

Cardiac troponins

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Abstract

Objective: To review the use of cardiac troponins as biomarkers for myocardial injury in human and veterinary medicine.

Data sources: Data sources included scientific reviews and original research publications.

Human data synthesis: Cardiac troponins have been extensively studied in human medicine. Finding an elevated cardiac troponin level carries important diagnostic and prognostic information for humans with cardiovascular disease. Troponin assays are used primarily to diagnose acute myocardial infarction in patients with ischemic symptoms such as chest pain. However, elevated blood levels may be found with any cause of myocardial injury.

Veterinary data synthesis: Several studies have shown that cardiac troponins are sensitive and specific for myocardial damage in veterinary patients and may have utility in diagnosis and prognosis for certain disease states. Human assays may be used in most animals due to significant homology in the troponin proteins between species.

Conclusions: Cardiac troponins are sensitive and specific markers of myocardial injury although they do not give any information regarding the mechanism of injury. They have redefined how acute myocardial infarction is diagnosed in humans. Their use in the clinical management of veterinary patients is limited at this time. Further prospective studies are warranted.

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Introduction

Cardiovascular diseases are commonly encountered in both human and veterinary medicine. Biological markers, or biomarkers, are tools used to identify high-risk individuals, quickly and accurately diagnose disease states, and determine treatment plans and prognoses. While the term biomarker was first introduced in 1989, a National Institute of Health group standardized the definition in 2001 as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.'^{1,2} Biomarkers commonly used in the diagnosis of cardiovascular disease may include measurements taken from blood samples, blood pressure, ECG recordings, radiographs, and echocardiograms. Cardiac troponins (cTn)

have a high sensitivity and specificity for myocardial damage and are considered the biomarker of choice for detection of cardiac cellular injury.^{3–6} The purpose of this paper is to review cardiac troponins and their utility in human and veterinary medicine.

Physiology

Troponins are regulatory proteins that are part of the contractile apparatus of skeletal and cardiac muscle tissue. They are not present in smooth muscle tissue. With the proteins actin and tropomyosin, they are part of the thin filaments within the myofibrils and are essential for the calcium-mediated regulation of muscle contraction. The troponin complex consists of 3 interacting and functionally distinct proteins (troponin I, T, and C).⁷ Tissue-specific isoforms exist for each type of troponin.⁸ Within the thin filament, tropomyosin dimers form a continuous chain along the groove of the actin helix. The troponin complex lies at regular intervals along the filament. Tropomyosin acts to block the myosin binding sites on actin. Each troponin protein has specific functions that regulate muscle contraction.

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This paper focuses on troponin I and T due to their specificity for cardiac injury.

Troponin C (TnC) is present in 2 isoforms. One isoform is present in fast-twitch muscle fibers and the other is present in both cardiac and slow-twitch muscle fibers. Homology between the cardiac isoform and 1 of the skeletal muscle isoforms reduces the cardiac specificity of TnC and therefore limits its diagnostic usefulness in heart disease.⁹ Troponin C binds calcium to initiate muscle contraction.

Multiple isoforms of troponin T (TnT) exist in skeletal muscle. Cardiac troponin T (cTnT) has a molecular weight of 37,000 Da.¹⁰ In human cardiac tissue 4 isoforms exist, but only 1 is characteristic of the adult heart. The other 3 cardiac isoforms are expressed in fetal tissue. The fetal isoforms may be re-expressed during heart failure or in damaged skeletal muscle. Troponin T attaches the troponin complex to tropomyosin and actin.⁸

Three isoforms exist for troponin I (TnI). Two are present in skeletal muscle and the other is present only in cardiac muscle. The cardiac isoform (cTnI), with a molecular weight of 24,000 Da, is larger than the other isoforms as it contains an additional 32 amino acid N-terminal peptide. The rest of the protein has greater than 40% dissimilarity in its amino-acid sequence compared with skeletal muscle TnI.^{8,10,11} Unlike cTnT, cTnI is not expressed in fetal skeletal muscle during development, nor after damage and regeneration in adult skeletal muscle.¹² Troponin I inhibits actomyosin ATPase and prevents the structural interaction of myosin with actin-binding sites. The binding of calcium to troponin C displaces troponin I and causes a conformational change in tropomyosin so that it no longer interferes with myosin/actin binding and muscle contraction can occur.

Mutations in the genes encoding for cTnT and cTnI cause hypertrophic cardiomyopathy in humans.^{13,14} Conversely, a knock out cTnI mouse model develops acute heart failure at 18 days of age.¹⁵

Troponin Release

The troponin protein exists in 2 populations within the cells. The majority of troponin is structurally bound within the thin filaments of the contractile apparatus. A small percentage of protein remains free in the cytosol. This percentage is approximately 2–4% for cTnI and 6–8% for cTnT.^{16,17} Troponins are considered leakage markers. Damage to cardiac myocytes resulting in loss of membrane integrity causes the release of cTn into the circulation. Apoptosis, a genetically programmed form of cell death, does not result in loss of cell membrane

integrity and therefore will not cause leakage of troponins.¹⁸

Troponin release kinetics are consistent with 2 separate intracellular populations. After acute cardiac injury, the cytosolic pool is released resulting in an early rise in blood levels. This is followed by the slower release of structurally bound troponin that results in a sustained elevation (see Figure 1).^{16,17,19} The half-life of troponin and its complex in the circulation is about 2 hours.²⁰ In humans with acute myocardial infarction (AMI), cTn levels begin to rise 4–12 hours after the infarction and reach peak values at 12–48 hours. The levels remain elevated for 7–10 days (cTnI) and 10–14 days (cTnT).^{10,11,21} A canine model of AMI showed release times similar to those observed in clinical human patients although the peak was attained earlier (range 10–16 hours).²² This earlier peak was hypothesized to be due to more rapid development of necrosis in the experimental situation. The sustained elevation of cTn for several days after AMI is likely due to ongoing release from damaged myocytes rather than impaired elimination.²³ The exact mechanism for elimination of troponins is unknown but it is thought to involve clearance by the reticuloendothelial system.²⁴ There is also some evidence that troponins may be broken down into small fragments that could be renally excreted.²⁵ Elevated cTn levels indicate myocardial damage but do not provide any information regarding its cause.

Reversible Versus Irreversible Injury

There has been debate over whether or not cTn is released after reversible cardiac injury or if it is only released following irreversible injury. Some investigators still believe cardiac troponin I release only results from irreversible membrane injury. Reversible ischemia after exercise stress testing in humans has not resulted in cTn elevations.²⁶ However, several studies have suggested that troponin I can be released in reversible ischemia. For example, Feng et al. showed in a porcine model of ischemic heart disease that reversible ischemia was associated with release of cTnI. The source of troponin is hypothesized to be from the free cytosolic pool leaking through a reversibly damaged myocyte membrane. This hypothesis is also supported by clinical observations of 2 protein release patterns in patients with unstable angina: an early transient pattern and a persistent pattern.^{27–29} Additionally, some studies involving prolonged strenuous exercise have shown transient cTn release that is speculated to be from the cytosolic pool rather than structurally bound cTn.^{30,31} The observation that myocardial dysfunction found during sepsis is reversible also supports the idea of troponin release associated with reversible injury.³²

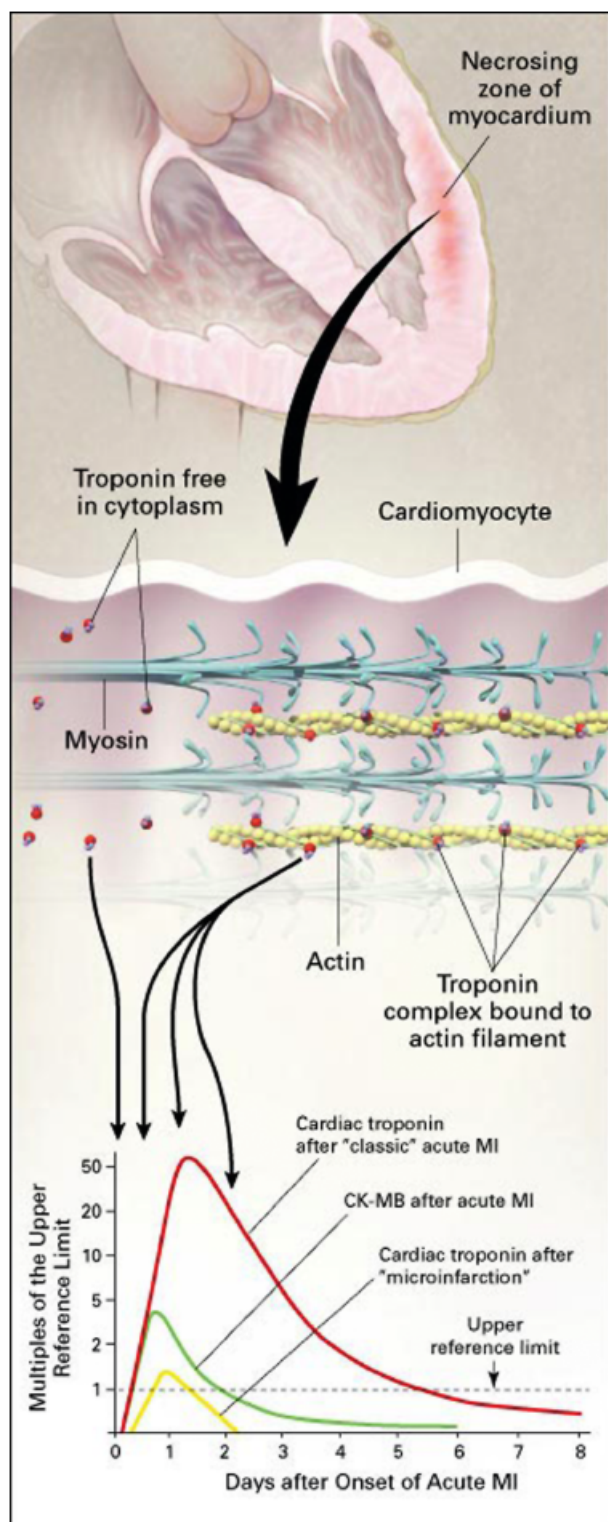


Figure 1: Release of cardiac troponins during acute myocardial infarction. After injury resulting in loss of sarcolemmal membrane integrity, the free cytoplasmic troponins are released first followed by a more prolonged release of the structurally bound troponin proteins. Reprinted from Antman EM. Decision making with cardiac troponin tests. *N Engl J Med* 2002;346(26):2080, with permission.¹⁰⁶

However, at this time it is not possible to differentiate which population of cTn is released so the debate continues.³³ Also, the clinical significance is unknown.

Assays

Troponin levels are determined using enzyme-linked immunosorbent assays (ELISA). The difference in amino-acid sequences from skeletal muscle and cardiac troponin I and T has allowed production of antibodies specific for cardiac troponins in these assays.^{34,35} The first assays for detection of cTn were developed in the late 1980s. These assays have evolved dramatically since their introduction with greater sensitivity and improved precision. The turnaround time for results has also decreased from several hours to a few minutes. Point-of-care assays now exist that may be run bedside or in the field. There are multiple assays available from a variety of manufacturers for cTnI. This has led to some confusion regarding interpretation of results. The assays are not standardized so manufacturers may design the tests using proprietary antibodies that target varying amino-acid sequences on the cTnI molecule. In the bloodstream, cTnI can be modified or complexed to other proteins, such as cTnC, and the antibodies used in the assays may have differing specificity for each circulating form of cTnI.^{36,37} There exists no gold standard assay for cTnI at this time. Comparison studies using a number of analyzers have concluded with the recommendation that, until assays are standardized, reference ranges should be established for each individual assay. Also, absolute values obtained from different assays cannot be compared.^{36,38,39} Serum, heparinized plasma, or whole blood may be sampled depending on which cTnI assay is used. Studies in dogs have shown that cTnI levels do not significantly change in serum stored at room temperature over a 5-day-period nor in serum that has undergone up to 5 freeze-thaw cycles.^{40,41} Only 1 manufacturer produces an assay for cTnT that eliminates interassay comparison issues for this protein. The first generation cTnT assays used an antibody that cross-reacted with skeletal muscle troponin T, thereby decreasing its specificity for cardiac injury.^{42,a} Subsequent generations of cTnT assays have replaced this antibody with 1 more specific for cTnT, thereby eliminated the false positives related to skeletal muscle leakage.³⁵ Although sensitivity of the assays for troponins has improved over the years, concern remains about their precision at low levels.⁴³ The occurrence of false positive troponin results due to interfering substances in the blood has also been reported. Rheumatoid factor, excess fibrin, heterophile antibodies, hemolysis, lipemia, elevated alkaline phosphatase, and immune complex formation have all been

implicated as causes of false positive troponin results. If a false positive result is suspected and instrument malfunction is ruled out, then repeating the test on a re-centrifuged or new blood sample is indicated. The use of blocking reagents for substances such as rheumatoid factor and heterophile antibodies may decrease false results due to these interferences. Alternatively, because the problem of interference is assay dependent, the sample may be tested using a different manufacturer's assay.⁴⁴

While some assays have been specifically validated for use in veterinary medicine, it is generally believed that human assays for cTn can be used to measure blood levels of cardiac troponins I and T in most species encountered.^{5,6,45,b,c} Recently, the genes for canine and feline cTnI were sequenced proving the protein structure is highly conserved among these species. Homology between canine and feline genes and humans was 95% and 96%, respectively. In the region targeted for detection by most assays, dogs and cats were identical to each other and humans differed from dogs and cats by only 1 amino acid.⁴⁵ Other studies have shown that cTnI and cTnT from many mammalian species can be measured using human assays and that these proteins are specific for myocardial injury.^{5,6} Species studied include dogs, mice, rats, pigs, monkeys, sheep, rabbits, horses, and cows. However, cardiac troponin I measurements appear less useful in birds and useless in fish due to a smaller ratio of cardiac to skeletal muscle reactivities in these species.⁶

Normal values for cardiac troponin I and T have been reported in veterinary species.^{46–53} Although each assay must have its own range established, reports of normal values for healthy animals have correlated closely.³⁹ Most normal animals have cTn levels below the threshold of detection for current assays.^{46–53} Normal cTnI ranges for dogs are reported at <0.03–0.07 ng/mL with a median of 0.02 ng/mL.⁴⁶ For cTnT all normal dogs had levels below the threshold for detection by the assay.^{48,51} Cats have ranges of <0.03–0.16 ng/mL.⁴⁶ A report of normal levels in adult horses including pastured and race trained Thoroughbreds demonstrated a mean cTnI of 0.047 ± 0.085 ng/mL.⁴⁷ There was no significant difference in cTnI concentration between horses undergoing race training and pastured horses. However, as already stated, normal ranges must be run on each system and result comparison using different systems is not possible.³⁹

Myocardial Infarction

Cardiovascular disease is the leading cause of morbidity and mortality in humans in the United States.⁵⁴ The primary role of cardiac troponin testing in human

medicine is for diagnosis of ischemic heart disease such as myocardial infarction (MI). MI refers to myocardial cell death due to ischemia.⁵⁵ In humans, MI occurs after the rupture of an atherosclerotic plaque in the coronary arteries resulting in platelet aggregation, clotting, and either large vessel occlusion or distal embolization.⁵⁶ For years, according to the World Health Organization (WHO), MI has been defined as a syndrome requiring at least 2 of 3 diagnostic criteria.⁵⁷ These criteria included an appropriate clinical history and presentation, ECG changes typical for MI, and elevated cardiac enzymes, such as total creatine kinase (CK) and its myocardial form (CK-MB), lactate dehydrogenase, and aspartate aminotransferase. Total CK, lactate dehydrogenase, and aspartate aminotransferase have poor specificity for cardiac damage.^{55,58} While CK-MB is more specific than total CK for injury to the heart, it is not as cardiac-specific as the troponins.³ CK-MB levels also return to baseline within 48 hours so late diagnosis of MI is not possible with this marker, whereas troponin levels remain elevated for approximately 10 days.⁵⁹ Because humans may not have typical clinical signs and ECG changes may be nondiagnostic, a joint committee of the European Society of Cardiology and the American College of Cardiology (ESC/ACC) developed a new definition for the diagnosis of MI in 2000.⁵⁵ This new definition was based predominately on the use of biomarkers such as the troponins in the diagnosis of MI (see Table 1). Any elevation of troponin above the reference range is considered abnormal. In humans, the reference ranges for troponins are set at the 99th percentile of the control group (3 SD from the mean). Owing to the release kinetics of troponins, it is possible that patients presenting within hours of an acute ischemic event may not have elevated cTn levels. It is therefore recommended that samples be taken at the time of admission, at 6–9 hours, and again 12–24 hours after presentation.⁵⁵ In situations where an early diagnosis is needed, a biomarker that rises rapidly, such as myoglobin or CK-MB, in addition to the later-rising troponin may be used.⁵⁵ Based on the new definition and use of

Table 1: ESC/ACC criteria for diagnosis of myocardial infarction in humans proposed in 2000⁵⁵

One of the following 2 criteria may be used to diagnose MI:

1. Typical rise and fall of biochemical markers such as troponin or CK-MB with at least 1 of the following:
 - Ischemic symptoms (e.g., chest pain)
 - Development of pathological Q waves on the ECG
 - ECG indicative of ischemia (ST-segment changes)
 - Coronary artery intervention (e.g., angioplasty)
2. Pathological findings of myocardial infarction

ESC/ACC, European Society of Cardiology/American College of Cardiology; MI, myocardial infarction; CK-MB, creatine kinase-MB.

Table 2: Reported causes of elevated cardiac troponins in humans and animals

<i>Humans</i> ^{11,30,31,55,70,72–78}	
Ischemic heart disease (e.g., myocardial infarction, unstable angina)	Hypotension/hypovolemia
Blunt chest trauma resulting in contusions	Renal failure
Trauma during cardiac surgery or myocardial biopsy	Drug toxicity (e.g., doxorubicin)
Electrical cardioversion, pacing, and implantable cardioverter defibrillator firings	Snake envenomation
Congestive heart failure	Coronary vasospasm
Hypertrophic cardiomyopathy	Inflammatory disease involving the heart (e.g., myocarditis, pericarditis)
Hypertension	Percutaneous coronary intervention
Sepsis	Pulmonary embolism and pulmonary hypertension
Rhabdomyolysis with cardiac injury	Infiltrative disease of the myocardium (e.g., sarcoidosis, amyloidosis)
Extreme exercise (marathon runners or Ironman triathlon competitors)	Sympathomimetic activity (e.g., cocaine use, massive catecholamine release such as in head trauma or stroke)
Abnormal cardiac rhythms (prolonged tachycardias, atrial fibrillation)	Cardiac transplantation
	Chronic obstructive pulmonary disease
<i>Animals</i> ^{22,40,48–53,79–88,d,g–m}	
Models of myocardial infarction	Ehrlichiosis
Congestive heart failure	Third degree heart block
Canine dilated cardiomyopathy	Arrhythmogenic right ventricular cardiomyopathy in Boxers
Mitral valve disease	Blunt chest trauma
Pericardial effusion	Subaortic stenosis
Feline hypertrophic cardiomyopathy	Sepsis
Gastric dilatation-volvulus	Aortic insufficiency jet lesions
Toxins (e.g., doxorubicin, cantharadin)	Endurance exercise in dogs and horses
Babesiosis	High dose isoproterenol
Feline hyperthyroidism	
Renal insufficiency	

highly sensitive troponin assays, many patients are now diagnosed with MI who would not have had that diagnosis using the previous WHO criteria. In a study of 2181 patients with chest pain presenting to an emergency department, the implementation of the new definition resulted in an increase in the diagnosis of MI by 195%.⁶⁰ Another study of patients with chest pain presenting to an emergency room showed that cardiac troponin testing was highly sensitive for the early detection of myocardial injury.⁶¹ In addition, this study suggested that a negative troponin test at admission and 6 hours after the onset of symptoms was associated with a low-risk of a heart-related event and patients could be discharged early from the hospital. This provides strong evidence that troponin testing is effective for rapid triage of emergent patients with chest pain.

Prognosis

Cardiac troponins also have a role in establishing prognosis. With MI, any troponin level above the reference range is associated with an increased risk of adverse events in both the short- and long-term.^{61–64} It has also been shown that the magnitude of troponin level elevation correlates with risk of future cardiac events or death and aids the identification of patients with greater disease severity who may benefit from more aggressive therapy.^{64–66} In fact, the size of the infarcted area

may be predicted based on peak cTnI levels or cTnT levels at 72 hours.^{67–69} In addition, elevations of cTn have prognostic significance in other forms of cardiovascular disease such as heart failure and pulmonary thromboembolism.^{70,71}

Other Causes of cTn Elevations in Human and Veterinary Medicine

MI is a clinical diagnosis and cannot be made based on troponin elevations alone. While cTn elevations indicate myocardial injury, they do not give any information as to the mechanism of injury. Serial samples may aid in diagnosis because acute injuries such as MI will have a typical rise and fall of serum values whereas other cardiac diseases such as chronic congestive heart failure may result in persistent, relatively lower troponin elevations.⁵⁶ Troponin levels can rise with very small amounts of myocardial cell necrosis and most studies show that cTnI levels are more sensitive than cTnT levels at detecting cardiac damage.^{53,61} There exist many causes of cardiac injury and therefore elevations in cTn (see Table 2).

Trauma

Direct trauma to the heart can result in cTn elevations. This may be secondary to mechanical injuries such as

cardiac surgery, catheterization procedures, myocardial contusions from blunt chest trauma, electrical injuries occurring during cardioversion, ablation procedures, or defibrillation.^{55,72,89} Human studies of patients with chest trauma have proven cTnI testing to be valuable in ruling out significant blunt chest injury leading to cardiogenic shock, severe arrhythmias, or structural damage related to trauma.^{73,89} The negative predictive values of cTnI in these 2 studies were 93% and 94%. When combined with a normal ECG, these values increased to 100%. This allows patients that normally would be monitored in the hospital for 1–3 days to be discharged early. Elevations of cTn have also been shown to be sensitive in detecting cardiac injury in dogs and cats with blunt chest trauma, although further studies are needed to determine if cTn levels can aid in the clinical management of veterinary patients with chest trauma.^{53,79,80}

Infection and Inflammation

Myocardial dysfunction and cTn elevations during sepsis are common.^{74,90} While the exact mechanisms are unknown, cardiac oxygen demand exceeding supply, septic microemboli, toxic effects from bacterial endotoxins, and cardiac depressant effects from cytokines such as tumor necrosis factor- α are postulated mechanisms.^{74,91} Ischemia and reperfusion injury secondary to microvascular dysfunction may also be involved. In humans, elevated cTn values during sepsis are associated with left ventricular dysfunction.⁷⁴ Cardiac troponin I elevations are also present with myocarditis.⁷⁵ Little work has been done to evaluate cTn levels during sepsis in veterinary medicine. A study involving septic foals showed that cTnT values were significantly elevated compared with healthy foals but there was no difference in levels among survivors compared with nonsurvivors.⁸¹

Although not common, canine babesiosis can cause cardiac lesions such as epi- and endocardial hemorrhage, inflammatory cell infiltrate, myocardial fiber necrosis, and pericardial effusion.⁸² These changes are thought to be related to the severe systemic inflammatory response and anemic hypoxia. Elevations in cTnI can be used to determine cardiac involvement in babesiosis and there is an association between cTnI levels and clinical severity and mortality. A study of dogs in Brazil naturally infected with *Ehrlichia canis* showed that 44% of patients had elevated cTnI concentrations without clinically apparent heart disease suggesting myocardial involvement.^d

Primary Heart Disease and Heart Failure

Cardiac troponins can be released during acute and chronic congestive heart failure in humans and veter-

inary patients. The evolution of the clinical entity of heart failure is accompanied by cardiac remodeling as a result of hypertrophy of myocardial myocytes, death of cardiac myocytes consisting of both cell necrosis and apoptosis, and formation of fibrotic replacement tissue. These are all a consequence of the complex interaction between mechanical, neurohumoral, inflammatory, and ischemic alterations within the myocardium.^{50,76,92,93} Both cTnI and cTnT may be elevated in humans with heart failure due to left ventricular dysfunction and these patients have a worse prognosis than those with normal cTn levels.^{71,94} Troponin levels often return to normal after successful treatment of the acute episode, suggesting that cTn levels can be used to monitor the clinical course of disease.⁷¹

Several studies in veterinary medicine have shown that cTn levels can be elevated in primary heart diseases.^{48–52} Hypertrophic cardiomyopathy (HCM) in cats can cause intramural coronary artery disease leading to microscopic areas of ischemia, and myocardial hypertrophy with cellular necrosis and cTn release into the circulation.^{95,96} Although cats with mild HCM may have normal cTnI levels, a study has shown that cats with moderate to severe HCM with and without heart failure have significantly higher levels of circulating cTnI than normal cats.^{49,e} A weak correlation existed between cTnI concentrations and ventricular wall thickness. Furthermore, cats with HCM and heart failure had levels significantly higher than those without heart failure suggesting that cTnI levels may be used to differentiate cats with cardiac and noncardiac causes of respiratory distress.^{49,f}

Cardiac troponin levels can identify dogs with mitral valve disease (MVD), subaortic stenosis (SAS), and dilated cardiomyopathy (DCM) and the cTn level may correlate with severity and prognosis.^{48,50–52} One study showed that by using the International Small Animal Cardiac Health Council's heart failure classification method, dogs with class II and IIIA heart failure had significantly higher blood levels of cTnI than normal dogs and dogs with class IA and IB heart failure.⁵⁰ Using a cut-off cTnI concentration of 0.095 ng/mL, this study identified dogs with class II or worse heart failure with a sensitivity of 96% and specificity of 88%. Another study which evaluated 93 dogs with heart disease (MVD, DCM, and SAS) showed that 47% of the dogs had elevated cTnI levels and there was a significant difference in cTnI concentration between dogs with heart disease and the normal control population.⁵² In the dogs with cardiomyopathy, prognostic significance was found using a cut-off cTnI level of 0.2 ng/mL. Median survival with a level >0.2 ng/mL was 112 days while dogs with levels <0.2 ng/mL had a median survival of 357 days. A correlation was also found between

heart chamber size and cTnI level in that study. Unfortunately, as described above, cTnI comparisons between different machines are not possible and limit the use of this data.³⁹ Similar studies in dogs using the cTnT assay have shown elevated levels in approximately 30% of patients with acquired heart disease, consistent with studies that show cTnI is more sensitive than cTnT.^{48,51}

Boxer dogs with arrhythmogenic right ventricular cardiomyopathy are reported to have cTnI levels significantly higher than control Boxers and non-Boxers.⁸ This is likely due to persistent membrane leakage from myocarditis and myofiber degeneration found with this disease.⁹⁷

Dogs with third degree atrioventricular block have also been found to have significantly elevated cTnI concentrations.^h The underlying cause of the dysrhythmia, such as fibrosis or inflammation, or the hypoxic damage secondary to decreased perfusion are thought to be potential reasons.

Little research involving cardiac disease and cTn levels has been performed in horses but there are reports of elevated cTnI levels in horses with ventricular arrhythmias. Reports of 2 horses with ventricular tachycardia showed that 1 had a ruptured aortic jet lesion and another had severe myocardial necrosis of unknown cause.^{83,98} Toxicities such as *Streptococcus* spp. myositis, red maple leaf ingestion, white snakeroot poisoning, and cantharadin intoxication from blister beetles have been reported to cause elevated cTnI in horses but the significance of this is unknown.^{i,j} Additionally, cTnI elevations were noted in some endurance horse athletes competing at the 50 and 100 mile distances, however, the significance was unclear.⁸⁴

Pericardial Disease

Pericardial disease has been shown to cause elevations in troponin levels in both humans and veterinary patients. Acute pericarditis in humans commonly causes troponin elevations.⁹⁹ The release is thought to be secondary to epicardial inflammation. Decreased coronary perfusion during tamponade may also be the cause of troponin release. Two studies have shown that dogs with pericardial effusion have significantly higher cTnI levels than normal dogs.^{85,k} One of these studies suggested that cTnI levels may be utilized to differentiate idiopathic pericardial effusion and pericardial effusion due to hemangiosarcoma. This study prospectively evaluated 26 dogs in which a definitive cause of pericardial effusion was identified. A significantly higher cTnI level was found in dogs with hemangiosarcoma *versus* dogs with idiopathic pericardial effusion.⁸⁵ However, a separate prospective study involving 20 dogs

found that cTnI levels did not differentiate the etiology in these cases.^k Clearly further research with larger case numbers is warranted.

Chemotherapy

Cardiomyopathy secondary to chemotherapy, particularly anthracyclines such as doxorubicin, is irreversible and usually fatal. Development of cardiomyopathy is related to the cumulative dose throughout the course of chemotherapy. Clinical signs of cardiac disease may be delayed, occurring after chemotherapy is finished.⁸⁶ In humans, cardiac troponin elevations in patients who have received chemotherapy can be predictive for the development of cardiac toxicity and decreased left ventricular function.^{77,100} Cardiac TnT became elevated in 2 dogs with lymphoma undergoing doxorubicin therapy and 1 of these dogs died from a suspected cardiac event.⁴⁸ Peak elevations of cTnT were noted in 1 dog 3.5 weeks after receiving a cumulative dose of 150 mg/m² and in the other dog 2 weeks after a cumulative dose of 180 mg/m². These dogs did not have ECG or echocardiographic evidence of cardiac disease at earlier time points. A retrospective study showed that cTnI levels were elevated in 32 of 44 dogs during doxorubicin chemotherapy for lymphoma and osteosarcoma, but the elevations did not predict development of cardiac disease based primarily on physical exam findings and thoracic radiographs.⁸⁶ In dogs with elevated cTnI levels that developed clinical heart disease, the cTnI elevation preceded recognition of cardiac dysfunction. Further prospective studies are needed to determine if troponins will be useful in the clinical management of patients receiving chemotherapy.

Exercise

Many studies have reported elevated cTn levels in humans after extreme endurance exercise such as marathons and Ironman triathlons.^{30,31,101} A study evaluating competitors in the 1994 Hawaii Ironman Triathlon showed that some athletes had elevated cTnT and cTnI levels and echocardiographic abnormalities following the race.³¹ It was not determined whether this represented temporary or long-term cardiac damage although it was believed to be transient based on other studies involving Ironman competitors showing echocardiographic abnormalities returning to normal after 48 hours. Moreover, the athletes continued to compete in these strenuous competitions. Troponin release in these cases may be from the cytosolic pool rather than structurally bound troponin. A report on serum chemistry alterations in Alaskan sled dogs during endurance exercise showed elevations in cTnI, with

highest levels attained after running 160 km.¹ Cardiac troponin I elevations were also noted in endurance horses (as mentioned previously).⁸⁴

Pulmonary Thromboembolism

Pulmonary thromboembolism (PTE) and pulmonary hypertension cause pressure overload of the right ventricle due to increased pulmonary arterial resistance. The resultant increase in right ventricular pressure leads to decreased myocardial perfusion and oxygen supply. These changes, in addition to hypoxemia with pulmonary thromboembolism, can cause cardiac damage and cTn leakage.⁷⁰ Pulmonary embolism has also been associated with right ventricular infarction, confounding the interpretation of elevated cTn in these patients.¹⁰² However, patients with PTE and elevated cTn have a worse prognosis than those without cTn elevation.⁷⁰ Troponins have not yet been evaluated in veterinary patients with PTE or pulmonary hypertension.

Feline Hyperthyroidism

Cats with hyperthyroid disease commonly have cardiovascular abnormalities. These may include tachycardia, myocardial hypertrophy, hypertension, arrhythmias, and congestive heart failure, particularly if primary cardiomyopathy is concurrently present. In a study of 23 hyperthyroid cats, 11 had elevated levels of cTnI before treatment with radioactive iodine.⁸⁷ Cats with elevated cTnI had significantly thicker interventricular septums; however, this increased thickness was still considered to be within the normal feline reference range. Although not reaching statistical significance, the cats with cTnI elevations also tended to have higher T₄ levels. Six months after treatment, only 3 cats still had cTnI elevations, suggesting the resolution of continued myocyte damage in the majority of these cats. The mechanism of troponin release was not determined although it was speculated to result from myocardial cell damage associated with intramural coronary ischemia or from the physiological effects of excess thyroid hormone.

Gastric Dilatation-Volvulus

Cardiovascular complications resulting from gastric dilatation-volvulus (GDV) are common. These include shock, ischemia and reperfusion injury, and arrhythmias. It has been shown that dogs with GDV can have myocardial degeneration, and necrosis.⁴⁰ Two studies in veterinary medicine have assessed the use of cTn measurement to identify myocardial damage in

dogs with GDV.^{40,53} One study evaluated 85 dogs with GDV and found elevated cTnI and cTnT in 87% and 51% of patients, respectively, and all dogs that died (19%) had elevated cTnI levels.⁴⁰ Peak cTnI levels were found 48–72 hours after surgery. Cardiac troponin I and cTnT levels were predictive of outcome. Results of the second study were similar with increased cTnI and cTnT values in 93% and 57% of patients, respectively.⁵³ Peak troponin levels were found 24–48 hours after surgery and all dogs that died (21%) had elevated cTnI levels. These studies suggest that cTn evaluation in dogs after GDV surgery may identify a group of patients requiring more intensive monitoring and therapy and may provide useful prognostic information as well.

Renal Failure

Cardiac disease is a common cause of death in humans with end-stage renal disease.⁷⁸ Chronic elevations of troponins exist in approximately 50% of patients with chronic renal insufficiency.¹⁰³ Although the exact cause is unknown, many mechanisms for these elevations have been proposed including silent myocardial necrosis, ventricular hypertrophy, and impaired renal clearance.⁷⁶ Troponin T is more commonly associated with elevations during renal disease with 1 study showing 82% of patients with cTnT elevations compared with only 6% with elevated cTnI.¹⁰⁴ However, evidence suggests that cTnT fragments accumulate in the bloodstream due to poor renal clearance making interpretation in these patients difficult.²⁵ Therefore, without knowledge of baseline levels, cTnI may be more specific for acute cardiac injury than cTnT in the face of renal failure. Regardless of cause, elevations of troponin I and T in patients with renal disease and patients on hemodialysis were found to be indicators of mortality.^{104,105} In a veterinary study, 11 of 14 cats and 29 of 36 dogs with moderate to severe azotemia due to renal insufficiency had elevated cTnI levels.^m

Conclusion

Owing to their high sensitivity and specificity for myocardial damage, evaluation of cardiac troponin levels has proven valuable and is firmly established in the management of human patients with cardiac disease. In veterinary medicine, troponin measurements have been shown to have the potential to be sensitive indicators of myocardial injury due to both cardiac and noncardiac disease processes, although their role in clinical practice remains to be determined. Perhaps future studies will provide further evidence supporting the use of troponins in diagnosis, prognosis, and management of diseases encountered in veterinary medicine.

Self-Quiz Questions

1. Which troponin may not be used to detect myocardial injury and why? *Answer: Cardiac troponin C. Its structure is homologous to an isoform of troponin C found in skeletal muscle, therefore reducing specificity for cardiac injury.*
2. Which is true regarding cardiac troponin I assays?
 - (a) There exists a gold standard assay for cTnI.
 - (b) Each assay targets the same sequence of the cTnI molecule.
 - (c) Results from different assays may be compared.
 - (d) The reference range is the same for all commercially available assays.
 - (e) Human assays may be used in veterinary medicine.

Answer: e

3. List 10 disease states that may cause elevated cardiac troponin levels in veterinary patients.

Answers: see Table 2.

4. An elevated cardiac troponin level indicates which of the following:

- a. Myocardial infarction.
- b. Heart failure.
- c. Myocardial injury.
- d. Cardiac hemorrhage or inflammation.

Answer: c. Cardiac troponins indicate myocardial injury but do not give any information regarding the mechanism of injury.

Footnotes

- ^a Dameron GW, Beck ML, Brandt M, et al. Tissue species specificity of two generations of cardiac troponin T immunoassays. *Clin Chem* 1997;43:S192 (abstract).
- ^b Adin DB, Berger KD, Engel C, et al. Cardiac enzyme concentrations in normal dogs and cats using a bedside analyzer. *Proc 22nd ACVIM* 2004;877 (abstract).
- ^c Oyama MA, Solter PF. Validation of a commercially available human immunoassay (AccuTnI[®], Beckman Coulter Inc.) for the measurement of canine cardiac troponin-I. *Proc 21st ACVIM* 2003 (abstract).
- ^d Diniz P, deMoraes H, Schwartz D, et al. Cardiac troponin I in dogs naturally infected by *Ehrlichia canis*. *Proceedings 23rd ACVIM* 2005 (abstract).
- ^e Herndon WE, Sammarco CD, Schroepe D, et al. Prospective evaluation of plasma cardiac troponin I concentration in cats with mild hypertrophic cardiomyopathy. *Proc 22nd ACVIM* 2004 (abstract).
- ^f Herndon WE, Schroepe D, Drobatz KJ, et al. Plasma cardiac troponin I concentration in cats with cardiac and noncardiac causes of respiratory distress. *Proc 22nd ACVIM* 2004 (abstract).
- ^g Baumwart RD, Orvalho J, Meurs KM. Elevated serum cardiac troponin I levels in Boxer dogs with arrhythmogenic right ventricular cardiomyopathy. *Proc 24th ACVIM* 2006 (abstract).
- ^h Church WM, Oyama MA, Sisson DD, et al. Troponin I elevations in dogs with third degree atrioventricular block. *Proc 24th ACVIM* 2006 (abstract).
- ⁱ Foreman JH, Oyama MA, Tennent-Brown BS, et al. Cardiac troponin-I plasma concentration in normal horses and in horses with arrhythmias and toxicities. *Proc 23rd ACVIM* 2005 (abstract).
- ^j Holbrook TC, Panciera RJ. Biochemical evidence of cardiac injury in horses with cantharidin toxicosis. *Proc 24th ACVIM* 2006 (abstract).

- ^k Linde A, Summerfield N, Clifford CA, et al. Cardiac troponin I levels in pericardial effusion and peripheral blood from dogs with neoplastic versus non-neoplastic etiologies. *Proc 21st ACVIM* 2003 (abstract).
- ^l McKenzie EC, Hinchcliff KW, Williamson KK, Davis MS. Serum chemistry alterations in Alaskan sled dogs during five successive days of prolonged endurance exercise. *Proc 24th ACVIM* 2006 (abstract).
- ^m Rishniw M, Porciello F, Herndon WE, et al. Cardiac troponin I concentrations in dogs and cats with renal insufficiency. *Proc ECVIM-CA:Barcelona* 2004;197.

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