Evaluation of Serum Cardiac Troponin-I Concentration and Cardiac Enzyme Activities in Neonatal Calves with Sepsis

Kirbas, A.,[1*] Degirmencay, S.,[2] Kilinc, A.A.[3] and Eroglu, M.S.[2]

[1]Department of Internal Medicine, Faculty of Veterinary Medicine, Bozok University, Yozgat, TURKEY.
[2]Department of Internal Medicine, Faculty of Veterinary Medicine, Atatürk University, Erzurum, TURKEY.
[3]Directorate of Poultry Research Institute, Ministry of Agriculture and Forestry, Ankara, TURKEY.

* **Corresponding author:** Assoc. Prof. Akin Kirbas (DVM, Ph.D), Department of Internal Medicine, Faculty of Veterinary Medicine, Bozok University, Yozgat, TURKEY; **Phone:** +90 354 502 0055; **Fax:** +90 354 502 0054; **E-mail:** akindahiliye55@yahoo.com; akin.kirbas@bozok.edu.tr

ABSTRACT

Sepsis is a serious condition with high mortality, which is frequently encountered in neonatal calves. Cardiovascular abnormalities due to sepsis frequently occur, therefore early diagnosis and treatment of sepsis is of great importance in the survival of calves. Cardiac troponin I (cTnI) is considered to be an excellent biomarker in the diagnosis of cardiac damage due to its properties such as rapid release and high tissue specificity to the heart. The present study aims at evaluating the concentration of serum cTnI and cardiac enzyme activities (CK-MB, LDH and AST) in neonatal calves with sepsis. To this end, 15 neonatal calves with sepsis (sepsis group, SG) and 10 healthy neonatal calves (control group, CG) were used. From serum samples, cardiac enzyme activities (CK-MB, LDH and AST) and concentrations of urea and creatinine (Cr) were determined using an autoanalyzer using commercial kits, while cTnI concentration was determined by the one-step sandwich method of a commercial immunoassay system. The parameters of SG were statistically significantly higher than CG group: total leukocyte (WBC) and neutrophil (NEU) counts ($P<0.01$), cTnI concentration ($P<0.01$), CK-MB, LDH and AST activities ($P<0.05$) and concentrations of UREA and Cr ($P<0.001$). Sensitivity values for myocardial damage were for cTnI: 100%, CK-MB: 66.7%, LDH and AST: 53.3%. The areas under the ROC curve were 0.98, 0.72, 0.69 and 0.80 for cTnI, CK-MB, LDH and AST respectively. In conclusion, sepsis may cause myocardial damage in neonatal calves. In this study, we have investigated the performances of cTnI, CK-MB, LDH and AST markers in the diagnosis and prognosis of myocardial damage and found that cTnI is superior to other markers based on both inter-group comparisons and ROC analyses. It should be taken into consideration by veterinarians that when endotoxemia develops in animals with sepsis, heart damage can occur which intensifies gradually. Based on the parameters tested in this study, this damage can be best indicated by cTnI. Further studies should be designed with various emerging cardiac parameters, to test their efficiency and sensitivity, such as FAPB3 also known as Heart-type Fatty Acid binding protein. Histopathological examination can also be considered in cases where the animals do not survive.

Keywords: Cardiac Enzymes; Cardiac Troponin I; Myocardial Injury; Neonatal Calf; Sepsis.

INTRODUCTION

Sepsis, is a major health problem in calves less than 2 weeks of age with a high mortality rate (1, 2), and is defined as the systemic inflammatory response syndrome (SIRS) to an active infectious process (3-5). Decreased or failed passive transfer (FPT) of immunity and exposure to virulent pathogens are two of the important risk factors for the development of sepsis. The most frequent etiological agent is

Escherichia coli (2, 6, 7). Sepsis is usually observed in multiple organs and most commonly affects the respiratory and gastrointestinal systems with rapid and often fatal progression of the disease. Early clinical signs are vague and nonspecific (2, 8) and laboratory values may be varying (6, 9). In human medicine, cardiovascular abnormalities are frequent in sepsis and septic shock which may result in a myocardial injury related to a non-coronary artery disease (10-12).

A meta-analysis on the prognostic value of troponin in sepsis was published by Bessière *et al.* where they reported that the increase in troponin was associated with high mortality in patients with sepsis (13). In sepsis cases, the mechanism of the increase in cTnI is not entirely understood. Myocardial depression and ventricular dysfunction are assumed to occur with the release of cytokines and endotoxin (14-17). Tumor necrosis factor-α (TNF-α) and interleukins (IL) which are myocardial depressants were found to be released in the event of sepsis (16, 18). TNF-α causes an increase in the permeability of endothelial monolayers which would allow the macromolecules and lower molecular weight solutes pass through (19). Similar permeability changes, leading to cytoplasmic cTnI leakage without cardiomyocyte necrosis can also occur at the level of myocardial cells (12, 20). Increased troponin in sepsis cases or SIRS may be caused by incomplete cardiomyocyte apoptosis, with irreversible cardiomyocyte damage due to hypoxia or activated clotting factors (21).

Cardiac troponin (cTn) is a myofibrillar protein that controls the contractions of the heart. It has two forms; cardiac troponin I (cTnI) and cardiac troponin T (cTnT) that are both used in the diagnosis of cardiac damage in humans and animals. cTn concentrations remain high as long as cardiac injury persists. cTn has high tissue specificity, diagnostic sensitivity, low basal blood concentration, rapid release, and persistence in the blood. Therefore, it is considered to be the gold standard biomarker of cardiac damage (22-25). Troponin analyses are found to be more sensitive and specific than creatine kinase-myocardial band (CK-MB) and lactate dehydrogenase (LDH) assays due to the fact that cardiac troponin is limited and specific to heart tissue, however CK-MB is expressed in several other tissues, like skeletal muscle and digestive tract. Therefore, cardiac troponin is more suitable for the specific detection of cardiac damage (26). This is due to the fact that cTn concentration which is present in the contractile apparatus is 13-15 times higher than CK-MB quantity per gram of myocardium. The blood levels of cTn rise within 4-12 hours after acute myocardial damage; peak at 12-48 hours, and continues to be high for 2 weeks (24).

It is proposed that cTnI could be a useful marker for the detection and quantification of an active myocardial damage in cattle (25). However, in veterinary medicine, and neonatal ruminant practice, there are no data available which show the levels of serum cTnI and cardiac enzyme activity (CK-MB, LDH and AST) in neonatal calves with sepsis. Therefore, the present study was aimed to investigate the concentration of serum cTnI and cardiac enzyme activities in neonatal calves with sepsis.

MATERIALS AND METHODS

Animals and study design

Fifteen Swiss Brown calves with sepsis were presented to the Large Animal Clinic of Atatürk University, Faculty of Veterinary Medicine, 1 to 2 days after showing signs of disease. These calves were assigned to the sepsis group (SG). Ten clinically healthy Swiss Brown calves were taken from the dairy farm of the Faculty of Veterinary Medicine and served as the control group (CG). All calves were 1 to 10 days old.

On clinical examination, body temperature (RT), heart rate (HR) and respiratory rate (RR), condition of mucous membranes, degree of dehydration, suckling reflex and the features the faeces of sick calves were inspected and recorded. Laboratory and clinical findings were recorded as described by Fecteau *et al.* (2) and Lofstedt *et al.* (6) and were used for the diagnosis of sepsis in the calves. Along with the presence or suspicion of infection, the SIRS criteria were evaluated for sepsis. A diagnosis of SIRS was made when at least two of the following criteria were fulfilled: leukopenia or leucocytosis (reference value, 4-12x10^3/μL), hypothermia and hyperthermia (reference value; 38.5-39.5°C), bradycardia or tachycardia (< 90 or > 120 beats per minute), and tachypnoea (> 36 breaths per minute).

Sample collection

Blood samples were collected by direct puncture of the vena jugularis of all calves into EDTA vacutainers (Vacutainer, K2E 3.6 mg, BD, UK) and plain tubes (Vacutainer, BD, UK) for the analyses of the haematological parameters, cardiac biomarkers and serum biochemistry parameters. Serum samples were stored -80°C until such analyses.

Haematological analyses

White blood cell (WBC) and neutrophil (NEU) counts and hematocrit (HCT) levels of the calves were determined by a hematologic analyser (Abacus Junior Vet5, Hungary).

Biochemical analyses

The serum cTnI concentrations were determined using a commercial immunoassay system in compliance with the one-step sandwich method (Unicel Beckman Coulter Access II, USA). The homology of Troponin I sequence between humans and cattle has been found to be greater than 96% (27), thus this assay was considered reliable for use in calves. The immunoassay system can measure troponin in a range of 0.01-100 ηg/mL. Serum CK-MB, LDH and aspartate aminotransferase (AST) activities, the concentrations of urea and creatinine (Cr) were determined using a biochemistry autoanalyzer (Beckman Coulter, AU5800, USA) employing commercial enzyme kits.

Statistical analysis

The SPSS software program (Version 20.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The distribution of the data between the groups was evaluated using a Shapiro-Wilk test. Levene's test was employed to test whether variances were homogenous. Parametrically distributed groups were compared using the Student's t-test (Independent-Samples t-Test). Receivers operating characteristic (ROC) curves were used to determine the cut-off values of cTnI concentrations and cardiac enzyme activities. ROC analyses were performed for both groups.

To assess the prognostic and diagnostic potential of cTnI and cardiac enzyme activity levels for sepsis, the areas under the curve (AUC) were recorded and cut-off values were analysed. The correlation among parameters was measured by the Pearson Correlation test. All data were presented as the mean and standard error of the mean (Mean ± SEM). The results were assessed at a 95% confidence interval and a significance level of P<0.05.

RESULTS

Hypothermia or hyperthermia, tachypnoea, tachycardia or bradycardia, dehydration, lack of sucking reflex, dry mouth, cool extremities and prolonged capillary refill time (CRT) in neonatal calves with sepsis were detected. WBC and NEU counts were significantly higher in SG than in CG (P<0.01). The body temperature (RT), respiratory rate (RR), heart rate (HR), and CRT of SG were significantly higher compared to the CG (P<0.001). (Table 1).

Table 1: cTnI concentrations, cardiac enzyme activities, some biochemical parameters, haematological and clinical findings of neonatal calves with sepsis and healthy calves (Mean ± SD)

Parameters	Control (n=10)	Sepsis (n=15)	P value
cTnI (ng/mL)	0.042±0.020	0.34±0.37	<0.01
CK-MB (U/L)	337.30±254.63	713.06±570.92	<0.05
LDH (U/L)	767.40±104.20	982.06±328.64	<0.05
AST (U/L)	61.10±15.78	118.40±86.21	<0.05
UREA (mg/dL)	17.00±7.94	78.80±40.48	0.000
Cr (mg/dL)	1.33±0.22	3.44±1.28	0.000
WBC(x10³/µL)	9.01±2.74	13.50±3.83	<0.01
NEU (x10³/µL)	4.19±1.94	7.53±3.44	<0.01
HCT (%)	32.50±4.24	44.33±5.24	0.000
RT (°C)	38.49±0.27	39.02±0.26	0.000
HR (beat/min)	95.80±9.25	132.93±17.64	0.000
RR (breaths/min)	29.20±4.63	40.66±10.73	<0.01
CRT (sec)	1.70±0.25	4.56±0.75	0.000

cTnI: cardiac troponin I; CK-MB: creatine kinase myocardial–band; LDH: lactate dehydrogenase; AST: aspartate amino transferase; UREA: urea; Cr: creatinine; WBC: White blood cells; NEU: neutrophil; HCT: hematocrit; RT: rectal temperature; HR: heart rate; RR: respiration rate; CRT: capillary refill time

The concentrations of cardiac troponin I, cardiac enzyme activities and serum biochemistry parameters of both groups are presented in Table 1. The levels of urea and creatinine of calves with sepsis were significantly higher than that of CG (P<0.001). In addition, the concentrations of serum cTnI (P<0.01), CK-MB, LDH and AST activities in SG were significantly greater than the CG (P<0.05). Besides, the concentrations of serum cTnI of SG showed a positive correlation with cardiac enzyme activities, but this correlation was not statistically significant (P> 0.05) (Table 2).

The results of ROC analyses of cardiac biomarkers are shown in Table 3 and Figure 1. The cut-off values of cTnI, CK-MB, LDH, and AST were 0.065 ηg/mL, 751.50 U/L, 915U/L, and 87 U/L, respectively. Sensitivity values for myocardial damage were cTnI: 100%, CK-MB: 66.7%, LDH and AST: 53.3%. The areas under the ROC curve were 0.98, 0.72, 0.69 and 0.80 for cTnI, CK-MB, LDH and AST respectively.

DISCUSSION

Neonatal sepsis can cause severe economic losses to the farms (1, 28-30). Therefore, the markers, such as cTnI, CK-MB, LDH and AST are valuable in the veterinary field since they can be used to monitor the early diagnosis and prognosis of sepsis. This preliminary study, aimed to determine the success of cTnI and cardiac enzyme activity in the diagnosis and prognosis of sepsis in neonatal calves.

In neonatal calves with sepsis findings such as mild depression and loss of sucking reflex in the early period of sepsis are non-specific. In sepsis, rectal temperature is variable (hypothermia or hyperthermia); however, a continuous tachycardia and even a tachypnoea may develop. Furthermore, clinical symptoms related to hypotension and decreased cardiac output are evident and usually hypovolemia develops due to dehydration and lipopolysaccharides (LPS), also called "endotoxins," activate NF-κB, which causes an overproduction of nitric oxice. Nitric oxide then causes vasodilatation, vascular hyporeactivity, and hypotension (2, 28, 30, 31). Along with the above-mentioned findings of sepsis in previous studies (2, 28-30), cold touch in the mouth, cooling down of extremities and in some cases, lateral recumbency, coma, prolonged capillary refill time and increased haematocrit levels were our findings in this study. Furthermore, body temperature, heart and respiratory rates capillary refill time and hematocrit levels of SG were significantly higher compared to the CG (P<0.001) (Table 1).

In calves with sepsis, certain changes occur in haematological parameters (9, 30, 32-34). The presence of leukopenia and leucocytosis is a diagnostic indicator of sepsis (2, 28, 35). Besides, leukocytic response, especially the presence of the band and toxic neutrophils are considered important for prognosis (2, 28). It was reported that the WBC numbers of calves with septicaemia (35), suspected septic shock (9, 32), septicemic colibacillosis (33), SIRS (36) and sepsis (29, 30, 34) were found to be significantly higher compared to healthy calves. Similarly, we observed that the WBC and NEU numbers of SG were significantly higher than CG (P<0.01) (Table 1).

It has been stated that the concentrations of urea and creatinine were determined to be greater in neonatal calves with sepsis (2, 28). The reason for this has been attributed to the disruption of renal perfusion resulting from dehydration (28, 34, 35). Similarly, in this study, urea and creatinine concentrations were statistically higher in SG than CG possibly due to hypovolemia (P<0.001) (Table 1).

Serum cTns are biochemical markers whose concentration in the blood increases rapidly during myocardial injury (12, 26, 37). cTnI is 100% tissue-specific to the heart which makes it a perfect marker to serve as a biochemical tool for the detection of myocardial damage (37, 38). cTnI has also a great diagnostic sensitivity due to its continuing cellular release and clearance (12, 22). In different types of myocardial damage, the leakage from the damaged myocardial cells leads to an increase in the serum cTnI concentrations (22, 24). Although no significant differences have been found between the surviving and non-surviving foals in cTnI concentrations in septic neonatal foals, its concentration was observed to be increased (39). In dogs with SIRS, it was stated that the cTnI concentration was increased which was associated with a poor prognosis. Furthermore, the daily follow-up measurement of cTnI concentration did not ensure supplementary prognostic data for short term mortality (40). Increased cTnI concentration has been reported in various diseases in terms of demonstrating myocardial damage,

Table 2: Correlation between cardiac biomarkers in neonatal calves with sepsis (n=15)

Parameters	cTnI	CK-MB	LDH	AST
cTnI	1.000	0.064	0.084	0.159
CK-MB		1.000	0.312	0.131
LDH			1.000	-0.094
AST				1.000

cTnI: cardiac troponin I; CK-MB: creatine kinase myocardial–band; LDH: lactate dehydrogenase; AST: aspartate amino transferase.

Table 3: Receiver operating characteristic (ROC) results of cardiac biomarkers of neonatal calves with sepsis (n=15)

Parameters	cTnI (ng/mL)	CK-MB (U/L)	LDH (U/L)	AST (U/L)
Area	0.987	0.727	0.690	0.803
Cut-off	0.065	751.50	915	87
Sensitivity (%)	100	66.7	53.3	53.3
Specificity (%)	80	90	90	90
SEM	0.017	0.108	0.107	0.088
P value	0.000	0.059	0.114	<0.05

cTnI: cardiac troponin I; CK-MB: creatine kinase myocardial–band; LDH: lactate dehydrogenase; AST: aspartate amino transferase.

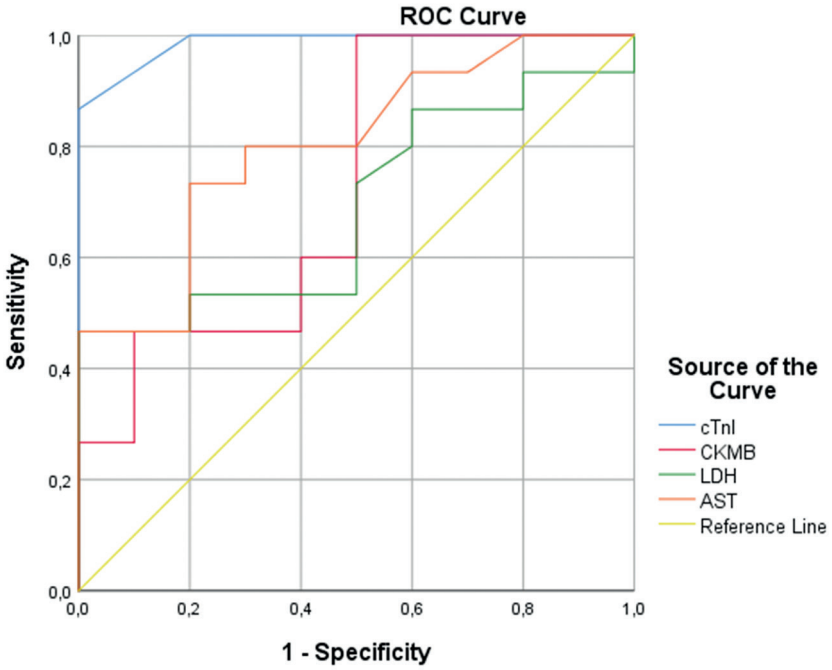

Figure 1: ROC curve analysis of cTnI concentration and CK-MB, LDH and AST activities.

such as endotoxemia (41), food-and-mouth disease (42-45), bovine respiratory disease (46, 47), respiratory distress syndrome (48), theileriosis (49), and congenital intestinal atresia (50, 51) in calves.

The antigenic similarity of human and bovine cTnI is 96.4% (27). Therefore, serum cTnI concentration was measured by the test produced for use in human medicine in this study. The cTnI concentration of SG was found to be significantly higher compared to CG. (Table 1). The results of this study showed that cTnI can be a useful and important marker in the diagnosis and prognosis of myocardial damage due to sepsis in neonatal calves. Supporting this view, Peek *et al.* (41) stated that troponin concentrations increased significantly in the diagnosis of cardiac injury in calves induced with endotoxin. Furthermore, Coskun *et al.* (50) reported that cTnI concentrations of dead calves with atresia coli were higher than those which survived compared to healthy control calves, and that myocardial damage could be caused by a developing endotoxemia. The pathophysiology of the rising of troponin in sepsis is thought to be due to myocardial dysfunction. Demand ischemia, direct cardiac myotoxic effects of endotoxins, cytokines or reactive oxygen radicals, and disturbances in regional coronary blood flow are the suggested mechanisms for myocardial dysfunction in sepsis (11, 18, 52). Although an increase in cTnI concentration has been noted in sepsis-associated myocardial dysfunction (12, 13, 53), the mechanism causing the increase has not been fully elucidated (11, 12).

In humans, after the initiation of acute cardiac injury, serum CK-MB activity peaks at 24 hours and serum LDH at the 48th-72nd hours (37, 38, 54), while cTn starts to increase at the third to fourth hours and peaks at the 12th hour (37, 38, 55). Therefore, it was reported that at the very early stages of myocarditis, CK-MB levels were found within the normal range (37, 56).

To the best of the knowledge of the authors, there has not been any report describing the stages of sepsis with respect to the concentration cTnI in calves. In this study, based on the increased concentration of cTnI and the activities of CK-MB and LDH in SG, it can be suggested that the disease was not at an early stage. Also, serum AST activity was higher in the SG than CG. Increased AST activity can be seen in several abnormalities, such as heart, liver, and muscle diseases. In SG, animals experienced lateral recumbency and coma. These findings are known to cause muscle damage which could also explain the high levels of CK-MB, LDH and AST which may have occurred at an earlier stage of the disease process. Therefore, it appears that cardiac troponin is a more

specific biomarker than CK-MB, LDH, and AST in the evaluation of myocardial injury (23, 24). Increased activity of CK-MB, LDH, and AST can be associated with myocardial injury only if there is an increased concentration of cTnI. In this study, CK-MB, LDH and AST activities increased significantly in calves with sepsis compared to healthy calves (Table 1) which suggested that myocardial myocytes might have been affected. Likewise, Naseri *et al.* (57) reported that CK-MB and AST activities were higher in a 10-day old calf with septic shock, and stated that these findings would indicate an organ (heart and liver) damage.

The superiority of cTnI was also demonstrated by ROC analysis. ROC was performed for cTnI, CK-MB, LDH and AST to determine the optimal cut-off value which represents a threshold value for diagnosing diseases, sensitivity and specificity of the relevant parameters with respect to this cut-off value. According to the results, the overall diagnostic performance of cTnI concentration was superior to the other markers for the detection of myocardial injury in neonatal calves with sepsis and may be an important marker for the prognosis of sepsis.

In this study, we did not investigate the inflammatory-related findings. This maybe a major shortcomings of this study. Such findings would have not only have shown the cardiac damage, but also the degree of that damage. Based on such findings, a comparative outcome could have been reached such as where more severe inflammation may have occurred, and the correlation with the cTnl concentration. Nevertheless, cardiac damage resulting from sepsis has been demonstrated in both human and animal studies (11, 18, 52).

In conclusion, this study indicates that sepsis may cause myocardial damage in neonatal calves. In this study, we have investigated the performances of cTnI, CK-MB, LDH and AST markers in the diagnosis and prognosis of myocardial damage and found out that cTnI was superior to other markers based on both inter-group comparisons and ROC analyses.

It is suggested that further studies be designed with various emerging cardiac parameters to test their efficiency and sensitivity, such as FAPB3 also known as Heart-type fatty acid binding protein. Histopathological examination should be considered in these cases where the animals do not survive as it could provide more definitive findings regarding the cardiac damage.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

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