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THE CARDIAC BIOMARKERS TROPONIN I AND CREATINE KINASE MYOCARDIAL BAND IN CAMELS (*Camelus dromedarius*)– A REVIEW

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ABSTRACT

Cardiac biomarkers are helpful in the early detection, diagnosis and prognosis of cardiac and non-cardiac diseases. Cardiac troponin I (cTnI), one of these biomarkers, is a highly sensitive and specific marker for myocardial injury in humans and in veterinary medicine. cTnI elevates in serum after acute myocardial injury because of leakage from the damaged myocardial cells. Creatine kinase myocardial band (CK-MB), another cardiac biomarker, has been found high following exercise. With chest pain in humans, the level of CK-MB increases and subsequently declines to normal range. In animals, however, a rise in CK-MB is not always indicative of acute myocardial infarction. cTnI therefore is currently the preferred cardiac biomarker in human medicine for assessing myocardial damage, with absolute specificity and higher sensitivity. The degree of increase in cTnI has been shown to correlate with the extent of myocardial damage and with survival in humans and animals. In camels, the evaluation of cardiac disease can be challenging; the patient history, clinical data and routine blood examination are often nonspecific. Therefore, blood-based biomarkers that are capable of detecting and staging cardiac disease are a subject of considerable interest. Myocardial damage, as demonstrated by elevated cTnI in blood, appears to be a common sequel to a wide variety of both primarily cardiac disease and of other diseases that do not primarily involve the cardiovascular system. This review was written to shed light on the commonly used cardiac biomarkers in camel medicine cTnI and CK-MB and its clinical significance.

Key words: Camels, cardiac biomarkers, cardiac troponin I, creatine kinase–myocardial band, heart diseases

Biomarkers can indicate physiological (such as growth and aging), or pathophysiological processes that occur with disease (e.g. cardiac damage and heart failure). Among these biomarkers, cardiac biomarkers can be helpful in the management of cardiac and non-cardiac diseases (Jesty, 2012). In humans, cardiac biomarkers aid in the early detection, diagnosis and prognosis of cardiac diseases (Ginsburg and Haga, 2006).

Among cardiac biomarkers, cardiac troponin I (cTnI), is a highly sensitive and specific marker for myocardial injury in humans (Ladenson, 2007; Reagan *et al,* 2013) and in veterinary medicine (Wells and Sleeper, 2008; Fonfara *et al,* 2010; Tharwat, 2012; Tharwat *et al,* 2012; Tharwat *et al,* 2013a,b,c,d; Tharwat and Al-Sobayil, 2014a,b,c; Tharwat *et al*, 2014a,b; Tharwat, 2015; Tharwat and Al-Sobayil, 2015). The serum concentration of cTnI elevates after acute myocardial injury because of leakage from the damaged myocardial cells (O'Brien *et al*, 2006). In veterinary medicine, cTnI has also a high sensitivity and specificity in animals with diseases of cardiac and noncardiac origin (O'Brien *et al,* 2006; Wells and Sleeper, 2008). The degree of increase in cTnI has been shown to correlate with the extent of myocardial damage and with survival in humans (Stanton *et al*, 2005) and animals (Oyama and Sisson, 2004; Fonfara *et al*, 2010).

Creatine kinase myocardial band (CK-MB) is another cardiac biomarker that has been reported to increase with exercise (Mamor *et al,* 1988; Rahnama *et al,* 2011). With chest pain in humans, the level of CK-MB reaches its peak at 10-24 hours subsequent to the initial injury and declines to normal range within 72-96 hours (Volz *et al,* 2012). Chronic occlusion of the coronary artery significantly increases the serum levels of CK-MB (Sharkey *et al,* 1991). However, a rise in CK-MB is not always indicative of myocardial damage; it has been elevated in patients with acute skeletal muscle trauma, dermatomyositis,

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polymyositis, muscular dystrophy and renal failure (Erlacher *et al,* 2001). Therefore, cTnI is nowadays the superior biochemical parameter in humans for assessing myocardial damage, with absolute specificity and sensitivity than CK-MB (Alpert *et al,* 2000; Collinson *et al,* 2012).

In camels, heart diseases include pericarditis, vegetative valvular endocarditis, hypertrophic cardiomyopathy necrotic myocarditis, congenital defects including septal defects, patent ductus arteriosus, transposition of the aorta and pulmonary artery, persistent aortic trunk, and persistent right aortic arch and sarcocystosis (Fowler, 2010). These are mostly diagnosed at slaughterhouses or incidentally discovered during postmortem (Fowler, 2010). The diagnosis of camel heart disease is a challenging task especially when typical clinical signs of heart failure are absent. Therefore, blood-based biomarkers capable of detecting and staging diseases of cardiac and non-cardiac origin are a subject of considerable interest in camels.

This review was designed to shed light on the commonly used cardiac biomarkers in camel medicine cTnI and CK-MB as indicators of cardiac injury.

Cardiac troponins

Troponins are 3 distinct myofibrillar proteins (I, C, and T) that regulate the calcium-mediated interaction between actin and myosin in both cardiac and skeletal muscle (Babuin and Jaffe, 2005). Of troponins, cTnI is the only one that is expressed in the myocardium. The amino acid sequence for cTnI is highly conserved among mammalian species so human kits can be used; however, the references and values can differently depend on the analyser used since they can give different results (Apple *et al,* 2008). Mildly elevated concentrations of cTnI alone will unlikely lead to a definitive diagnosis, but together with the clinical presentation and findings on ECG and echocardiography it can become an important marker for myocardial disease. On the other hand, marked elevations of cTnI alone could be considered as a strong indication of myocardial disease (Nostell and Haggstrom, 2008). However, A constant elevation of cTnI indicates persistent damage to the cardiomyocytes (O'Brien *et al,* 2006; Wells and Sleeper, 2008), and the degree of elevation has been shown to be correlated with the extent of myocardial damage and with survival in humans (Stanton *et al,* 2005) and in animals (Fonfara *et al,* 2010; Tharwat, 2012; Tharwat and Al-Sobayil, 2014a).

Low to non-detectable cTnI levels have been found in healthy mammals (Baker *et al,* 2011). Elevated cTnI has been reported in calves (Peek *et al,* 2008), cattle (Varga *et al,* 2009; Mellanby *et al,* 2009), horses (Kraus *et al,* 2010; Holbrook *et al,* 2011), foals (Slack *et al,* 2005), dogs (Herndon *et al,* 2002; Spratt *et al,* 2005) and lambs (Gunes *et al,* 2010) indicating that elevations in the blood would serve as useful biomarkers of myocardial injury.

Creatine kinase myocardial band

Creatine kinase is a dimeric enzyme found primarily in brain and muscle tissue. Three isoforms are known for creatine kinase: BB, MM, and MB. The isoform BB is found in the brain. The second isoform MM is found primarily in skeletal muscles. Cardiac muscles also primarily contain the MM isoform, but with higher amounts of MB, typically around 20% of CK activity (Moss and Henderson, 1994). In humans, serum from healthy individuals typically contains the MM isoform and a small amount of the MB isoform. CK-MB can be released into the bloodstream by a number of actions, including skeletal muscular injury and myocardial damage.

Cardiac biomarkers in camel medicine

In humans, nonprimary cardiac diseases can induce myocyte damage leading to increased serum troponin concentrations (Mahajan *et al,* 2006). For example, study of 144 patients with increased cTnI concentrations identified a wide range of diseases that can be associated with increased cTnI concentrations including sepsis, collagen vascular disease, gastrointestinal bleeding, pulmonary embolism, diabetic ketoacidosis, and chronic obstructive pulmonary disease (Mahajan *et al,* 2006). Other studies in dogs with gastric dilatation and volvulus and in dogs and cats with azotaemia renal failure and in dogs with non-cardiac systemic disease had increased cTnI concentrations indicating cardiomyocyte degeneration and necrosis (Schober *et al,* 2002; Porciello *et al,* 2008). Similar findings have been found in cattle with noncardiac and intrathoracic diseases, even though no gross cardiac abnormalities were detected at postmortem examination (Mellanby *et al,* 2009). Most of these studies concluded that the heart may be a non-target tissue bystander in these processes that leads to elevations in cTnI, but there is little strong data to definitively identify the mechanism.

In recent years, our research group has observed significant elevations of cTnI in camel blood

following prolonged recumbency (Tharwat, 2012), general anaesthesia (Tharwat *et al,* 2013a), long road transportation (Tharwat *et al,* 2013b), racing (Tharwat *et al,* 2013c), tick infestation (Tharwat and Al-Sobayil, 2014) and after stimulation by electroejaculation (Tharwat *et al,* 2014a) and following parturition stress (Tharwat, 2015). In humans, studies on the prognostic significance of cTnI concentrations in patients with non-primary cardiac disorders have found that cTnI can predict disease outcome. Recently, in cattle with haemolytic anaemia, long-term follow-up of serum cTnI concentrations was valuable in assessing the relationship between anaemia and myocyte damage (Fartashvand *et al,* 2012). In addition, an elevated serum concentration of cTnI has been used as a poor prognostic indicator in goats with pregnancy toxaemia (Tharwat *et al,* 2012), in downer camels (Tharwat, 2012) and in camels infested with ticks (Tharwat and Al-Sobayil, 2014a).

In a study published recently in camels with tick infestation (Tharwat and Al-Sobayil, 2014a), 14 recovered out of 15 camels (93.3%) had a serum concentration of cTnI lower than 1.0 ng/ml, and the remaining camel (6.7%) had a higher cTnI concentration (1.65 ng/ml). In the same study, all 8 died camels had a serum concentration above 1.22 ng/ml, with a maximum value of 5.22 ng/ml (Fig 1). Therefore, it was assumed that the increased serum concentration of cTnI above 1.0 ng/ml at initial examination was a bad prognostic indicator in the camels with tick infestation. Elevated serum concentration of cTnI has been reported in cattle with theileriosis (Fartashvand *et al,* 2013).

In camels infected with *Trypanosoma evansi* (n=74), the values of cTnI and CK-MB were significantly higher in *T. evansi* infected camel compared to controls (n=20) (El-Deeb and Elmoslemany, 2015). Successfully treated camels (n=43) had lower levels of cTnI and CK-MB compared to camels with treatment failure. cTnI showed better sensitivity and specificity than CK-MB. Similar in cattle, serum concentration of cTnI was significantly higher (P=0.003) in cattle with theileriosis (mean: 0.028 ng/mL; range: 0.005–0.21 ng/mL) compared to controls (mean: 0.011; range: <0.005–0.09 ng/mL) (Fartashvand *et al,* 2013). Anaemia followed by hypoxia and increased oxygen consumption by the myocardium during a prolonged period of tachycardia will possibly cause myocardial injury and subsequent increased serum concentration of cTnI in animals with parasitic infestation (Fartashvand *et al,* 2012; Tharwat and Al-Sobayil, 2014a).

In a study carried out on 33 long-standing recumbent camels (Tharwat, 2012), marked elevations of cTnI in the downer camels was considered as a strong indication of myocardial damage and was used to predict treatment outcome and mortality (Fig 2). In the same study (Tharwat, 2012), the serum concentration of cTnI in the 11 cured camels was 0.05±0.02 ng/ml. In the remaining 22 camels that did not recover, the serum concentration of cTnI was 0.53±0.64 ng/ml. A recent study in dairy cows with downer cow syndrome concluded that cTnI concentrations could help to rapidly identify cows that have poor chances of recovery and would benefit from a more aggressive treatment or euthanasia (Labonte *et al,* 2018).

In 25 camels transported for a 5km round trip, the mean cTnI concentration was 0.032±0.023 ng/mL comparing to resting values of less than 0.08 ng/mL

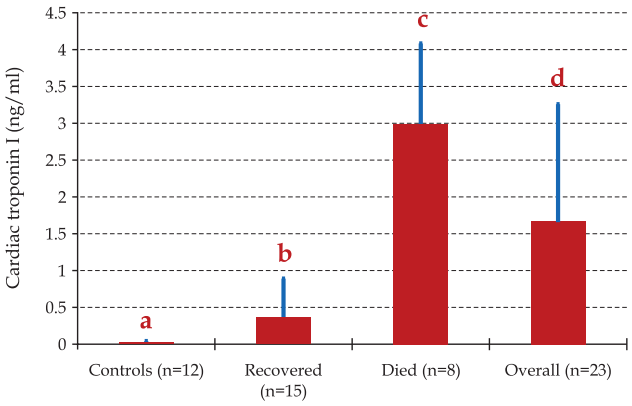

Fig 1. Mean serum concentrations of serum cardiac troponin I in camels with tick infestation. [a,b,c,d] Differ significantly (Tharwat and Al-Sobayil, 2014a).

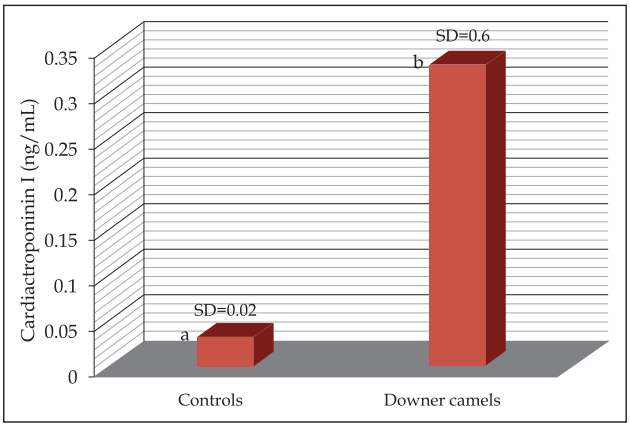

Fig 2. Cardiac troponin I values in downer camels compared to control healthy camels. [a,b] different letters indicate a significant difference (P=0.019). SD = standard deviation (Tharwat, 2012).

(Tharwat *et al,* 2013b). The cTnI concentration was significantly higher (P<0.001) in all the 25 camels compared to values before transportation. The CK-MB concentration in the same camels was 0.19±0.05 ng/mL compared to resting values of less than 0.33 ng/mL. Only in 3 of the 25 camels (12%), the CK-MB values were above values before transportation and no statistical differences were recorded (Fig 3). Transportation is a well-known stressor that has adverse effects on livestock production and health including muscular damages, generating concerns of an economic as well as a welfare-related nature (Tharwat *et al,* 2013b).

Following a 5 km race in 23 camels, 91.3% of the camels had increases in serum cTnI concentrations, while concentrations remained unchanged in 8.7% (Tharwat *et al,* 2013c). The cTnI concentration (median 0.06 ng/mL; range, 0.03–0.15 ng/mL) was significantly higher (P<0.001) than the pre-race values (median 0.04 ng/mL; range, 0.01–0.07 ng/mL). Twenty-four hours post-race, the cTnI concentrations had returned very nearly to their pre-race values (median 0.04 ng/mL; range, 0.00–0.09 ng/mL) and were not significantly different (P=0.35) from the pre-race values (Fig 4). Following the 5 km race, increases in CK-MB mass were seen in 17.4% of the camels, with no changes in 4.3% and decreases in 78.3%. The CK-MB mass (median 0.41 ng/mL; range, 0.19–0.60 ng/mL) did not differ significantly (P=0.84) when compared to the pre-race values (median 0.42 ng/mL; range, 0.32–0.55 ng/mL). Twenty-four hours post-race, the CK-MB mass concentrations (median 0.41 ng/mL; range, 0.15–0.55 ng/mL) did not differ significantly (P>0.05) compared to pre-race or immediate post-race values (Fig 4). Post-exercise cTnI release and clearance were also reported in normal Standardbred racehorses. All horses experienced an increase in cTnI post-exercise, with peak occurring 2-6 h post-exercise (Rossi *et al,* 2019). In a study carried out on 32 racing greyhounds following a 7 km race, 31/32 greyhounds showed increases in cTnI concentrations which were significantly higher than the pre-race concentrations (P<0.0001). cTnI concentrations dropped back 24h post-race to values were not significantly different from the pre-race concentrations. Only 5/32 greyhounds showed mild increases in CK-MB concentrations but these were

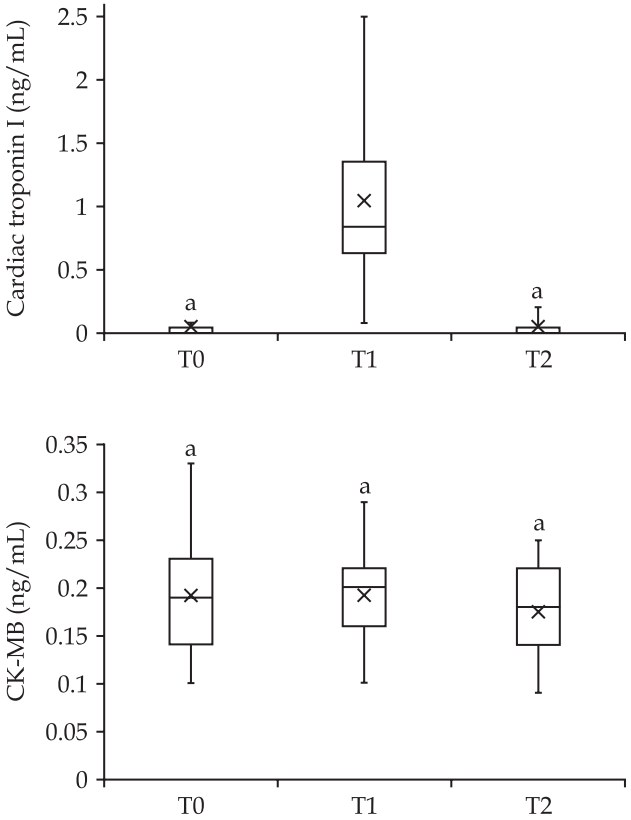

Fig 3. Box and "whisker" plots of cTnI and CK-MB values in camels before (T0), within 2h of transportation (T0) and 24h after transportation (T2). Values with different letters differ significantly (P<0.001) (Tharwat *et al,* 2013b).

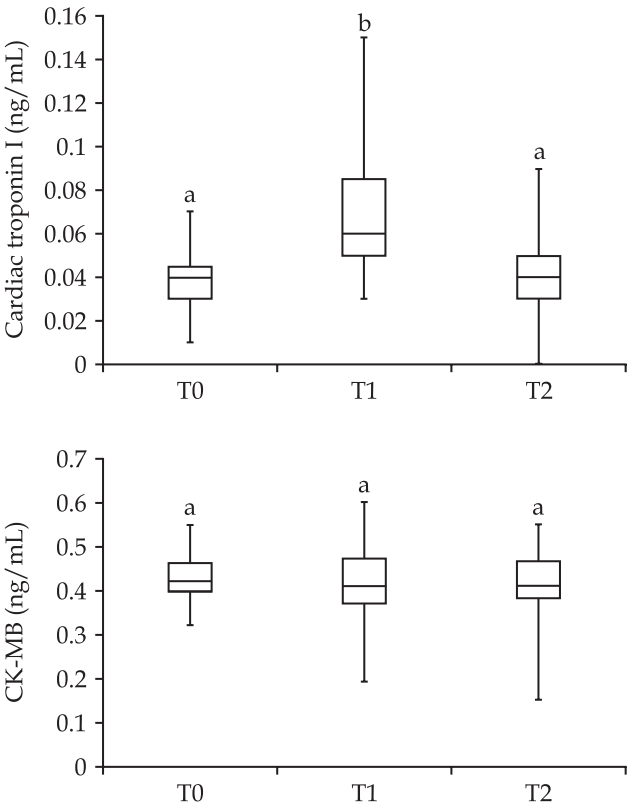

Fig 4. Cardiac troponin I values in camels before (T0), 2h after (T1) and 24h after (T2) a 5 km race. [a,b] different letters indicate a significant difference (P<0.05) (Tharwat *et al,* 2013c).

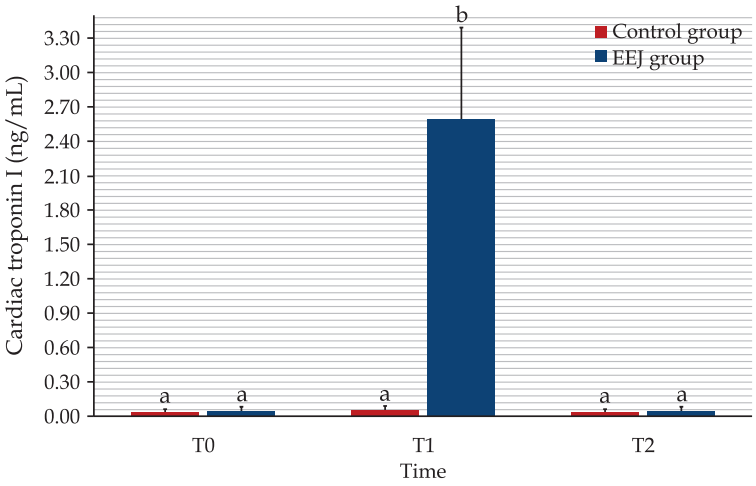

Fig 5. Effect of stimulation by electroejaculation (EEJ) on cardiac troponin I in male dromedary camels (mean ± SD, n=20) compared to control group (n=10). T0: just before EEJ; T1: directly after EEJ; T2: 24h after EEJ. [a,b] Values differ significantly (P=0.0001) (Tharwat *et al,* 2014a).

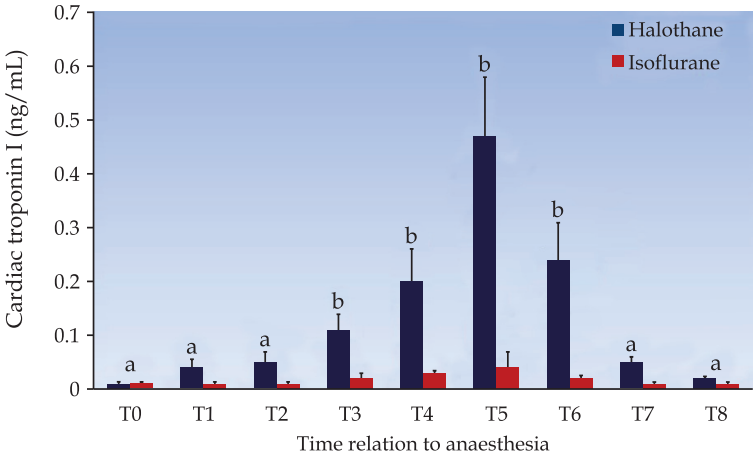

Fig 6. Pre-anesthetic, anesthetic and post-anesthetic serum concentration of cardiac troponin I (means ± SEM) in camels (n = 6) undergoing isoflurane and halothane anesthesia.T0, immediately before anesthesia; T1, 20 min after xylazine administration; T2, 20 min after ketamine administration; T3, 60 min during inhalation anesthesia; T4, 40 min of recovery; T5, 80 min of recovery; T6-T8, 24 h, 48 h and 72 h after anesthesia. bDiffers significantly between the two anesthetic agents at P<0.05 (Tharwat *et al,* 2013a).

not significantly different from the pre-race values (Tharwat *et al,* 2013e).

After EEJ (electroejaculation) in 20 male camels, the mean serum concentration of cTnI had increased significantly in all camels following EEJ, but not in controls (Fig 5) (Tharwat *et al,* 2014a). However, at 24h post-EEJ, the serum concentration of cTnI did not differ significantly compared to baseline values. Because the serum concentration of cTnI increased significantly in the EEJ camels, it is therefore recommended that the status of the cardiovascular system of the camel be checked prior to applying the EEJ technique. In another study, the serum concentration of cTnI has been increased significantly (P=0.0001) in 18 male camels with erectile dysfunction compared to 10 healthy controls (Derar *et al,* 2017). The rise of cTnI in the males with erectile dysfunction is probably indicative of myoctitic damage which support the concept that failure to erect the penis or maintain an erection is primarily related to the inability to maintain a closed blood circuit at the penile tissue (Barassi *et al,* 2015)

Cardiac injury had been reported in camels with halothane and isoflurane general anaesthesia (Tharwat *et al,* 2013a). In this study, camels had mildly and significantly elevated cTnI with isoflurane and halothane anaesthesia, respectively; however, in the isoflurane group the upper limit for the camel reference range was not exceeded (Fig 6). The cause of the cardiac cell compromise during halothane anaesthesia was likely due to extreme changes in heart rate and blood pressure, and the increased arterial concentration of PCO_2. Based on the results of this study, it was concluded that isoflurane is superior to halothane as an inhalation anaesthetic in camels especially in those with suspected cardiac diseases. The influence of general anaesthesia on serum concentration cTnI in healthy dogs has also been studied (Verbiest *et al,* 2013). Fifty-five percent of the dogs had a post-anaesthetic increase of cTnI concentration relative to their pre-anesthetic cTnI concentration, whereas a decrease was observed in eleven percent of the dogs.

Conclusions

In camel medicine cardiac biomarkers are an exciting and growing science. The most established applications involve the use of cTnI to help detect early myocardial injury following prolonged recumbency, after general anaesthesia, secondary to long road transportation, following racing, as an influence of parasitic infestation and after semen collection by electroejaculation. The cTnI assay helps to rapidly determine the prognosis in camels and thereafter deciding either continuing treatment or euthanasia. CK-MB is a less sensitive biomarker

for myocardial activity when compared with cTnI in detecting myocardial injury. Finally, cardiac biomarker tests are complementary to existing cardiac diagnostic testing and should be interpreted in the context of the overall clinical picture rather than being used as a stand-alone test.

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