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Review
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Cardiac Troponins in Dogs and Cats

R. Langhorn and J.L. Willesen

Cardiac troponins are sensitive and specific markers of myocardial injury. The troponin concentration can be thought of as a quantitative measure of the degree of injury sustained by the heart, however, it provides no information on the cause of injury or the mechanism of troponin release. Conventionally, the cardiac troponins have been used for diagnosis of acute myocardial infarction in humans and have become the gold standard biomarkers for this indication. They have become increasingly recognized as an objective measure of cardiomyocyte status in both cardiac and noncardiac disease, supplying additional information to that provided by echocardiography and ECG. Injury to cardiomyocytes can occur through a variety of mechanisms with subsequent release of troponins. Independent of the underlying disease or the mechanism of troponin release, the presence of myocardial injury is associated with an increased risk of death. As increasingly sensitive assays are introduced, the frequent occurrence of myocardial injury is becoming apparent, and our understanding of its causes and importance is constantly evolving. Presently troponins are valuable for detecting a subgroup of patients with higher risk of death. Future research is needed to clarify whether troponins can serve as monitoring tools guiding treatment, whether administering more aggressive treatment to patients with evidence of myocardial injury is beneficial, and whether normalizing of troponin concentrations in patients presenting with evidence of myocardial injury is associated with reduced risk of death.

Key words: Biomarker; Cardiac troponins; Companion animals; Myocardial injury.

A biomarker is "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] The field of cardiac biomarkers is continuously evolving. No cardiac marker has yet gained its place in the general veterinary biochemical profile along with, for instance, renal and hepatic biomarkers, and the status of the heart is evaluated mainly through auscultation, ECG, and echocardiography. However, the benefit of applying cardiac biomarkers in the clinical work-up of critically ill patients (with or without heart disease as their primary diagnosis) is being explored and is showing promise. Among such promising biomarkers are the cardiac troponins. The aim of this review is to describe the current knowledge of cardiac troponins as diagnostic and prognostic markers in dogs and cats compared with that in humans.

Abbreviations:

AMI	acute myocardial infarction
APPLE	Acute Patient Physiologic and Laboratory Evaluation
ARVC	arrhythmogenic right ventricular cardiomyopathy
cTnC	cardiac troponin C
cTnI	cardiac troponin I
cTnT	cardiac troponin T
DCM	dilated cardiomyopathy
EDTA	ethylenediaminetetraacetic acid
GDV	gastric dilatation volvulus
HCM	hypertrophic cardiomyopathy
HP	heparin plasma
ICU	intensive care unit
IL	interleukin
IMHA	immune-mediated hemolytic anemia
MMVD	myxomatous mitral valve disease
MODS	multiple organ dysfunction syndrome
PS	pulmonic stenosis
S	serum
SAS	subaortic stenosis
SIRS	systemic inflammatory response syndrome
TNF-α	tumor necrosis factor α

Cardiomyocyte Physiology

The myocardial muscle cell is known as a cardiomyocyte. Each cardiomyocyte consists of multiple myofibrils arranged in parallel (Fig 1). A myofibril consists of a linear series of sarcomeres, the functional contractile unit of the cell. A sarcomere contains two types of protein filaments. Thin actin filaments, each consisting of a double helix of actin monomers, project from so-called Z disks at the ends of the sarcomere. Thick myosin filaments cross-link at the sarcomere center from where they interdigitate with the actin filaments. A myosin filament contains a series of myosin molecules, each with a helical tail and two globular heads.[2–4] During muscle contraction the many globular heads of a myosin filament repetitively interact with actin in a cross-bridge cycle, thereby pulling the thin filament along the thick filament to shorten the sarcomere. During muscle relaxation the sites of actin and myosin interaction are sterically blocked by the protein tropomyosin residing in the actin helical groove and a ternary cardiac troponin protein complex located at regular intervals along the actin filament.[2–6] Troponin consists of 3 subunits which together function as the molecular switch of cardiomy-

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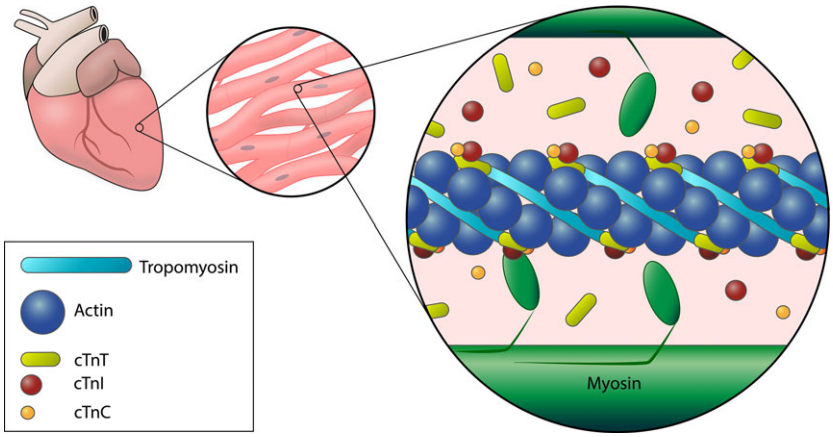

Fig 1. The contractile apparatus of a cardiomyocyte. Interaction of thin (actin) and thick (myosin) filaments is mediated by the troponin complex (troponin I, T, and C) in the presence of calcium. The majority of troponin is structurally bound to the actin filament and its associated protein tropomyosin. A small percentage is found free in the cytosol.

ocyte contraction. Cardiac troponin T (cTnT), the tropomyosin-binding subunit, secures the complex to the thin filament. The additional subunits are responsible for inhibition and promotion of contraction mediated through calcium and ATP. In the absence of calcium, cardiac troponin I (cTnI), the inhibitory subunit, inhibits the hydrolysis of ATP necessary for actin and myosin interaction. Calcium is the initiator of contraction, removing the steric blockage of filament interaction through binding to the calcium-binding subunit, cardiac troponin C (cTnC).[2,3,5,7,8]

Troponin Characteristics

Troponin I and T subunits have tissue-specific isoforms for cardiac and skeletal (slow and fast-twitch) muscle.[9] For troponin C the cardiac isoform and one skeletal isoform are completely homologous,[9] making the subunit unfit to be used as a cardiac marker. In the remainder of the text the term cardiac troponins will, therefore, refer only to cTnI and cTnT. Cardiac troponin T isoforms share more than 50% homology with skeletal isoforms, but can be separately identified.[10,11] Fetal cardiac isoforms are sometimes expressed in diseased or injured skeletal muscle,[12] however, and could, in rare cases, compromise the cardiac specificity of cTnT.[13] Adult heart cTnT has a molecular weight of 37 kDa. Cardiac troponin I is a slightly smaller protein of 24 kDa.[9] It shares <50% homology with skeletal isoforms and contains a unique N-terminal peptide.[10,11] It is not expressed in skeletal muscle during disease states and is, thus, uniquely cardiac.[14–16] The full gene sequence of cTnI in dogs and cats has been determined, and the homology between canine/feline and human cTnI genes is 95 and 96%.[17]

As the troponins are purely intracellular proteins, their presence in circulation reflects intracellular content release from cardiomyocytes.[18] The majority of troponin in the cell is structurally bound in the contractile apparatus and is sometimes referred to as the structural pool, while a minor amount of free cytosolic troponin makes up the so-called cytosolic pool (Fig 1). In humans the cytosolic pool accounts for approximately 6–8% of cTnT[19] and 3–4% of cTnI,[20] whereas one study comparing humans and dogs found 8% cytosolic cTnT in humans, but only 2% in dogs.[21] When destruction of a cardiomyocyte occurs, the cytosolic pool is released quickly with a resultant early rise in circulating troponin. This is followed by the slower release of the structural pool as the contractile apparatus is broken down, resulting in a sustained increase in circulating troponin for days to weeks.[19,20,22,23] It is believed that the cytosolic pool alone can also be independently released.[22,24] A blood sample cannot be used to distinguish between the release of only cytosolic or both cytosolic and structural troponin. Release kinetics are complex as the time to peak concentrations and the size of this increase depend on the cause and mechanism of troponin release.[22,25] However, after a cardiac insult, a rise can be seen within 2–3 h,[26] and peak concentration is frequently reached in 18–24 h.[23]

Six pathobiological mechanisms are believed to be responsible for cardiac troponin release either individually or in combination (Fig 2).[16,27] Three mechanisms refer to cell death with resultant release of both cytoso-

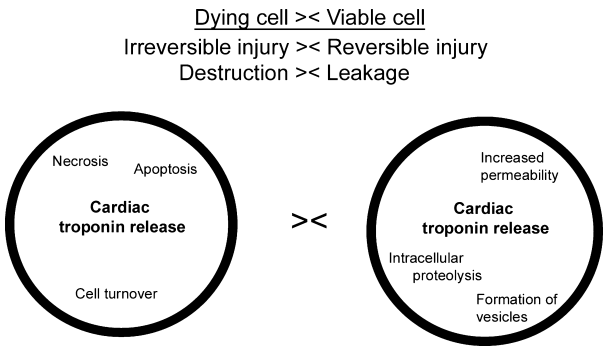

Fig 2. Possible mechanisms of troponin release from dying and from viable cardiomyocytes.

lic and structural troponin. Although troponin release is well-described and always occurs with cell necrosis,[28] it is currently unknown whether troponin release does, in fact, occur with cell apoptosis[29–31] or with normal cardiomyocyte turnover.[32] Three other mechanisms account for the release of only cytosolic troponin without cell death. Troponin molecules can be subjected to intracellular proteolysis with subsequent release of degradation products small enough to pass through the cell membrane.[33] Increased membrane permeability has also been documented in some disease states, resulting in membrane gaps large enough to allow release of the intact protein.[34,35] Finally, it is possible that formation and release of membranous vesicles containing cytosolic troponin can occur from viable cells.[22,36]

Cardiac troponin I is released in several fold higher concentrations than cTnT after a cardiac insult.[8,37,38] This might reflect the smaller molecular size of cTnI, but it has also been suggested that cTnT is more tightly bound to the contractile apparatus.[38,39] Accordingly, presence of increased cTnT and cTnI concentrations appears to reveal more severe cardiac injury than increased cTnI alone.

The half-life of cTnI and cTnT in humans is approximately 2 h when only the cytosolic pool is released, whereas a considerably longer half-life is seen with release of the structural pool caused by a slow breakdown of the contractile apparatus.[22,40] In the dog, the half-life of free (experimentally injected, corresponding to cytosolic) cTnI is 1.85 h,[41] and release kinetics of cTnT have also been found similar to those of humans.[21] Accordingly, release kinetics in dogs and cats are assumed to mimic those of humans. In humans, cardiac troponin is released as the complete ternary complex, as free subunits, but predominantly as a complex of cTnI-cTnC.[42,43] Whether the same applies for dogs and cats is currently unknown. Additionally, cTnI is often released in a phosphorylated form,[44] and troponins undergo proteolysis, oxidation, and reduction in circulation resulting in a variety of different circulating peptides.[19,43]

The pathway of elimination of cardiac troponin has not been clarified. Because of its size it has been thought to be eliminated through the reticulo-endothelial system.[45,46] However, renal clearance of smaller degradation products might also be involved.[47]

Summing up the above, circulating cardiac troponins have many characteristics of an ideal biomarker: cardiac specificity, high sensitivity for injury (high myocardial tissue content and early release after a cardiac insult),[10,22] negligible presence in circulation of healthy individuals, a high dynamic range, persistence in circulation for days post injury, and correlation with severity of injury.[8] Troponins are heart-specific, but it is important to keep in mind that they are not disease-specific. Accordingly, an increased troponin concentration reflects myocardial injury irrespective of its cause.[18] Another important fact is that troponins do not replace advanced cardiac diagnostics (ie, echocardiography and ECG) in evaluating the heart. Mild primary cardiac disease does not always result in cardiac injury, and exclusion of cardiac disease should, therefore, only follow a complete cardiac work-up.[48,49]

Measurement of Cardiac Troponins

The first troponin assays were described in 1987 (cTnI)[50] and 1989 (cTnT).[51] The cTnT assay has only been produced by a single manufacturer, and its sensitivity has increased with newer generations of the assay, the most recent being the 5th generation assay. It has been speculated, however, that some of the assay's cross-species reactivity with animal cTnT might have been lost in the process.[52] The cTnT assay has not been validated for use in dogs and cats, but numerous studies exist in which the various generations of the assay have been used in dogs with satisfactory results (Table 2). Only one study has been published in which the cTnT assay has been applied in cats.[48] For cTnI, multiple assays have been developed by a range of manufacturers, and, accordingly, assays apply antibodies targeting different amino acid sequences.[10] Consequently, results are not easily comparable. Studies comparing different assays have found a reasonable correlation at low concentrations, but a considerable disagreement at high concentrations.[53] This disagreement could be due to the release of a higher percentage of modified troponin peptides in severe cardiac injury, with assays having varying ability to detect these forms.[53] Two cTnI assays have been validated for use in dogs and one in cats, showing acceptable analytical and overlap performance.[54,55]

In recent years increasingly sensitive assays have been introduced, and the term "high-sensitivity" has often been used indiscriminately to include all these assays with a higher sensitivity than the so-called conventional assays. With conventional assays troponin concentrations in healthy individuals were below the detection limit. This meant that the true upper reference limit could not be determined and led to many studies assessing the biomarker qualitatively, with patients classified as "troponin positive" (detectable) and "troponin negative" (undetectable).[56,57] With the sensitivity of current assays, the actual concentrations of cardiac troponins in healthy individuals are becoming apparent, and a quantitative interpretation of troponin concentrations is strongly recommended as troponin concentrations correlate well with both clinical disease severity[58,59] and with the degree of cardiac injury seen histopathologically.[60–62] A definition of the term "high-sensitivity cardiac troponin assay" has recently been published to help navigate in the terminology.[10] Applying the published definition of the term "high-sensitivity", it should be reserved for assays that 1) have an imprecision below 10% at the 99th percentile of a healthy population and 2) are able to measure concentrations below the 99th percentile, but above the detection limit in more than 50% (ideally more than 95%) of healthy individuals. Recent studies using the Siemens ADVIA Centaur CP TnI-ultra assay indicate that this assay might be a true high-sensitivity assay in dogs and cats as it detected cTnI in more than 95% of healthy dogs and cats exam-

ined and had a low imprecision at both high and low concentrations.[48,55,63] The true upper reference limits for dogs and cats (the 99th percentile of a large healthy population) using this or any other assay have, however, not been reported.

Several factors can influence the results of cardiac troponin analysis. Serum and plasma values are significantly correlated, but a tendency toward slightly lower serum concentrations has been documented in dogs,[54] whereas the opposite has been found in humans.[54,64] Separate reference intervals might, therefore, be needed. Troponin reportedly has long-term stability at −70 to −80°C,[8,65] but is not stable at room temperature,[54] refrigerator temperature,[60] or −20°C.[60] Short-term storage (up to 24 h at 4°C and up to 3 months at −20°C) before analysis might be acceptable according to studies in alpacas and in cats.[48,66] The effect of freeze–thaw cycles has varied with different studies, but might also affect troponin concentrations.[60] Interfering substances in the blood such as seen with hemolysis, lipemia, fibrin, increased alkaline phosphatase, rheumatoid factor, heterophilic antibodies, or immune complexes can falsely increase troponin concentrations.[18,67] Circulating troponin autoantibodies can cause negative interference.[68]

Troponin T has not been measurable in healthy dogs and cats in published studies. Reported cTnI concentrations of healthy dogs and cats are shown in Table 1.

Greyhounds and Boxers might have inherently higher cTnI concentrations than other breeds.[78,79] The minute amounts of troponin present in circulation in healthy individuals can likely be attributed to normal cardiomyocyte turnover.[18,80] In humans, male sex has been found to be correlated with increased troponin concentration,[81] but similar findings have not been reported in dogs or cats. In humans,[82] dogs,[52,58,83] and cats,[52] however, mildly increased concentrations have been documented in older individuals, possibly reflecting increased myocardial remodeling with cardiomyocyte loss.[18] Biological variation of both cTnI and cTnT should also be taken into account when interpreting small increases in seemingly healthy individuals.[84,85] Finally, it is noteworthy that extreme exercise can cause transient myocardial injury in both humans and dogs.[86–89]

Table 1. Reported cardiac troponin I (cTnI) concentrations from studies examining at least 20 healthy dogs or cats.

Species	*n*	cTnI (ng/mL)	Sample	% screened
Dog	54	<0.05–0.12	EP	100[69]
	41	<0.03–0.07	HP	25[70]
	176	<0.02–0.15	HP	100[71]
	24	<0.006–0.128	S	100*[72]
	22	0.004–0.095	S	100*[55]
	30	<0.006–0.136	S	100[73]
	26	<0.1–0.17	S	100[74]
	58	<0.01–0.05	EP	100*[75]
Cat	58	<0.05	EP	100[69]
	21	<0.03–0.16	HP	25[70]
	23	<0.003–0.09	S	100*[48]
	20	0.004–0.091	S	100*[55]
	37	<0.02–0.17	HP	100[76]
	33	<0.03–0.16	HP	16[77]

cTnI, Cardiac troponin I; % screened, Percentage of dogs and cats screened free of cardiac disease with echocardiography; EP, EDTA plasma; HP, Heparin plasma; S, Serum.

*The study included hematological and biochemical profiles in the health screening protocol.

Primary Myocardial Injury

Acute Myocardial Infarction

Cardiac troponins are the biomarkers of choice for diagnosis of acute myocardial infarction (AMI) in humans.[28,90] Atherosclerosis of the coronary arteries is generally the underlying cause, and spontaneous rupture of an atherosclerotic plaque leads to platelet aggregation, clotting, vessel stenosis or occlusion, ischemia, and ultimately cardiomyocyte necrosis and myocardial infarction.[28,67] A diagnosis of AMI is made in the presence of a dynamic pattern in cardiac biomarker concentrations (preferably troponins) over 3–6 h with at least one measurement above the upper reference limit (with acceptable precision, that is, a coefficient of variation (CV) <10% at this cut-off) together with clinical, electrocardiographic, or imaging findings consistent with myocardial ischemia.[28] Troponins can be regarded as the clinical pathological correlate of myocardial lesions as evidenced by histopathology, as the size of the infarcted area correlates with cTnT concentration at 72 h postinfarction and with peak cTnI concentration.[61,62] In parallel with the increase in circulating cardiac troponin, a decrease in myocardial tissue troponin content occurs, reflecting release of the myocardial contractile apparatus.[21,91] Interestingly, AMI occurs very rarely in dogs and cats, most likely due to the infrequent occurrence of atherosclerosis in these species,[92,93] and possibly to a well-developed coronary lateral circulation[62,94] which could provide a certain protection against infarction.

There is an independent association between cardiac troponin concentration and case fatality in AMI, and risk stratification according to level of troponin concentration has revealed that even small elevations result in an increased risk of death both short-term and long-term.[95–98] With the increasing use of high-sensitivity assays, it has become apparent that even mild elevations, within the range undetected by conventional assays, are associated with an increased risk of death.[99] Therefore, cardiac troponins are prognostic markers not only in patients with AMI, but also in patients with stable coronary artery disease.

Cardiac Trauma

Cardiac trauma resulting from penetrating chest trauma with cardiac involvement, blunt chest trauma causing myocardial contusions, cardiac surgery, catheterization procedures, or cardiopulmonary resusci-

tation causes direct mechanical damage to the heart.[100–103] In the veterinary clinic, direct cardiac trauma occurs frequently in conditions such as hit-by-car trauma, high-rise syndrome, and thoracic bite injuries.[38,104,105] The diagnosis of traumatic injury to the heart is important as it can lead to cardiogenic shock, acute heart failure, life-threatening arrhythmias, or structural damage.[38,67] Troponin measurement is of value in detecting or ruling out significant blunt cardiac injury.[106]

Primary Cardiac Disease

When evaluating cardiac disease, cardiac injury is not limited to cases with overt myocardial ischemia, but is also very common in those with primary structural cardiac disease. Most human studies in this area have focused on patients in heart failure regardless of cause, whereas studies in dogs and cats have focused more on the individual heart disease, revealing that increased troponin concentrations occur in both congenital and acquired heart diseases (Tables 2 and 3).

Table 3. Myocardial injury in cardiac and noncardiac diseases in cats

Species	Cardiac disease	Noncardiac disease*	cTnI measured	cTnT measured
Cat	HCM		48,77,148–150	48
		Anemia	52,151	
		Neoplasia (mixed)	52	
		Respiratory disease	52,76,152	
		Hyperthyroidism	153,154	

cTnI, Cardiac troponin I; cTnT, Cardiac troponin T, HCM: Hypertrophic cardiomyopathy.

*NB: Not all studies in the noncardiac disease group have ruled out primary cardiac disease as a cause of myocardial injury.

Longitudinal studies have revealed that humans as well as animals with cardiac disease have chronically increased troponin concentrations signifying ongoing myocardial injury.[30,48] Generally, although influenced by the chosen assay, the concentrations of cardiac tro-

Table 2. Myocardial injury in cardiac and noncardiac diseases in dogs

Species	Cardiac disease	Noncardiac disease*	cTnI measured	cTnT measured
Dog	SAS		71	
	PS		107	
	MMVD		49,58,71–74,108–111	109
	DCM		49,71,75,83,108,112,113	112,114,115
	ARVC		71,79,116	
	Myocarditis		117	
	Dirofilariasis		118–120	118
	Cardiac hemangiosarcoma		121	
	Pericardial effusion		39,49,122	39
		Pancreatitis	52	
		Pyometra	123,124	
		Parvoviral enteritis	125,126	
		Leptospirosis	127	
		Leishmaniasis	128,129	
		Babesiosis	130,131	130
		Erhlichiosis	132	
		Systemic inflammation	63	63
		SIRS	133	
		Meningitis-arteritis	134,135	
		IMHA	136	
		Anemia	52	
		Neoplasia (mixed)	52,121,137	115
		Lymphoma	52	
		Meningioma	138	
		Hemangiosarcoma	121	
		Respiratory disease	52,139	
		Brachycephalic syndrome	140	
		Hypoadrenocorticism	52	
		Hyperadrenocorticism	52	
		Snake envenomation	141–143	143
		Heatstroke	144	
		GDV	145,146	146,147

cTnI, Cardiac troponin I; cTnT, Cardiac troponin T; SAS, Subaortic stenosis; PS, Pulmonic stenosis; MMVD, Myxomatous mitral valve disease; DCM, Dilated cardiomyopathy; ARVC, Arrhythmogenic right ventricular cardiomyopathy; HCM, Hypertrophic cardiomyopathy; IMHA, Immune-mediated hemolytic anemia; GDV, Gastric dilatation-volvulus; SIRS, Systemic inflammatory response syndrome.

*NB: Not all studies in the noncardiac disease group have ruled out primary cardiac disease as a cause of myocardial injury.

ponins in primary cardiac disease are only mildly increased (<1 ng/mL) in dogs and cats, and even in those with severe congestive heart failure concentrations rarely increase above 1–2 ng/mL.[48,58,110] Nevertheless, this limited, persistent, and often subclinical cardiac injury seems to play a significant role. Importantly, unlike AMI in which dynamic changes in a patient's troponin concentrations can be used for a diagnostic purpose, troponins have limited value in diagnosing primary heart diseases. This is not only true because noncardiac diseases can cause cardiac injury, but also because an overlap between troponin concentration in healthy individuals and those with cardiac disease has been repeatedly shown.[48,49,71] Those with only mild disease might not have any evidence of cardiac injury, and, consequently, troponins should not be used to either confirm or exclude primary cardiac disease without the simultaneous use of echocardiography and ECG. They might, however, have a diagnostic purpose in distinguishing between cardiac and noncardiac dyspnea in the emergency setting although conflicting evidence exists with more promising results in cats.[76,139,152,155]

The pathogenesis of myocardial injury in primary structural heart disease is believed to be multifactorial, resulting from complex interactions of mechanical, neuro-humoral, inflammatory, and ischemic alterations in the myocardium.[67] These factors reflect underlying disease (eg, coronary artery disease or sarcomeric gene mutations associated with development of hypertrophic cardiomyopathy (HCM)), initiating cause of injury (eg, arrhythmia or treatment with cardiotoxic drugs), and possible amplifying factors (eg, renal dysfunction).[90] Specifically for HCM, mild chronic ischemia has often been suggested as a cause, mediated through an oxygen demand-supply mismatch due to the hypertrophied left ventricle.[156,157] An association between troponin concentration and left ventricular free wall thickness has been reported in both humans and cats,[77,148,158,159] but a recent study failed to show an association between changes in myocardial wall thickness and in troponin concentrations over time.[48] Ongoing myocardial injury in HCM is, therefore, not simply explained by the degree of hypertrophy. Table 4 lists known or suspected factors initiating or contributing to myocardial injury in structural cardiac disease.

Rather than simply being a result of cardiac disease, myocardial injury itself might also be a possible cause of disease progression.[16] The gradual development of heart failure is accompanied by cardiac remodeling as a result of cardiomyocyte death, hypertrophy, and replacement fibrosis.[111,158] As the remodeling progresses, a concurrent reduction in tissue content of troponin occurs.[177] It has been hypothesized that myocardial remodeling increases susceptibility to further cardiac injury,[18] and, in support of this, higher circulating troponin concentrations have been found in humans as well as dogs with myocardial fibrosis.[111,158] Therefore, the consequence of myocardial injury in cardiac disease, independent of its causes and mechanisms, is thought to be a worsening of cardiac function.[16]

Table 4. Possible causes of myocardial injury in primary cardiac disease.

Initiating or contributing cause
Genetically abnormal myocyte function[160,161]
Ventricular hypertrophy (subendocardial ischemia)[156,162]
Fibrosis[111,158]
Hemodynamic overload (altered calcium-handling)[33]
Increased myocardial wall stretch[34,163]
Endothelial/microvascular dysfunction[157,164]
Activation of the renin–angiotensin–aldosterone system[165]
Activation of the sympathetic nervous system (norepinephrine toxicity)[30,166,167]
Toxic effects of inflammatory cytokines[168,169]
Oxidative stress[170]
Troponin autoimmunity[171,172]
Systemic hypotension[46,173,174]
Anemia[175]
Arrhythmia[90,175,176]
Inotropic drugs[46,173,174]

In addition to structural heart disease, other diseases directly involving the heart have been associated with myocardial injury. These include infiltrative cardiac disease, cardiac neoplasia, inflammatory cardiac disease, pericardial effusion, and parasitic cardiac disease (Table 2 lists those described in dogs).

Prognostic capacity of troponins has been detected in humans with HCM,[178] dilated cardiomyopathy (DCM),[179] and heart failure,[180] cats with HCM,[48,150] and dogs with myxomatous mitral valve disease (MMVD),[110,181] cardiomyopathies,[71,75] and a combined group of congenital and acquired heart diseases.[59] Long survival times are generally seen with low troponin concentrations, whereas even patients who are clinically stable but have evidence of myocardial injury are at risk of poorer outcome.[182] Interestingly, not all human studies have found an association between degree of cardiac injury and risk of death,[180] and it is possible that presence rather than degree of injury is the actual prognostic indicator. A recent study of cats with HCM, however, found a prognostically significant increase in cTnT concentrations in nonsurvivors over the course of the study.[48] Similarly, a study in dogs with various heart diseases revealed a significantly higher risk of death with increasing concentrations of cardiac troponins.[59] Accordingly, the value of measuring cardiac troponin longitudinally in the individual is a matter of great interest. Research in humans with chronic heart disease has indicated that for the individual patient an increase over time could be associated with a higher risk of death,[182,183] and conversely, that outcome tends to improve in patients with decreasing concentrations.[182,183] This is supported by a recent study in dogs which showed a decrease in cTnI in dogs with severe MMVD during the first two weeks after initiation of treatment.[73] However, it has been reported in both human and feline research that longitudinal changes in troponin concentrations in a population only slightly improve the discriminative power of the baseline measurements for fatal outcomes.[48,184] Thus, while longitu-

dinal measurements might be of value in monitoring the individual, it appears that a single measurement of cardiac troponin at any time during disease progression provides strong and independent prognostic information.[184]

Secondary Myocardial Injury

Noncardiac Disease

Myocardial injury has been documented in a large number of noncardiac diseases, most of them involving critically ill patients, and especially those with inflammatory diseases and shock[56,185–187] (Tables 2 and 3 lists those described in dogs and cats). Many dogs and cats have mildly increased cTnI concentrations (<1 ng/mL), however, severe myocardial injury is rather common in critically ill dogs and cats with noncardiac disease in the experience of the authors (concentrations >10 ng/mL are relatively common and even concentrations >100 ng/mL have been reported in several cases).[63,143,146] Accordingly, most human studies and an increasing number of veterinary studies focus on populations hospitalized in the intensive care unit (ICU). In most human ICU patients increased troponin concentrations are found already at or within 24 h of admission,[188,189] and a similar tendency has recently been reported in dogs.[190] This fact has led to speculation that in-hospital complications follow rather than precede development of myocardial injury.[189] This supports a theory of myocardial injury as a partial cause rather than purely a result of the patient's critical status.[189]

The pathogenesis of myocardial injury in noncardiac disease is still being investigated, and possible causes are listed in Table 5.

Overall, with the use of high-sensitivity assays, myocardial injury has been detected in a large percentage of the critically ill.[63,204] Importantly, those with and without myocardial injury generally have similar clinical characteristics.[189,205] Measurement of cardiac troponin is, therefore, necessary to discover the involvement of myocardial injury in the individual's critical status.[125]

Myocardial dysfunction is a serious complication of critical disease, most frequently of sepsis, in both humans and animals. It is characterized by ventricular dilatation, hypocontractility, and diminished relaxation.[56,206,207] Myocardial dysfunction is frequently associated with troponin elevations,[56,187,191,195]whereas it remains unclear whether the dysfunction results from, accompanies, or causes myocardial injury.[187,195] Myocardial dysfunction as visualized on echocardiography is reversible with recovery from sepsis.[208,209] This argues against major cardiomyocyte death, and it is believed that cardiomyocyte injury can thus also occur reversibly with release of mainly the cytosolic troponin pool.[198] In human medicine, a necropsy case study of deceased septic patients failed to show irreversible cardiomyocyte necrosis in half of those that had increased cardiac troponin concentrations antemortem,[195] which supports the theory of reversible cardiac injury in some of these patients.

Cytokines are thought to play a very important role in causing myocardial injury in inflammatory disease. Increased troponin concentrations in critically ill patients can be associated with significantly higher tumor necrosis factor-α (TNF-α) and interleukin- (IL-) 6 concentrations,[56] and improvement of echocardiographically visible myocardial dysfunction in one study occurred in parallel with decreases in cTnI, TNF-α, IL-8, and IL-10.[210] Additionally, TNF-α and IL-1 cause reduced cardiomyocyte contractility in *in vitro* studies.[211] In critically ill dogs with systemic inflammation, several cytokines, especially IL-10 and IL-15, are thought to play a role in the events leading to myocardial injury.[63] The mechanism underlying cytokine-mediated injury is believed to be a toxic effect on the cardiomyocyte membrane leading to increased permeability.[35,56] With resolution of this effect, the injury might be reversible.

Intoxication is another cause of increased troponin concentrations. In dogs receiving doxorubicin, a directly cardiotoxic drug, an increased troponin concentration is the first indicator of impending cardiac failure.[137] Envenomation such as seen with snake bite is also a cause of cardiac injury.[141–143] Some venoms contain directly cardiotoxic substances, but systemic inflammation induced by envenomation could also be a possible cause of myocardial injury in these cases.[141,142]

Interestingly, critically ill patients with noncardiac disease often have higher troponin concentrations than patients with severe primary cardiac disease. The cause of this has not been established, but it could be speculated that systemic critical disease that affects the heart most likely affects all cardiomyocytes, whereas primary cardiac disease is more likely to chronically overburden the heart, causing death of consecutive cells over time as part of the ongoing remodeling process.

Even today the case fatality rate of the critically ill (dogs and cats as well as humans) admitted to ICUs is

Table 5. Possible causes of myocardial injury in noncardiac critical disease.

Initiating or contributing cause
Hypotension[186,188,189]
Hypoxemia[36,191]
Anemia[136,191,192]
Fever[193,194]
Tachycardia[188,191]
Increased myocardial wall stress[195,196]
Arrhythmia[188,189]
Endothelial/microvascular dysfunction[194,195,197]
Microthrombosis[198,199]
Pulmonary thromboembolism[200]
Toxic effects of endotoxin[194,195,201]
Toxic effects of inflammatory cytokines[35,56]
Oxidative stress[188,195]
Epi- and endocardial hemorrhage[130]
Reperfusion injury associated with resuscitation procedures[194,195]
Inotropic/vasopressor drugs[187,188,202]
Cardiotoxic drugs (eg, doxorubicin)[137]
Envenomation (eg, snake venom)[203]

high despite increasingly sophisticated diagnostic and therapeutic management. Though, clinically, myocardial injury is often unrecognized, its presence is associated with prolonged morbidity and increased risk of death: Humans and dogs with evidence of myocardial injury have an up to 4 times higher case fatality rate than those with normal troponin concentrations,[56,63,189,191,205] and increased troponins have also been associated with prolonged ICU hospitalization[189,212] (only found in humans, likely because of euthanasia of many dogs with poor prognosis). Cardiac troponins have been shown to contribute independently to established prognostic composite scores in both humans and dogs.[56,63,191] In dogs cTnI provided additional prognostic specificity to the Acute Patient Physiologic and Laboratory Evaluation (APPLE) score without compromising its prognostic sensitivity.[63] It seems that myocardial injury, thus not accounted for by the scores, supplies additional prognostic information to already powerful prognostic scoring systems, a fact that reveals the prognostic strength of the troponins and identifies a possible need for a general inclusion of the status of the myocardium in patient evaluation and prognostic scoring.[197]

Development of multiple organ dysfunction syndrome (MODS) is a frequent complication and cause of death in critical illness.[213] Troponin is not a dysfunction marker, but it correlates well with echocardiographic evidence of myocardial dysfunction[56,187,191,195] and has also been significantly associated with other organ failure in human ICU patients.[191] Inflammatory or hypoxic stimuli that affect the heart will likely affect other organs simultaneously. Thus, the association between increased cardiac troponins and case fatality could be attributable to an independent progression to MODS occurring along with myocardial injury, but a myocardial injury-related increased risk of MODS is also a possibility if impaired organ perfusion follows dysfunction of the myocardium.[191] Increased cardiac troponin in critically ill individuals might, therefore, indicate a critical state of a noncardiac condition, and troponin has been referred to as a marker of multiorgan failure.[214]

In veterinary studies an association between cardiac troponin concentrations and short-term case fatality has been found in dogs with gastric dilatation volvulus (GDV)[145], parvoviral enteritis[125], babesiosis[130], systemic inflammatory response syndrome (SIRS)[133], and systemic inflammation of any cause in dogs without primary structural cardiac disease.[63] Two studies looked into temporal changes of circulating troponin in hospitalized dogs, and these changes did not distinguish short-term nonsurvivors from survivors.[133,190] Larger studies are necessary in order to examine the value of serial troponin measurements in monitoring the individual.

It is still debated whether cardiac troponins have prognostic significance for long-term outcome. Some studies have failed to show an association,[215] whereas other studies indicate that myocardial injury might be a predictor of long-term negative outcome,[196] perhaps even being a partial cause of eventual clinical deterioration. In dogs, an association of admission (cTnT) and peak (cTnI) troponin concentrations with 1-year case fatality has been shown, although considerably weaker than that with short-term case fatality.[190] The study suggested that cTnI was a better short-term predictor, whereas cTnT appeared to predict long-term outcome with greater certainty. Troponins might thus complement each other as prognostic markers. Because of the possible association of long-term outcome with cardiac troponin concentrations, critically ill individuals with evidence of myocardial injury might have a need for close follow-up after hospital discharge. Cardiac troponins could, therefore, play a role in identification of long-term risk patients (animals as well as humans) in the ICU.

Renal Disease

Renal disease poses a dilemma for interpretation of cardiac troponins because it is presently unknown whether the markers are reliable when renal function is compromised. Many human studies have shown an increase in circulating cardiac troponins, especially cTnT, in patients with renal disease.[57,216] The troponin detected is definitely of cardiac origin,[90] but it is an ongoing debate whether its rise is caused by a reduced renal clearance, concurrent cardiac disease, or a deleterious effect on the myocardium caused by uremic toxins.[27,216,217] Troponins have been considered too large for renal elimination in total, but fragments of these molecules also occur in circulation at a size that could possibly be cleared by the kidneys.[45,47] Interestingly, cTnT is often increased in humans with renal insufficiency, whereas cTnI does not appear to be as frequently affected by renal disease.[57,217,218] In dogs and cats, however, two studies found frequent elevations of cTnI in azotemic animals.[219,220] These studies, unfortunately, did not include echocardiographic examination in their protocols, but one reported histopathological findings of cardiac pathology in three of four necropsies, suggesting a concurrent cardiac disease as a cause of troponin release.[219] A high risk of death or cardiac events is known to exist in humans with end-stage renal disease and increased concentrations of troponins,[57,90] a fact which further supports this theory. Importantly, troponins have been shown to retain their prognostic ability in humans even after adjustment for renal function,[221] but, as a rule, it is still recommended to interpret an increased troponin concentration cautiously in the presence of renal disease.

Perspectives

Cardiac troponins are quantitative markers of myocardial injury which can be reliably measured in dogs and cats and which provide prognostic information, seemingly irrespective of clinical presentation (acute or chronic), suspected type of myocardial injury (reversible or irreversible), and underlying disease (cardiac or noncardiac). Clinically, the greatest strength of

troponins can be summed up in their exceptional negative predictive value in both cardiac and noncardiac disease with low troponin concentrations generally associated with improved chances of survival. Increased concentrations, on the other hand, identify individuals at increased risk of death.

In veterinary medicine, cTnI has generally been the chosen marker. Cardiac troponin T is less sensitive than cTnI, being released only with more severe cardiac injury. As dogs and cats rarely develop AMI, and primary cardiac disease is often associated with low-grade myocardial injury, cTnI became the obvious choice in the initial studies of troponins in animals which involved mainly this disease category. Today more sensitive cTnT assays are available as well, and the marker is becoming increasingly available for veterinary research. Cardiac troponin I and cTnT might differ slightly in their prognostic potential, but overall the two markers are highly correlated sources of similar information, and clinically, it is considered sufficient to measure one or the other.[60] With the prognostic importance of even minimal myocardial injury, the authors recommend cTnI as the cardiac injury marker of choice in dogs and cats. Publication of upper reference limits for relevant assays based on large healthy populations is warranted for optimal use.

There are many possible causes of cardiac injury, each of which leads to a rise in circulating cardiac troponins through one or more mechanisms of troponin release. However, questions still in need of answering include whether reversible and irreversible injury occur as two separate entities in different disease processes or occur simultaneously; whether cardiac disease and noncardiac disease each might be most likely to cause either reversible or irreversible injury; and whether one is "worse" than the other from a prognostic point of view. Shedding light on the pathophysiology behind myocardial injury in renal disease is also crucial in order to be able to apply the marker to all disease categories.

Researchers increasingly recommend using a multimarker approach in the evaluation and prognostication of any patient.[181] The combined potential of troponins with markers of hemodynamic stress on the heart (eg, natriuretic peptides), other markers of cardiomyocyte injury (eg, fatty acid binding protein 3), and markers of cardiac remodelling (eg, matrix metalloproteinases) is of high importance in cardiology and requires further research.[18] In noncardiac disease, the contribution of cardiac troponins to prognostic scoring systems shows great promise, and it is believed that inclusion of troponins in future scores will have both clinical and research benefits. As assays hopefully become increasingly available, and costs are reduced, it is also considered worthwhile to include measurements of cTnI among the routine biochemical variables examined in the clinical work-up of dogs and cats, just as biochemical variables reflecting renal and hepatic status are routinely measured.

Because of its possible reversible nature, it has been discussed whether patients with evidence of myocardial injury might benefit from more aggressive treatment, in which case normalizing of troponin concentrations might be associated with an improved outcome.[189,222] At this point in time, whether troponins are useful in monitoring effects of intervention, and whether administering more aggressive treatment to individuals with evidence of myocardial injury is beneficial, are still unanswered questions. Further studies, for example, using troponins as surrogate endpoints for clinical trials, are necessary to examine whether normalizing of troponin concentrations in cases presenting with evidence of myocardial injury is associated with improvement in outcome.[18] It is hoped that treatment strategies will be developed which have the ability to reduce the risk associated with myocardial injury.

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