SIGNALMENT:

Sheena, Warrier Princess, a 7 year old feline, domestic short hair, spayed female, 7.5 kg. Medical record # 111111. Case #3

HISTORY:

On January 24th, 2013, Sheena, presented to her referring veterinarian (RDVM) within 30 minutes of being unable to walk. She is an indoor only cat with no known trauma and no history of lameness. She did not have any pre-existing medical problems. The RDVM administered buprenorphine, a kappa antagonist/mu partial agonist/antagonist opioid, and referred Sheena to the emergency service at Garden State Veterinary Specialists for evaluation and treatment of acute hind limb paresis.

PHYSICAL EXAM:

Upon presentation, Sheena was found to be quiet, alert and responsive (QAR); with pink mucous membranes (MM), and a capillary refill time (CRT) of less than two seconds (reference range [ref]: 1-2 seconds). She was hypothermic, with a rectal temperature of 97.2°F/36.2°C (ref: 100-102°F, 37.5-39.0°C). Her heart rate (HR) was 180 beats per minute (bpm) (ref: 120-200 bpm), and a grade II/VI systolic murmur was auscultated. Femoral pulses were absent on palpation, and no blood flow was detected by Doppler in both hind legs. Respiratory rate (RR) was 30 respirations per minutes (rpm) (ref: 16-40 rpm) with increased bronchovesicular sounds bilaterally. No crackles were auscultated. Conscious proprioception (CP) deficits were noted in both hind legs, with minimal motor function elicited. Subjectively, the hind legs felt cooler to the touch then the front limbs. Motor function and CPs were normal in both front legs. The rest of the physical exam was unremarkable.

INITIAL DIAGNOSTICS:

Thoracic radiographs showed generalized cardiomegaly with perihilar venous congestion and moderate diffuse interstitial alveolar pattern. Initial blood work including a CBC, biochemistry panel, and electrolytes, showed hyperglycemia (313 mg/dL/17.4 mmol/L; ref: 74-159 mg/dL/4.1-8.8 mmol/L); the rest was unremarkable. An aortic thromboembolism (ATE) commonly referred to as a "saddle thrombus" and congestive heart failure (CHF) were suspected.

FIRST INTERVENTIONS:

Sheena was admitted to the hospital and a 22 gauge intravenous catheter was placed in the right cephalic vein. Treatment goals for the first night were oriented toward stabilization until a more thorough cardiac evaluation could be performed the following morning. Buprenorphine was administered (0.01 mg/kg IV TID) for pain control. Enoxaparin, a low molecular weight heparin (LMWH), was administered (1 mg/kg SC BID) to inhibit further clot formation by inhibiting factor Xa. Furosemide, a loop diuretic, was administered (1 mg/kg IV BID) to promote diuresis and reduce pulmonary edema. A cardiologist examined Sheena the following

day and confirmed the diagnosis of CHF, hypertrophic cardiomyopathy (HCM), and ATE. A 5.5 French triple lumen central venous catheter was aseptically placed in the jugular vein to reduce vascular trauma from repeated venous blood draws, and to facilitate the simultaneous administration of medications.

Sheena was transferred to my care that evening (23 hours after presentation). She was quiet and resting comfortably. A venous blood sample was drawn for a blood gas, blood glucose (BG), and electrolytes, which showed hyperglycemia (218 mg/dL/12.1 mmol/L; ref: 60-130 mg/dL/3.3-7.2 mmol/L). All other values were unremarkable. Medications were similar to the night prior: buprenorphine (0.01 mg/kg IV TID), enoxoparin (1 mg/kg IV BID; changed to IV by cardiologist), and furosemide (1 mg/kg IV BID). At 33 hours post presentation, I observed tachypnea (RR 78 rpm), and auscultated a HR of 152 bpm. I pulled a venous blood gas which showed hyponatremia (134 mmol/L; [ref: 147-162 mmol/L]), a severe hyperkalemia (7.2 mmol/L; [ref: 2.9-4.2 mmol/L]), and hyperglycemia (260 mg/dL; [ref 60-130 mg/dL]). Her acid/base status was unremarkable at this time. I set-up a continuous lead II electrocardiogram (ECG) monitor, and recognized a mildly altered QRS complex with deep S waves and tall T waves. P waves were still visible at that time. A bolus of 50% dextrose (0.5 ml/kg diluted 1:1 with 0.9% NaCl IV) was administered slowly, followed by calcium gluconate (40 mg/kg IV) over 10 minutes. The bradycardia slowly resolved within a half hour (HR increased to 212 bpm). Her RR improved, but remained mildly elevated (48 rpm). A hypotonic intravenous fluid (IVF), 0.45% NaCl with 2.5% Dextrose, was started at 9 ml/hr (30 ml/kg/day) to induce diuresis and decrease the hyperkalemia. I auscultated Sheena's lungs to monitor for crackles (none auscultated) every 2 hours. I performed general nursing care for a recumbent patient that included: rotating position to prevent pressure sores, changing the bedding, and cleaning her (performed every 4 hours or as needed). Thirty six hours after presentation I observed her HR decreasing to 160 bpm, RR was stable at 40 rpm with no increase in effort. The P waves were no longer visible. I drew a venous blood sample which showed hyperkalemia (8.0 mmol/L; [ref: 2.9-4.2 mmol/L]), and hyperglycemia (259 mg/dL/14.3 mmol/L; [ref: 60-130 mg/dL/3.3-7.2 mmol/L]). Calcium gluconate was again administered (40 mg/kg IV) over 10 minutes. This was followed by a bolus of 50% dextrose (1 ml/kg diluted 1:1 with 0.9% NaCl IV slowly) and regular insulin (0.3 U/kg IV). The ECG showed a HR of 200; the QRS complexes were decreased in height; the T waves were unchanged (tall); and small P waves were visible.

SECOND INTERVENTIONS:

Throughout the day, the potassium levels began to normalize (5.4 mmol/L) but she became profoundly hypoglycemic with a BG of 37 mg/dL/2.1 mmol/L. Dextrose boluses (0.5 ml/kg IV diluted 1:1 with 0.9% NaCl) were given three times throughout the day, and the dextrose concentration in the IVF was increased first to 5% and later to 7.5% to counter the hypoglycemia. The increased dextrose concentration (>5%) in the IVF necessitated it be administered through the central venous catheter due to hyperosmolality and increased risk of vasculitis if administered through a peripheral vessel. The IVF rate was increased to 15 ml/hr (48 ml/kg/day). Her HR was variable during the day with some episodes of bradycardia (as low as 80-90 bpm) and one episode of ventricular

tachycardia observed. A metabolic acidosis developed as the day progressed {pH 7.214 [ref: 7.25-7.4], HCO_3^- 11.4 mmol/L [ref: 16-20 mmol/L]}. By early evening the potassium level exceeded 9.0 mmol/L. Calcium gluconate (40 mg/kg IV) was repeated twice in conjunction with regular insulin (0.15 U/kg IV) once. Sheena was hyperglycemic (BG of 365 mg/dL/20.3 mmol/L) on 7.5% dextrose supplementation.

When I came on shift (47 hours post presentation) Sheena was obtunded and minimally responsive. Her ECG showed a lack of P waves and tall T waves. Her mentation temporarily improved following additional doses of calcium gluconate (40 mg/kg IV), 50% dextrose (0.5 ml/kg IV diluted 1:1 with 0.9% NaCl), and regular insulin (0.3 U/kg IV). Three hours later, I observed an increase in RR and irregular respiratory pattern, with a decrease in HR (150 bpm). Her pupils were rhythmically constricting and dilating, a condition known as hippus, suggestive of severe forebrain dysfunction. Thromboembolism to the brain was considered as a cause for the neurologic signs, but not investigated further due to imminent life threatening hyperkalemia. A venous blood gas showed a marked mixed acidosis {pH 7.054 [ref: 7.25-7.4], HCO_3^- 12.3 mmol/L [ref: 16-20 mmol/L], PCO_2 44.1 mmHg [ref: 28-34 mmHg]}, hyperkalemia (>9.0 mmol/L; [ref: 2.9-4.2 mmol/L]), hyperglycemia (243 mg/dL; [ref: 60-130 mg/dL]), and hypercalcemia (1.80 mmol/L; [ref: 1.2-1.32]). Calcium gluconate (40 mg/kg IV), 50% Dextrose (0.5 ml/kg IV diluted 1:1 with 0.9% NaCl), and regular insulin (0.3 U/kg IV) were repeated. I recognized an episode of ventricular tachycardia (HR of ~200) lasting three to five minutes. At 52 hours post presentation, severe bradycardia (HR < 100 bpm) developed with an abnormal ECG showing widened QRS complexes, absent P waves, and tall T waves, all consistent with worsening hyperkalemia. A repeat venous blood gas showed a severe mixed acidosis (pH 7.074 [ref: 7.25-7.4], HCO_3^- 14.4 mmol/L [ref: 16-20 mmol/L] PCO_2 49.2 mmHg [ref: 28-34 mmHg]), and a severe hyperkalemia (>9.0 mmol/L; ref 2.9-4.2 mmol/L). Calcium gluconate (40 mg/kg IV), 50% dextrose (0.5 ml/kg IV diluted 1:1 with 0.9% NaCl), and regular insulin (0.3 U/kg IV) were again administered. The HR improved (172 bpm), RR was 30 rpm with intermittent vocalizations, and the QRS complexes were improved but still wide.

CASE DISCUSSION:

Thromboembolism is the obstruction of blood flow to tissue by a portion of a blood clot that has broken off from a primary clot. Clinical signs are variable and depend on the location and severity of the obstruction. In cats, the major cause of aortic thromboembolism is heart disease, including HCM, as was the case here. The thrombi are suspected to form within the left atrium due to abnormal blood flow, a hypercoagulable state, and endothelial change/damage (Virchow's triad). Once dislodged, the clot can obstruct the blood flow (embolus), most commonly at the trifurcation of the caudal aorta. In this case, the "saddle thrombus" affected both hind legs resulting in decreased CPs, lack of palpable femoral pulses, hind limb paralysis, and subjectively decreased temperature in rear extremities. Infarction causes a severe ischemia to the area affected resulting in reperfusion injury. Ischemia and reperfusion injury can lead to electrolyte imbalances, arrhythmias, and death.

Treatment for ATE is aimed at preventing further thrombus formation as thrombi may form and obstruct blood flow in additional sites, such as the lungs, brain and kidney. Low molecular weight heparin, such as enoxparin, can be administered to inhibit clot formation. It inhibits factor Xa and to a lesser extent factor IIa, and is considered a safer method of anticoagulation than unfractionated or "regular" heparin. Unfractionated heparin acts by inhibiting antithrombin III which then inhibits factors IIa, V, VIII, IXa, Xa, and XIIa. Enoxaparin can decrease unwanted side effects such as bleeding or heparin induced thrombocytopenia (seen in humans). Thrombolytic therapy can be used to break down the clot with drugs such as streptokinase or tissue plasminogen activator (t-PA). The major disadvantage of thrombolytic therapy is an increased potential for reperfusion injury and death. Reperfusion injury can result when prolonged ischemia causes tissue damage and cell death, and sudden return of normal circulation results in inflammatory and oxidative damage via reactive oxygen species. Hyperkalemia, metabolic acidosis, and fatal arrhythmias can occur. Reperfusion injury is possible in any case where ischemia is present, not just with thrombolytic therapy. Sheena showed signs consistent with reperfusion injury including refractory hyperkalemia, a severe metabolic acidosis, and arrhythmias.

As her case progressed, abnormalities developed in sodium, chloride, potassium, and calcium. The hyponatremia (and hypochloremia) may have been attributed to the use of furosemide. Furosemide, a loop diuretic, inhibits the reabsorption of sodium and water by blocking the Na-K-Cl co-transporter in the thick ascending loop of henle. Inhibiting reabsorption of sodium and increased water excretion aids in the removal of interstitial edema (such as pulmonary edema) but can also lead to a decrease in the sodium, potassium, and chloride levels. Hypotonic IVF were chosen at a conservative rate to reduce water retention and worsening volume overload given the concurrent CHF and HCM. It may have also contributed to the hyponatremia. The hyponatremia and hypochloremia were not considered to be clinically significant in this patient. The transient hypercalcemia was most likely iatrogenic in nature, caused by repeated infusions of calcium gluconate (six doses) for its cardioprotective effects.

While furosemide may promote some potassium loss, Sheena developed severe hyperkalemia, a common sequela of ATE. Sodium and potassium levels are maintained through Na-K-ATPase pumps in cell walls. In cases of ischemia and reperfusion, cell death can release potassium into circulation contributing to reperfusion injury. Acidosis can also cause potassium to shift into the extracellular fluid. The major concern with hyperkalemia is its effect on cell membrane depolarization; specifically it decreases the resting membrane potential making the cell hyperexcitable. This can lead to cardiac arrhythmias including ventricular fibrillation and asystole. Common ECG changes associated with hyperkalemia include bradycardia, decreased or absent P waves (atrial standstill), wide and bizarre QRS complexes, as well as tall T waves. In severe hyperkalemia, the waveforms flatten out and widen to form what appears like a sine wave. Multiple drugs were administered to protect the heart and decrease serum potassium levels. Calcium gluconate was administered to restore the difference between the resting membrane and threshold potentials for depolarization of cardiac muscle. This cardio protective feature is short acting (usually less than 1 hour) but is utilized to gain time for the primary cause of the hyperkalemia to be treated. Regular insulin was administered to drive potassium intracellularly. Dextrose administration

also helps to drive potassium into cells by promoting the release of endogenous insulin. In addition, dextrose helps to prevent the hypoglycemia seen with insulin administration. An amplified effect may be achieved by providing both dextrose and regular insulin concurrently. In cases of acute or chronic renal failure, decreased filtration by the kidneys can lead to a reduction in the amount of potassium excreted resulting in hyperkalemia. While chronic renal failure can be ruled out by initial blood work (renal values within normal limits) and history, acute kidney injury (secondary to thromboembolism) remained a possibility. During her hospitalization, Sheena's renal values were not rechecked, but adequate urination was noted.

A metabolic acidosis developed during Sheena's hospitalization. There are many causes of metabolic acidosis, including electrolyte abnormalities, the presence of unmeasured anions, and changes in protein and phosphorus. In Sheena's case, the cause of the metabolic acidosis was most likely from lactate, an unmeasured anion. In cases of tissue hypoxia, cells can turn to anaerobic metabolism to continue to provide ATP for cellular processes. Lactate synthesis is a vital step in producing nicotinamide adenine dinucleotide for continued glycolysis. During anaerobic metabolism, pyruvate is not efficiently utilized via the Krebs cycle leading to a buildup of lactate levels. In healthy patients the pyruvate can be cleared and lactate levels reduced once aerobic metabolism is restored. Increases in lactate can cause a metabolic acidosis (lactic acidosis) when utilization is unable to keep up with production. The key to correcting lactic acidosis is to address the underlying problem and restore aerobic metabolism. In cases of extensive tissue injury/hypoxia, damage may be so severe that the body is unable to restore normal metabolism and clear the lactate levels even with appropriate oxygenation. Sheena experienced a localized tissue hypoxia in her hind legs secondary to ATE. Lactate levels were likely increased and a metabolic acidosis resulted.

OUTCOME:

Fifty-four hours post presentation I observed a dramatic change in Sheena's respiratory pattern. It became very irregular and then an agonal pattern developed (inefficient gasping), suggesting cardiopulmonary arrest was imminent. I took her to the treatment table for further evaluation/intervention. Sheena's HR was 150 and she was in respiratory arrest. I intubated her in lateral recumbency and began positive pressure ventilation. At this point a heart beat was not auscultated and chest compressions were initiated. Atropine, an anticholinergic, (0.05 mg/kg) and epinephrine, a catecholamine, (0.1 mg/kg) were administered IV twice. Ventricular tachycardia was observed on ECG after the second round of drugs. This lasted approximately 2 minutes before becoming irregular. A total of 3 rounds of atropine and epinephrine were administered during the code. One dose of 50% dextrose (0.5 ml/kg IV) was also administered. Chest compressions were performed until the patient was declared deceased and a time of death called by the doctor in charge, approximately 35 minutes after initiation of CPR.