, and all other cranial nerve reflexes were intact. Serum biochemical analysis revealed markedly high cardiac troponin-I concentration and creatine kinase and aspartate aminotransferase activities. Urinalysis revealed myoglobinuria. Results for thoracic and abdominal radiography, blood pressure measurement, and an ECG were within anticipated limits. Echocardiographic findings were consistent with secondary systolic myocardial failure. Arterial blood gas analysis confirmed hypoxemia and hypoventilation. The dog had negative results when tested for infectious diseases. Examination of skeletal muscle biopsy specimens identified necrotizing myopathy.

Treatment and Outcome—Treatment included ventilatory support; IV administration of an electrolyte solution supplemented with potassium chloride; administration of dantrolene; vasopressor administration; parenteral administration of nutrients; use of multimodal analgesics; administration of clindamycin, furosemide, mannitol, and enrofloxacin; and dietary supplementation with l-carnitine and coenzyme Q10. Other medical interventions were not required, and the dog made a rapid and complete recovery.

Clinical Relevance—Necrotizing myopathy resulting in rhabdomyolysis and myoglobinuria can lead to life-threatening physical and biochemical abnormalities. Making a correct diagnosis is essential, and patients require intensive supportive care. The prognosis can be excellent for recovery, provided there is no secondary organ dysfunction. (J Am Vet Med Assoc 2009;234:1049–1054)
blood pressure measurement, and ECG. The CBC revealed mild lymphopenia (0.9 X 10^3 lymphocytes/µL; reference range, 1.0 to 4.8 X 10^3 lymphocytes/µL). Serum biochemical analysis revealed a noticeable increase in CK activity (116,419 U/L; reference range, 50 to 275 U/L), AST activity (5,611 U/L; reference range, 16 to 50 U/L), and ALT activity (658 U/L; reference range, 10 to 110 U/L), with mild increases in phosphorus (6.5 mg/dL; reference range, 2.1 to 6.0 mg/dL) and magnesium (2.9 mg/dL; reference range, 1.9 to 2.7 mg/dL) concentrations. The urine was concentrated (specific gravity, 1.061) and dark brown in color, and myoglobinuria was confirmed by use of an ammonium sulfate precipitation method. Initial arterial blood gas values, including pH and lactate concentration, were within reference limits. Examination of abdominal and thoracic radiographs did not reveal abnormalities. Indirect measurements of systolic, diastolic, and mean arterial blood pressure (137 mm Hg, 77 mm Hg, and 94 mm Hg, respectively) were within reference limits, and continuous ECG revealed a normal sinus rhythm.

A tentative diagnosis of rhabdomyolysis was made, and the dog was hospitalized (day 1). Treatment was instituted with IV administration of a crystalloid electrolyte solution (3.7 mL/kg/h [1.68 mL/lb/h]) and a continuous rate infusion of potassium chloride solution (0.07 mEq/kg/h [0.032 mEq/lb/h]). A urinary catheter was inserted, and a closed urinary collection set was maintained for the remainder of the dog’s hospitalization. Because acute rhabdomyolysis is precipitated by metabolic failure of muscle fibers and acute breakdown of sarcotendinous membranes, coenzyme Q (3 mg/kg [1.4 mg/lb], PO, q 24 h) and L-carnitine (30.8 mg/kg [14.0 mg/lb], PO, q 8 h) were added for support of oxidative metabolism, and dantrolene (1.5 mg/kg [0.68 mg/lb], PO, q 8 h) was initiated for muscle relaxation and inhibition of calcium leakage. Fentanyl was administered for analgesia (1 to 5 µg/kg/h [0.45 to 2.27 µg/lb/h]). Mannitol (0.5 g/kg [0.23 g/lb], IV) and furosemide (2 mg/kg [0.9 mg/lb], IV) were each administered once within the first 24 hours after onset of hospitalization. Central venous pressures and urine output were measured throughout hospitalization, and fluid administration was titrated to achieve central venous pressure between 3 and 5 cm H₂O and urine output > 1.5 mL/kg/h.

On day 2, the dog became nonambulatory and had firm muscles that appeared to cause pain, an increased rectal temperature (40.8°C [105.6°F]), and progressive pigmenturia. The dog had pulmonary crackles, progressive hypoxemia, and evidence of hypoventilation (PaO₂, 44.3 mm Hg; PaCO₂, 42.9 mm Hg) with impairment of gas exchange indicated by an increase in the alveolar-to-arterial oxygen difference (25 mm Hg; reference limit, < 10 mm Hg). In addition, there was a subjective increase in the amount of work required for breathing. Additional diagnostic tests included a serum biochemical analysis that revealed increased activities of CK (939,950 U/L), AST (31,262 U/L), and ALT (3,315 U/L) and increased concentrations of phosphorus (6.9 mg/dL) and magnesium (3.6 mg/dL). Botulism was ruled out on the basis of negative results for serum concentrations of toxin.

Echocardiography revealed moderate to severe dilatation of the left ventricle and left atrium, marked systolic dysfunction of the left ventricle, and moderate functional insufficiency of the mitral valve. Thickness of the interventricular septum was 9.8 mm (reference limit, 10.3 to 11.5 mm), and thickness of the left ventricular wall during diastole was 9.6 mm (reference limit, 8.3 to 9.3 mm). Diameter of the left ventricular chamber during diastole and systole was 30.3 mm and 90.5 mm, respectively (reference limit, 38.7 mm and 23.4 to 24.6 mm, respectively). Diameter of the left atrium was 35.7 mm (reference limit, 24.2 to 26.3 mm), and fractional shortening was 35.7% (reference limit, 33.0% to 46.0%). The echocardiographic findings were consistent with secondary systolic myocardial failure (Figure 1).

Local anesthesia was used for collection of biopsy specimens from the triceps brachii and cranial tibial muscles. Muscle specimens were fixed via immersion in neutral-buffered 10% formalin for embedding in paraflin or shipped refrigerated but unfixed to the Comparative Neuromuscular Laboratory at the University of California at San Diego. At the laboratory, refrigerated, unfixed muscle specimens were flash-frozen in isopentane precooled in liquid nitrogen and subsequently evaluated by use of a standard panel of histologic and histochemical methods. Numerous necrotic fibers were detected in both muscles without obvious phagocytosis or regeneration (Figure 2). Several necrotic fibers had a ragged-red appearance and were highlighted by use of modified Gomori trichrome stain and NADH-dehydrogenase reactions. Numerous small vacuoles were evident in many type 1 fibers, which were determined by use of oil red O stain to contain lipid droplets. No lymphocytic infiltration, vasculitis, or infectious agents were detected in the biopsy sections. Necrotizing myopathy of undetermined

![Figure 1](image-url)

Figure 1—Left ventricular M-mode echocardiographic image obtained on day 2 (day 1 was the first day of hospitalization) from a 6-year-old dog that had rhabdomyolysis with cardiac and respiratory failure. The image was obtained by use of the right parasternal long-axis left ventricular outflow view. The echocardiographic findings are consistent with secondary systolic myocardial failure. IVS = Interventricular septum. LVIDd = Left ventricular internal diameter during diastole. LVIDs = Left ventricular internal diameter during systole. LVFW = Left ventricular free wall.
origin was diagnosed. Evaluation of serum antibody titers against Toxoplasma gondii, Ehrlichia canis, Borrelia burgdorferi, Dirofilaria immitis, and Anaplasma spp and an indirect fluorescent antibody test for Neospora caninum yielded negative results.

On day 2, the dog was anesthetized and orotracheally intubated. Anesthesia was maintained via continuous IV infusion of a combination of fentanyl (1 to 5 µg/kg/h), propofolb (0.05 to 0.2 mg/kg/min [0.023 to 0.091 mg/lb/min]), midazolama (0.1 to 0.4 mg/kg/h [0.045 to 0.182 mg/lb/h]), and lidocainec (30 µg/kg/min [13.6 µg/lb/min]) to facilitate mechanical ventilation for approximately 24 hours. Ventilation was achieved via synchronous intermittent mandatory ventilation and spontaneous modes with 3 cm H2O positive end expiratory pressure or continuous positive airway pressure, respectively, at 40% inspired oxygen to maintain adequate oxygenation and ventilation. The dog's rectal temperature returned to within reference limits by 2 hours after initiation of ventilation. Furosemide (0.25 mg/kg/h [0.11 mg/lb/h]) was administered as a continuous infusion for 2 hours because of suspected cardiogenic edema, dobutamine (2 µg/kg/min) was administered as a continuous rate infusion for 96 hours to provide inotropic support, and clindamycin1 (9 mg/kg [4.1 mg/lb], IV, q 12 h for 5 days) was administered, pending results of serologic testing for infectious diseases.

The dog was weaned from mechanical ventilation on day 3 and was ambulatory when assisted with support by use of a sling within hours after extubation. Diuresis was continued by infusion of a crystalloid electrolyte solution (2.5 mL/kg/h) supplemented with potassium chloride (0.1 mL/kg/h) and saline (0.45% NaCl) solution for 2.5 mL/kg/h for 120 hours to maintain urine output ≥ 1.5 mL/kg/h. Pigmenturia resolved by day 4 of hospitalization, and the urinary catheter was removed.

Parenteral administration of nutrients consisting of 20% fat emulsion, multiple vitamins for infusion, 50% dextrose injection, B-complex injection, 10% amino acid injection, 20% magnesium chloride, and saline solution was administered via a central vein for 48 hours. Development of melena, ptyalism, and inappetence prompted the administration of famotidine (0.5 mg/kg, IV, q 12 h) and ondansetron (0.5 mg/kg, IV, q 12 h) because of suspect gastrointestinal tract bleeding and nausea. The opioid analgesics were discontinued, and analgesia was achieved by infusion of ketamine hydrochloride (2 µg/kg/min) and administration of gabapentin (3 mg/kg, PO, q 8 h). The dog became febrile (39.9°C [103.9°F]) on day 7 of hospitalization, and a nosocomial urinary tract infection caused by Escherichia coli was identified. Enrofloxacin (8 mg/kg [3.6 mg/lb], PO, q 24 h) was administered on the basis of results of antimicrobial susceptibility testing.

Serum biochemical analysis, including measurement of CK, AST, and ALT activities and whole blood cardiac troponin-I concentration, was performed daily on days 1 through 8 (Table 1). The cardiac troponin-I concentration had a marked increase (12 ng/mL; reference limit, < 0.06 ng/mL). However, the cardiac troponin-I concentration on day 7 was substantially lower (0.2 ng/mL). Peak activities of CK, AST, and ALT and the highest troponin-I concentration were achieved by the morning of day 3, and then they progressively decreased. The decrease in laboratory values coincided with clinical improvement of the dog.

Additional echocardiograms were obtained on days 5 and 7, which revealed marked improvement in chamber size (diameter of left ventricle during systole, 28.1 mm and 23.4 mm for days 5 and 7, respectively) and fractional shortening (37% and 38% on days 5 and 7, respectively).
respectively). Thickness of the interventricular septum during diastole was 10.6 mm and 15.0 mm on days 5 and 7, respectively, and thickness of the wall of the left ventricle during diastole was 9.2 mm and 11.5 mm on days 5 and 7, respectively. Diameter of the left ventricle during diastole was 44.5 mm and 41.0 mm on days 5 and 7, respectively. Diameter of the left atrium was not measured on day 5, but it was 29.8 mm on day 7.

The dog was discharged from the hospital 13 days after admission. The owner was instructed to continue administration of coenzyme Q<sub>10</sub> (3 mg/kg, PO, q 24 h) and L-carnitine (30.8 mg/kg, PO, q 8 h) for 2 weeks, irbesartan* (2.3 mg/kg [1.04 mg/lb], PO, q 12 h) and enrofloxacin (8 mg/kg, PO, q 24 h) for 10 days, and gabapentin (3 mg/kg, PO, q 8 h) for 5 days.

On day 15, the dog was returned to the veterinary medical teaching hospital, and a serum biochemical analysis, measurement of cardiac troponin-I concentrations, and echocardiographic examination were performed. Serum biochemical analysis revealed that CK activity (143 U/L) was within the reference limits, but activities of ALT (989 U/L) and AST (107 U/L) remained higher than the reference limits. Cardiac troponin-I concentration was 0 ng/mL.

Examination of the echocardiogram obtained on day 15 revealed marked improvement for systolic function and a trivial degree of mitral valve insufficiency (Figure 3). Thickness of the interventricular septum during diastole was 15.0 mm, and thickness of the wall of the left ventricle during diastole was 11.2 mm. Diameter of the left ventricle was 42.4 mm and 28.1 mm during diastole and systole, respectively. Fractional shortening was 34%, and diameter of the left atrium was 28 mm.

A urine sample was collected 48 hours after the end of enrofloxacin administration; aerobic bacterial culture yielded no growth. Examination of thoracic radiographs obtained 33 days after initial admission at our facility did not reveal any abnormalities.

**Discussion**

The 6-year-old dog described here had acute onset of rhabdomyolysis and myoglobinuria that progressed to cause recumbency, cardiomyopathy, and respiratory failure, which necessitated ventilatory support. Rhabdomyolysis is a clinical syndrome consisting of acute muscle necrosis with swollen muscles that cause pain, limb weakness or collapse, marked increases in serum CK activity, and myoglobinuria. Direct sarcolemmal injury or failure of muscular energy supply leads to an uncontrolled increase in free intracellular calcium concentration and subsequent activation of calcium-dependent proteases. Alterations in the intracellular milieu culminate in destruction of myofibrils and lysosomal digestion of muscle fiber contents, collectively termed myonecrosis. Myoglobinuria results because myoglobin (the major protein of the muscle sarcoplasm) is released from damaged myocytes. Early recognition of rhabdomyolysis is essential because myoglobinuria can lead to acute tubular necrosis and life-threatening metabolic derangements.

To the owner’s knowledge, the episode described here was the first clinical event in the life of the healthy 6-year-old dog; thus, a recurrent congenital metabolic disorder of muscle bioenergetics or a dystrophic myopathy was unlikely. The histologic lack of myofiber regeneration and rapid reduction in CK activity supported the likelihood of a single bout of rhabdomyolysis, rather than ongoing muscle injury. The ragged-red fibers could have been indicative of a mitochondrial myopathy with abnormalities of the electron transport chain. However, early necrotic fibers can also have this appearance, and caution must be used in interpretation. Lack of lactic acidemia makes a mitochondrial myopathy unlikely. Excessive numbers of intramyofiber lipid droplets may be indicative of altered fatty acid oxidation and were found in an acute toxic myopathy in horses with severe rhabdomyolysis and multiple acyl-CoA dehydrogenase deficiency.

The cause of the clinical syndrome in the dog reported here remains unknown. Causes of rhabdomyolysis and myoglobinuria as a recurrent condition or an isolated event are diverse and can be difficult to identify. Specific causes of a single bout of acute rhabdomyolysis include excessive exertion as described in racing sled dogs and Greyhounds, crushing injuries, hyperthermia, drugs and toxins, loss of membrane integrity as a result of snake venoms, red spider toxin and venomous insects stings, salt and water imbalances resulting from electrolyte disorders, and infectious diseases that include viral, bacterial, rickettsial, and protozoal diseases.

The dog did not have a history of trauma, thromboembolic disease, or exposure to drugs or toxins, and screening for infectious diseases yielded negative results. Myoglobinuria resulting from strenuous exercise (exertional rhabdomyolysis) was unlikely given the history of intense hunting throughout the dog’s life without previous evidence of the condition. A thorough search of the dog failed to reveal discernable evidence of rattlesnake, spider bite, or bee envenomation that could have resulted in rhabdomyolysis. Furthermore, review of the CBC failed to reveal the type III echinocytosis commonly detected with prairie rattlesnake envenomation. On the basis of the rapid recovery and prior health history, a toxin was considered the most likely cause. Although exposure may be difficult to confirm in veterin-
nary medicine, there are many drugs and toxins associated with myonecrosis and myoglobinuria.\textsuperscript{2,3} Organophosphates inhibit acetylcholinesterase at the neuromuscular junction, causing excessive acetylcholine accumulation and calcium influx into muscle cells, which results in myonecrosis\textsuperscript{12}; however, there was no history of exposure for the dog described here. Ingestion of tremorgenic mycotoxins from garbage is unlikely because this typically leads to peracute skeletal muscle tremors and seizures\textsuperscript{13,15} and not to rhabdomyolysis. However, hyperthermia from excessive seizure activity can result in rhabdomyolysis.\textsuperscript{7} Botulism was also considered unlikely; however, the dog did ingest garbage and had gastrointestinal signs prior to the onset of neuromuscular weakness.

To the authors’ knowledge, this is the first report of cardiac muscle involvement in a dog with rhabdomyolysis. However, it is not unusual to have concurrent cardiac disease in a patient with muscle disease. Myocarditis has been reported in a dog with polymyositis,\textsuperscript{13} and cardiomyopathy is commonly associated with muscular dystrophy.\textsuperscript{8,16} Marked increases in cardiac troponin-I concentrations combined with the echocardiographic changes suggested acute myocardial injury in the dog reported here. Troponins are structurally bound proteins of the contractile apparatus that regulate calcium-mediated interaction between actin and myosin in skeletal and cardiac muscle. Genes distinct from those encoding for the skeletal muscle isoforms encode cardiac troponin-I, and this troponin is a marker of myocardial cellular injury. Thus, cardiac troponins are more specific for cardiac damage, compared with the specificity for lactate dehydrogenase and CK activity.\textsuperscript{10,19} Cardiac troponin-I has been used in combination with serum CK activity to confirm skeletal and myocardial damage in horses with atypical myopathy.\textsuperscript{20} The constellation of physical examination, clinical pathologic, and echocardiographic changes suggested widespread necrosis of cardiac and skeletal muscle in the dog described here. On the basis of our findings, we believe that measurement of cardiac troponin-I concentrations in addition to CK activity is warranted in dogs with acute rhabdomyolysis.

Evaluation of the muscle biopsy specimens obtained on day 2 was an invaluable diagnostic step in the overall management of this dog, which allowed us to rule out inflammatory causes of muscle disease that would warrant treatment with corticosteroids. Corticosteroid treatment may have been contraindicated in this dog, given the myopathic potential of these drugs.\textsuperscript{21,22} Corticosteroids generally cause a painless myopathy with atrophy of type 2 fibers,\textsuperscript{22} but large IV doses of glucocorticoids in sedated human critical-care patients receiving mechanical ventilation can precipitate myonecrosis.\textsuperscript{21} In addition, a specific critical-care myopathy with loss of myosin heavy chains has been reported.\textsuperscript{23} Although there are beneficial effects of corticosteroid treatment in humans with muscular dystrophies, prednisone administration to dogs with Golden Retriever muscular dystrophy may have detrimental consequences.\textsuperscript{24} The constellation of clinical signs, acute onset, and noninflammatory nature of the biopsy specimens provided a reasonable foundation to recommend ongoing supportive care with a good prognosis for recovery (providing there was no secondary organ damage). Given the paucity of information in the veterinary literature on acute necrotizing myopathies in dogs, the case management described here provides a useful outline for the diagnostic approach to a patient with rhabdomyolysis and the supportive care necessary for recovery.

The pathophysiogenesis of acute renal failure secondary to rhabdomyolysis and myoglobinuria is multifactorial, consisting of prerenal and renal causes.\textsuperscript{25} Massive muscle necrosis can lead to renal hyperperfusion, ischemic damage, and acute tubular necrosis. Supportive care in the dog described here was achieved via diuresis by use of a crystalloid solution, mannitol administration, vasopressor treatment (ie, dobutamine), and continuous infusion of lidocaine to ameliorate myoglobin-induced acute renal injury. Mannitol is an osmotic diuretic with potential benefit in nonoliguric patients attributable to a perceived ability to flush tubular debris and to serve as a scavenger of oxygen free radicals.\textsuperscript{26} Increased cardiac output secondary to the positive inotropic effect of dobutamine was used to promote renal afferent arteriolar flow and overall renal perfusion. Lidocaine is a class Ib antiarrhythmic agent with the ability to scavenge hydroxyl radicals, and it is believed that lidocaine can attenuate ischemia-reperfusion injury. Lidocaine also inhibits sodium-calcium exchange through cell membranes, thus limiting cytosolic calcium accumulation and attenuating activation of proteases that lead to cell damage.\textsuperscript{27} Thus, we believe that lidocaine administration in the dog ameliorated free radical–induced renal injury as well as decreased the acute phase of myonecrosis.

In addition to promoting renal blood flow and perfusion, a continuous rate infusion of dobutamine was used to provide positive inotropic properties via cardiac β-receptor stimulation as a means of increasing forward flow and indirectly reducing left-sided filling pressures and resultant pulmonary venous congestion in the dog, which had depressed systolic function as a result of cardiomyopathy. Results of serial echocardiographic examinations, measurement of cardiac troponin-I concentrations, and serum biochemical analyses provided confirmation of substantial improvement in myocardial function in concert with improvement in values for CK activity and a clinical improvement in muscle strength.

The dog described here also developed respiratory failure characterized by hypoxemia, hypoventilation, and an increased amount of work needed for respiration, which necessitated mechanical ventilation. Myalgia and weakness of the intercostal muscles and diaphragm resulting from myonecrosis were the most likely causes of the life-threatening hypoventilation. The 24-hour period of ventilatory support, which was facilitated via analgesia achieved by use of a combination of agents, was an essential step in the management of this dog because it allowed for improved control and protection of the airway and a reduction in myalgia. Parenteral administration of nutrients was used for maintenance of caloric needs, given the probable hypermetabolic state. Although the authors recognize that enteral provision of nutrients may have been preferred, the parenteral route was selected because of the orotracheal intubation and the relative risk of aspiration with feeding via a nasoesophageal or nasogastric tube.

Interestingly, high infusion rates (>5 mg/kg/h) of propofol for >48 hours have been associated with rhabdomyolysis, severe metabolic acidosis, renal failure, and cardiac dysfunction in humans.\textsuperscript{27} The pathophysiogenesis of this
clinical syndrome has not been fully elucidated, although it has been proposed that propofol interferes with mitochondrial fatty oxidation, which leads to accumulation of unused free fatty acids and proarrhythmogenic effects. Considering the preexisting rhabdomyolysis in the dog, propofol may not have been the most appropriate choice for sedation, although this syndrome has not been described in the veterinary literature and the dose and duration used in this dog were much less than those in the reported risk ranges.

The dog responded well to supportive care and was discharged 13 days after admission. There was a complete return to normal function and activity, with almost all laboratory values (including CK activity and cardiac troponin-I concentration) returning to within the respective reference limits. Rapid recovery is consistent with the regenerative capacity of muscle and renal tubular epithelium following acute insults. Evidence also suggests that the heart is not a terminally differentiated organ and may have the ability to regenerate regions of injury in physiologic and pathologic conditions. It is important that clinicians be aware of this acute rhabdomyolysis syndrome in dogs. Because of the clinical course of this disorder, which could possibly necessitate ventilatory support and intensive care, a poor prognosis could incorrectly be given for this condition. We believe that acute rhabdomyolysis syndrome in dogs is a reversible disorder, providing there is appropriate supportive care. Although the dog described here was in critical condition during the initial 3 days, gradual improvement was evident during the next 10 days until the dog was considered clinically normal. To our knowledge, the dog is still clinically normal and continues to perform strenuous activities.

References