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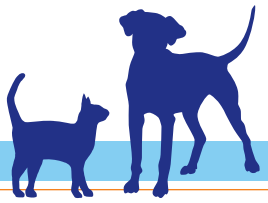

Ischemia–Reperfusion Injury

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The term *ischemia–reperfusion (IR) injury* denotes a complicated cascade of cellular events that can ultimately lead to increased vascular permeability, cell damage, cell death, tissue necrosis, and multiorgan dysfunction syndrome. During ischemia, substances such as reactive nitrogen species, hypoxanthine, and xanthine oxidase build up in affected tissue. When oxygen is reintroduced to the tissue, these substances form reactive oxygen species (ROS). IR injury is believed to be mediated primarily by excessive levels of ROS, which cause extensive damage to DNA, proteins, carbohydrates, and lipids. Cell death due to apoptosis and necrosis is triggered by the substances released during IR injury.

IR injury can occur after any ischemic event. Conditions that frequently lead to clinically significant IR injury include gastric dilatation–volvulus (GDV), aortic thromboembolism (ATE), organ transplantation, diaphragmatic hernia, head trauma, mesenteric torsion, intestinal incarceration, spinal cord trauma, and resuscitation from shock. Although reestablishment of adequate perfusion is essential for cell survival, it paradoxically leads to more cellular damage than ischemia alone.

Ischemia can be classified as cold or warm. Cold ischemia occurs during organ removal for transplantation. Warm ischemia occurs when blood flow to internal organs is compromised, such as during GDV. Endothelial cells that line blood vessels are damaged early in cold IR injury, and hepatocytes show early damage during warm IR injury. Clinically, coagulation abnormalities may reflect IR injury during organ transplantation, and elevated liver enzyme levels may be the earliest manifestations of warm IR injury.

It is important, though often difficult, to determine if perfusion is adequate following IR injury or if the patient is developing the "no-reflow" phenomenon. In this phenomenon, initial restoration of tissue perfusion is followed by diminishing blood flow due to microthrombi and vasoconstriction. If perfusion treatment has been maximized and tissue perfusion remains inadequate, or if perfusion improves initially and then declines, the no-reflow phenomenon should be considered.

DIAGNOSTIC CRITERIA

The diagnosis of IR injury is generally based on clinical suspicion in patients with known ischemic disease (e.g., GDV, ATE) after attempts to establish reperfusion. It is supported by evidence of organ injury (i.e., arrhythmias, elevated hepatic enzymes, azotemia) or patient deterioration.

Historical Information

- Onset of clinical signs associated with the ischemic event may be acute; specific signs vary depending on tissues affected.

Editorial Mission

To provide busy practitioners with concise, peer-reviewed recommendations on current treatment standards drawn from published veterinary medical literature.

This publication acknowledges that standards may vary according to individual experience and practices or regional differences. The publisher is not responsible for author errors.

Reviewed 2015 for significant advances in medicine since the date of original publication. No revisions have been made to the original text.

Standards of Care *was a refereed publication. Published articles were reviewed and approved by at least two diplomates of the American College of Veterinary Emergency and Critical Care.*

Editor-in-Chief

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KEY TO COSTS

$ *indicates relative costs of any diagnostic and treatment regimens listed.*

- Often, signs of IR injury are nonspecific; owners may only recognize lethargy, dull mentation, or weakness that will likely be progressive.
- The history varies depending on the underlying condition and the organ(s) affected by ischemia.

Gender/Age/Breed Predisposition

- None.

Owner Observations

- Varies with underlying disease process. The syndromes most commonly recognized by owners are GDV in dogs and ATE in cats.
- May be nonspecific, such as lethargy, weakness, increased respiratory rate or effort, or other changes associated with the primary disease process.

Other Historical Considerations/Predispositions

- Longer periods of ischemia are more likely to induce clinically significant IR injury.

Physical Examination Findings

- Specific findings are generally referable to the underlying disease process.
- Cats with ATE: Sudden loss of function of both hindlimbs (more common) or a single limb. Affected limbs are cold, painful, and paralyzed (or paretic); associated footpads are pale or cyanotic. Pulses are absent or very weak in affected limbs.
- Dogs with GDV: Distended, tympanic abdomen; tachycardia; weak femoral pulses; pale, muddy, or cyanotic mucous membranes; and cardiac arrhythmias.
- May see GI signs following gut reperfusion: painful abdomen (cramping), hemorrhagic vomiting or diarrhea, or signs of sepsis secondary to bacterial translocation (e.g., hypoglycemia, hypotension).
- Central nervous system changes: mentation changes, anisocoria, or unresponsive pupils, which may indicate increased intracranial pressure.
- Cardiac injury may manifest as an arrhythmia; the most common abnormalities are ventricular premature contractions, ventricular tachycardia, or tall, tented T waves secondary to myocardial hypoxia or hyperkalemia (muscle ischemia, see Other Diagnostic Findings).
- IR injury can cause signs consistent with poor perfusion, including dull mentation, poor peripheral pulses, pale mucous membranes, decreased urine output, and cold extremities.

Laboratory Findings

- Testing: Testing generally involves measuring markers of IR but has not been standardized. Some current research involves measuring F2-isoprostane, which is a by-product of lipid peroxidation.
- Upon reperfusion after treatment, recognition of specific laboratory abnormalities may allow early intervention:
  - Serum lactate: Frequently rises following reperfusion due to mobilization of lactate produced by ischemic tissue. Initial lactate levels of >6 mmol/L (normal: <2.5 mmol/L) have been shown to correlate with gastric necrosis and worse prognosis in dogs with GDV. An initial rise in lactate level followed by rapid normalization suggests successful reperfusion and may be associated with a better prognosis.
  - Ionized calcium levels may rise after IR injury when calcium is released from injured muscle tissue; phosphorus levels may be decreased or normal following IR injury.
  - Potassium: In cats (or dogs) with ATE, serum potassium levels may rise after reperfusion. Potassium is released during muscle ischemia and, when mobilized upon reperfusion, can lead to significant hyperkalemia and subsequent bradycardia.
  - Coagulation panel: Prothrombin time, activated partial thromboplastin time, and levels of fibrinogen degradation products and D-dimers may be elevated; platelet count and antithrombin level may be decreased. Coagulation changes upon reperfusion suggest widespread endothelial damage and disseminated intravascular coagulation (DIC).
  - Thromboelastography is the only means of reliably detecting hypercoagulability in veterinary patients.
  - Complete blood count (CBC): Thrombocytopenia and neutropenia may suggest no-reflow phenomenon. A nonspecific stress leukogram may be obtained.
  - Urinalysis: If, upon reperfusion, the no-reflow phenomenon causes plugging of renal capillaries, signs associated with acute renal damage (i.e., isosthenuria, casts, polyuria, oliguria, or anuria) may be present.
  - Hepatic enzymes: Hepatocytes are exquisitely sensitive to IR injury, and elevation of liver enzymes (AST, ALT, GGT) may occur. Persistent elevation of liver enzymes (>48 hours after reperfusion) suggests hepatic injury or insufficient reperfusion (e.g., no-reflow phenomenon).

Other Diagnostic Findings

- ECG: Changes associated with hyperkalemia after ATE treatment may include bradycardia; small or absent P waves; tall, tented T waves; and, eventually, sinoventricular rhythm. In other diseases, a large T wave may occur secondary to myocardial hypoxia.
- Pulse oximetry: Readings below normal (<98%) may be associated with the primary disease (e.g., ARDS) or secondary to the primary disease (e.g., aspiration pneumonia in GDV, congestive heart failure in ATE). Normal readings do not rule out IR injury.
- Arterial blood gas/acid–base status: Evidence of metabolic acidosis (decreased perfusion and anaerobic metabolism), respiratory alkalosis (increased respiratory frequency due to hypoxemia, pain, or compensation for metabolic acidosis), and hypoxemia (ARDS, pneumonia) may be observed.
- Blood pressure: Hypotension suggests decreased fluid volume or systemic vasodilation. Systemic vasodilation from severe hypoxemia (upon reperfusion) is critical and must be

TABLE 1. Antioxidants for Use in Animals with Ischemia–Reperfusion Injury

Drug or Supplement	Action	Dogs	Cats
Lidocaine	ROS scavenger	25–50 µg/kg/min IV as CRI	Avoid because of toxic effects
N-acetylcysteine	Antioxidant	50 mg/kg diluted 1:4 with 0.9% saline and given IV over 1 hr q6h	50 mg/kg diluted 1:4 with 0.9% saline and given IV over 1 hr q6h
SAMe	Antioxidant	20 mg/kg/d; may be divided into bid dosing; give PO 30 min before meal	20 mg/kg/d may be divided into bid dosing; give PO 30 min before meal
Superoxide dismutase (SOD) + catalase	ROS scavenger	5 mg/kg of each or 15,000–19,000 U/kg SOD + 10,000–12,000 U/kg catalase IV	30,000 U/cat of each given IV
Ubiquinone	Antioxidant	2 mg/kg PO q24h	2 mg/kg PO q24h
Vitamin C	Antioxidant	500–1000 mg PO q24h; decrease if soft stool develops	125 mg PO q12h; decrease if soft stool develops
Vitamin E	Antioxidant	400 IU PO q24h	30 IU PO q24h

addressed promptly. Continued hypotension contributes to hypoperfusion and tissue/organ hypoxia.

- Radiography/ultrasonography: Changes associated with the primary disease.
- Echocardiography: Decreased fractional shortening from decreased contractility caused by reperfusion release of cytokines, inflammatory mediators, nitric oxide, or continued cardiac hypoperfusion.

Summary of Diagnostic Criteria

- No specific tests for IR are currently available.
- Diagnosis is made based on a strong clinical suspicion coupled with supportive laboratory evidence.

Diagnostic Differentials

- Inadequate fluid restoration.
- No-reflow phenomenon.
- Late decompensatory shock.
- Cardiogenic shock.
- Sepsis/DIC.
- Multiple organ system dysfunction.

TREATMENT RECOMMENDATIONS

Initial Treatment

- Address the specific underlying cause as appropriate (e.g., gastric decompression). **$–$$$$**
- Initiate measures to maximize perfusion. Administer bolus IV fluids at increments of shock rates (e.g., one-half to one-third shock bolus). Immediate reassessment of perfusion parameters (e.g., mucous membrane color, pulse quality, extremity temperature, mentation, urine output, lactate level) should direct further boluses. Consider colloid therapy when large volumes of crystalloids would be needed to restore perfusion. **$$–$$$**
- If perfusion parameters remain unacceptable, consider treatment with vasopressors or positive inotropes. With hypotension, vasopressors are generally suggested. If blood pressure is adequate and perfusion remains poor, consider positive inotropes (dopamine, dobutamine), although these agents are contraindicated in feline patients with hypertrophic cardiomyopathy. Dopamine (3–10 µg/kg/min IV as a constant-rate infusion [CRI]) can be used for hypotension. Vasopressin (0.5–2 mU/kg/min IV as a CRI in dogs; there is no known dose for cats) may cause significant vasoconstriction with physiologic dosages. Dobutamine (2–20 µg/kg/min IV as a CRI in dogs, 1–5 µg/kg/min IV as a CRI in cats) is often chosen when positive inotropy is needed. **$–$$**
- Packed red blood cells (RBCs): Consider in cases of anemia from decreased production/destruction of RBCs. Conduct crossmatching before blood product transfusion due to emergence of new RBC antigens in dogs and cats. **$$–$$$**
- Fresh whole blood: Consider in cases of anemia from loss of both RBCs and plasma. **$$–$$$**
- Fresh-frozen plasma: Consider in animals with coagulopathy. **$$–$$$**
- Consider anticoagulant therapy with disease syndromes that predispose to hypercoagulable states. If the initial period of reperfusion is followed by a period of diminished perfusion, consider the no-reflow phenomenon and initiate anticoagulant therapy to prevent further microthrombi deposition. Low-dose aspirin (0.5–1.0 mg/kg PO q24h in dogs and q48–72h in cats), unfractionated heparin (100–250 IU/kg SC q6–8h), or low-molecular-weight heparin (dalteparin; 100 IU/kg SC q12–24h) are good options. **$–$$$**
- Oxygen support via cage, hood, nasal line, or mechanical ventilation may be necessary if the patient is hypoxemic from pulmonary dysfunction (e.g., ARDS, pneumonia). **$$–$$$$**
- Analgesia as indicated by underlying disease process and need for potentially painful intervention (e.g., chest tube placement).

Multimodal, continuous analgesia (e.g., CRI) is preferred over single-agent, intermittent therapy. Fentanyl, lidocaine, and ketamine can be combined into a syringe and given as a CRI.
  — Fentanyl (2.0–5.0 µg/kg/hr) ± lidocaine (25–50 µg/kg/min) ± ketamine (2.0–10.0 µg/kg/min) can be used in any combination. $–$$
  — Lidocaine is generally avoided in cats because of toxicity. $–$$
- Mannitol (0.5–2 g/kg given as a slow IV infusion) should be used in patients in which cerebral edema and increased intracranial pressure are suspected. It also has been shown to scavenge hydroxyl radicals and may have some neuroprotective properties when used following spinal cord injuries. $

Alternative/Optional Treatments/Therapy

- Optional (unproven, but unlikely to cause harm) therapy includes administration of antioxidants (Table 1).
- The first line of defense against ROS damage is glutathione, a sulfur-containing antioxidant composed of three amino acids (glycine, glutamine, cysteine). Cysteine is the rate-limiting amino acid; supplementation with *N*-acetylcysteine or *S*-adenosylmethionine enables production of more glutathione.
- Vitamin E, composed of mixed tocopherols and tocotrienols, is the second line of defense. Vitamin C is a cofactor for vitamin E regeneration.
- Additional areas of investigation include iron chelators, superoxide dismutase, L-arginine, and metalloporphyrins, although none has yet been proven clinically beneficial in veterinary patients.

Supportive Treatment

- Antibiotics if signs of infection are present.
- Soft, dry, padded bedding.
- Gastric protectants should be considered to prevent or treat GI ulceration. Sucralfate (1.0 g/dog and 0.5 g/cat PO q8h) or an H_2 blocker (ranitidine 2.0 mg/kg IV q8–12h) should be considered.
- TLC: Visits with owner, time outside, and other positive actions may help speed recovery.

Patient Monitoring

- Check perfusion parameters at least every 4 hours (more frequently if still critically ill) until the animal is stabilized. Goals suggestive of optimal perfusion include pink mucous membranes, strong pulses, warm extremities, alert mentation, normal heart and respiratory rates, normal respiratory pattern, urine output >1 mL/kg/hr, lactate value <2.5 mmol/L, and systolic arterial blood pressure >90 mm Hg.
- Continued monitoring of packed cell volume and total solids, electrolytes, and acid–base status q8–12h, depending on patient status.
- Daily CBC: Monitor for signs of infection and thrombocytopenia.
- Daily biochemical panel: Monitor for signs of liver dysfunction (indicative of poor hepatic perfusion, hepatic necrosis, etc.), renal dysfunction (differentiate prerenal azotemia and renal failure), and electrolyte abnormalities.

Home Management

- Educate owners on preventing recurrence of the underlying problem (e.g., antiplatelet medication in cats with ATE, several small meals daily to dogs with GDV).
- Continue GI protectants.
- Nutritional support.
- Antibiotic therapy.
- Probiotics should be considered in animals receiving antibiotics.
- Antioxidant supplements (Table 1).

Milestones/Recovery Time Frames

- Normalization of CBC, biochemical profile.
- Normalization of appetite and mentation.
- Appropriate weight gain.
- Time frames for recovery vary with underlying disease and severity of injury.

PROGNOSIS

The prognosis for IR injury depends on the extent of tissue injury and the rate and timing of reperfusion.

Favorable Criteria

- Rapid return to function of ischemic tissue (e.g., stomach rapidly becomes pink upon derotation in GDV, cat with ATE begins moving hindlimbs).
- Rapid normalization of perfusion parameters upon reperfusion.
- Normalization of CBC and hepatic and renal function.
- Return of appetite.

Unfavorable Criteria

- Continued poor perfusion that is unresponsive to aggressive medical therapy after reperfusion of tissues.
- Continued elevation of liver enzymes or signs of poor hepatic function (low albumin, glucose, cholesterol, or BUN level; elevated bilirubin level).
- Renal failure unresponsive to aggressive medical therapy.
- Persistent dull mentation or poor appetite.

RECOMMENDED READING

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