Assiut University web-site: www.aun.edu.eg

TROPONIN-1, CK-MB, D-DIMER, AND NT-proBNP LEVELS BEFORE AND AFTER TWO DIFFERENT ANESTHESIA PROTOCOLS IN DOG

GÜLSAH AKGUL [1]; MUSTAFA BARIS AKGUL [2]; ERMAN GULENDAG [3]; MAHSUM BASAK [1]AND SEVDET KILIC [2]

[1] Department of Internal Medicine, Faculty of Veterinary Medicine, Siirt University, Siirt, Turkey
[2] Department of Surgery, Faculty of Veterinary Medicine, Siirt University, Siirt, Turkey
[3] Department of Biostatistics, Faculty of Veterinary Medicine, Siirt University, Siirt, Turkey

Received: 6 December 2022; **Accepted:** 26 January 2023

ABSTRACT

This study aimed to determine the cardiac effects of two different anesthetic protocols by measuring serum levels of Troponin 1, CK-MB, NT-proBNP and D-Dimer in healthy castrated non cardiac dogs. Thirty adult, healthy, and noncardiac male dogs were brought to the animal hospital affiliated to the Animal Health Application and Research Center of Siirt University for castration. The animals were sedated with intramuscular administration of 2 mg/kg of xylazine HCl and anesthesia was induced by intramuscular administration of 10 mg/kg Ketamine HCl. The animals were intubated and connected to the closed-circuit anesthesia device. Following induction of general anesthesia, dogs were divided into two groups. Group 1 (G1) (*n*=15) was administered with 2-3% Isoflurane inhaler, the other group (G2) (*n*=15) was administered with 2-3% Sevoflurane inhaler to maintain anesthesia. Blood samples were collected before and 12 hours after anesthesia. Results revealed non-significant changes in serum levels of CK-MB over time. However, a significant difference was observed in CK-MB values between sevoflurane and isoflurane. No significant changes in Troponin values were recorded. Significant changes in Nt-Pro BNP values over time were observed, but the changes were not significant between anesthetic protocols. With the present study, we can partially say that sevoflurane is safer than isoflurane, but we believe that more studies should be done with more samples.

Keywords: D-Dimer, Cardiac, Troponin- I, Nt-ProBNP

INTRODUCTION

Many hemodynamic parameters are impacted depending on the type of anesthesia chosen for patients undergoing general anesthesia. Changes occur in heart rate, heart rhythm, myocardial contractility, and vascular tonus through the autonomic nervous system. Ketocalamine increase, depression of myocardial contractility, myocardial ischemia, and postoperative pain-related hypertension can be observed in patients administered general anesthesia due to excessive excitement and intubation during induction. Moreover, hypoxia, hyperapnia, and acidosis resulting from inadequate respiration may depress the myocardium and increase the tendency to arrhythmia. The impact of pharmacological agents used in general anesthesia on the

Corresponding author: Mustafa Barıs Akgul
E-mail address: mbakgul@hotmail.com
Present address: Department of Surgery, Faculty of Veterinary Medicine, Siirt University, Siirt, Turkey

cardiovascular system may vary depending on the dose (Esener, 2004).

Almost all inhalation agents can reduce myocardial depression, stroke volume, and blood pressure. Sevoflurane, one of the inhaler agents, mildly depresses myocardial contractility and can cause a decrease in systemic vascular resistance and arterial blood pressure. Isoflurane depresses the myocardium but does not depress ventricular conduction. Blood pressure can be reduced by decreased systemic vascular resistance (Morgan and Maget, 2008).

Troponin (Tn) is a regulatory protein of thin filaments of striated muscle. Troponins are released into the blood as T, I, and C complexes (a ternary complex of cTnT-I-C and a binary complex of cTnI-C) and as free subunits. Troponin T and I act together as important components of the contraction process in striated muscle. Although the troponin complex is similarly involved in striated muscle, the isoforms of troponin T and I are different in cardiac muscle as the proteins are encoded by different genes in the tissue. Cardiac troponins are biomarkers specific to cardiomyocyte injury (Liquori *et al.,* 2014). Cardiac injury induces myocyte destruction and membrane rupture, and high concentrations of free cardiac troponin are released into the bloodstream. This process is followed by a slow and continuous release of structurally linked troponins, which explains the reason for the constantly high serum concentration (Wells and Sleeper, 2008).

In dog serum, cTnI can be detected in 4-6 hours and peaks at 10-16 hours after an induced trauma (experimental myocardial infarction) faster than in humans (Cummins and Cummins, 1987). Cardiac troponin is associated with arteriosclerosis fibrosis in pathological changes described in cardiac failure due to mitral valve disease, and this fibrosis occurs due to severe ischemia (Falk *et al.,* 2013).

Cardiac troponin I, one of the cardiac biomarkers, and creatine kinase MB (CK-MB), one of the cardiac enzymes, are used as valuable markers in the diagnosis and prognosis of ischemia, trauma, and septic myocardial damage in human medicine (Slack *et al.,* 2005). The amount of cTnI in circulation is determined to identify the presence of acute and chronic myocardial damage in many species and its determination also leads to the guidance of other diagnostic methods, such as thorax radiography, electrocardiography, and echo-cardiography and provides additional information to these tests. Furthermore, the amount of cTnI in circulation gives information about the degree of cardiac damage (Suzuki *et al.,* 2012)

Although the creatine phosphokinase (CK-MB) isoenzyme is used for the diagnosis of myocardial infarction, its effectiveness in detecting myocardial damage is still controversial, since it is also found in tissues and organs such as skeletal muscle, vascular smooth muscles, the brain, the uterus, and placenta (Abramov *et al.,* 1996). CK-MB is diagnostically sensitive to myocardial damage, but it is not specific. Skeletal muscle has a higher CK activity and a CK-MB activity of up to 3% (Adams *et al.,* 1993). However, a high CK-MB level in the serum is generally evaluated in favor of myocardial cell damage. Creatine kinase is a product of muscular activation in the organism and has two subunits. The subunits have three iso-enzymes as a result of their interaction with each other. CK-MM, CK-MB and CK-BB are characterized as iso-enzymes, M indicating muscle subunit and B indicating brain subunit (Boyd, 1983).

It is found in different tissues and organs in the organism at different rates. In many species, CK-MM can be detected at a rate of 100% in skeletal muscle. CK-MM predominates in cardiac muscle; CK-MB is found at a rate of 3% in dogs and approximately 10% in horses (Aktas *et al.,* 1994). In human medicine, CK-MB is used

for prognostic purposes, especially in acute cardiac damage. In veterinary medicine, its exact effectiveness is unknown, and further studies are recommended (Guan *et al.,* 2014).

D-dimer is a general indicator of fibrinolysis and activation of the coagulation system for any reason, and is therefore used as an indirect marker of thrombotic activity. In medicine, D-dimer levels may increase very rarely in healthy individuals. Clinically, D-dimer is most frequently used in the diagnosis and follow-up of venous thromboembolism (VTE) and disseminated intravascular coagulation (DIC). In addition, D-dimer levels have been reported to be elevated in all conditions that promote fibrin formation and destruction, such as acute coronary syndromes, peripheral vascular diseases, deep vein thrombosis, pulmonary embolism, acute stroke, pregnancy, hemolytic crises in sickle cell anemia, malignant diseases, post-surgery, congestive heart failure, and chronic renal failure (Hager and Platt., 1995; Chapman *et al.,* 1990).

Natriuretic peptides are a class of hormones that control body fluid homeostasis through natriuretic and diuretic effects and act on the renin-angiotensin-aldosterone mechanism (Liquori *et al.,* 2014). ANP and BNP are the main cardiac hormones in circulation and are called cardiac natriuretic peptides. The majority of ANP is synthesized in atrial myocytes. This polypeptide is more abundant in the right atrium compared to the left. Unlike ANP, which is mainly stored in the atria, the main source of BNP is cardiac ventricles. Therefore, unlike other natriuretic peptides, BNP is a specific indicator in the diagnosis of ventricular diseases (İçen *et al.,* 2009). Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are useful in evaluating the diagnosis of cardiac diseases, whereas the expression of C-type natriuretic peptide (CNP) has been associated with paracrine function and also has a role in the regulation of vascular tonus (Ciaramella *et al.,* 1995; Van Kimmenade and Januzzi, 2009).

Brain natriuretic peptide (BNP) is released from cardiac ventricles and increases proportionally with ventricular enlargement and pressure increase, giving information on cardiac performance. B-type natriuretic peptide has proven to be more stable than ANP after release into circulation (Van Kimmenade and Januzzi, 2009). NT-pro BNP has the same sensitivity and specificity as BNP and a high biological half-life (Fox *et al.,* 2009). The two fractions of BNP and NT-proBNP (N-terminal pro-brain natriuretic peptide) have been successfully used to evaluate cardiac failure, acute coronary syndrome, or ischemic heart disease, and for monitoring cardiac failure treatment in human medicine, and have been reported to serve as a model for veterinary medicine (Maisel *et al.,* 2002; Braunwald, 2008; Liquori *et al.,* 2014).

In recent years, especially NT-proBNP has played a very important role in the diagnosis of cardiac failure and heart diseases in veterinary medicine. ProBNP can provide information about the disease before symptoms occur, especially in asymptomatic heart diseases (Uçar and Turhan, 2005). Monitoring cardiac function has gained importance for the follow-up of myocardial lesions. For this purpose, various hormones and peptides, such as atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-proBNP), and cardiac troponin are used in the diagnosis of cardiac failure (Gönül *et al.,* 2017).

In patients with cardiac problems, changes in autonomous system activity, body temperature, blood pressure, ventricular filling pressure, heart rate, and blood volume create additional stress. In addition to anesthesia, complications such as surgery-related bleeding, infection, fever, pulmonary embolism, and myocardial infarction increase the burden on the cardiovascular

system. In order to reduce possible events that may develop due to cardiovascular complications, the risks in patients should be determined beforehand and measures should be taken. On such an important issue, it is important to determine the risks and benefits of anesthesia based on the anesthetic agents to be selected. Several risk factors increase cardiac complications during surgery. Knowing the cardiac risks is important in order to be prepared for the negativities that may occur in the intraoperative period. The present study aimed to compare the cardiac effects of two different anesthesia protocols by measuring serum levels of Troponin I, CK-MB, NT-proBNP, and D-Dimer levels in healthy castrated noncardiac dogs.

METHOD

1. Materials:

1.1 Animal Material:

The animal material of the study consisted of 30 adult, healthy and non-cardiac dogs with all values within normal limits on physical examination. They were male crossbreed dogs aged 1-3 years (mean±SE age of Sevoflurane (G2) dogs was 1.8±0.22, and for Isoflurane (G1) dogs was 2±0.2), which were brought to the animal hospital affiliated with Siirt University Animal Health Application and Research Center for Castration. Dogs that did not have any abnormality in the clinical and laboratory evaluations and were considered healthy based on the anamnesis were included in the study.

2. Anesthesia protocols:

In the pre-anesthetic period, vascular access was first established from V. cephalica antebrachi. Then xylazine HCl 2 mg/kg (Xylazinbio 2%, Bioveta, Czech Republic) was administered i.m. for sedation and ketamine HCl 10 mg/kg (Ketasol 10%, Arion, Turkey) was administered i.m. for induction. For the maintenance of anesthesia, the patient was intubated and connected to a closed-circuit anesthesia system (SMS 2000 Classic Automatic Anesthesia Device CWH 1020, SMS, Turkey). Following the injectable general anesthesia, one group (*n*=15) was given 2-3% Isoflurane (Isoflurane USP, Piramal Critical Care, USA) (mean±SE duration of inhalation anesthesia was 24.8±0.79 min) and the other group (*n*=15) received 2-3% Sevoflurane (Sevoflurane, Aeseica Queenborough Limited, UK) (mean±SE duration of inhalation anesthesia was 24.5±0.86 min) with an inhaler in order to maintain anesthesia.

3. Collection and Evaluation of Samples:

3.1 Collection and storage of samples:

Blood samples were collected from the dogs to be castrated into sterile gel biochemical tubes before anesthesia and post-anesthesia 12th-hour and centrifuged immediately at 3000 rpm for 15 minutes. Serum samples were taken and stored at -20 °C until the analysis.

3.2 D-Dimer and NT-proBNP analysis:

D-dimer and NT-proBNP concentrations were measured with a Fluorescent Immunoassay rapid test (Finecare, Wondfo Biotech Co. Limited, Finecare, Atateknik, Turkey). Commercial FIA meter test kits (D-dimer test, Finecare, Wondfo Biotech Co. Limited) were used to measure serum D-dimer concentration. Serum samples were stored at -20 °C until the analysis.

3.3 Troponin I and CK-MB Serum troponin I and CK-MB concentrations were measured using the ADVIA 1800 Automated Biochemistry analyzer. Serum samples were stored at -20 °C until the analysis.

4. Statistical Analyses

In the study, measurements made 12 hours after anesthesia administration were accepted as the dependent variables. The 12th-hour measurements were evaluated as the covariates, which had an effect on the independent variable, which was pre-anesthesia measurements (0th-hour), except for the Sevoflurane and Isoflurane groups.

Accordingly, the Analysis of Covariance was used in the statistical analysis of the obtained data. Prior to the hypothesis testing, interaction assumptions in normal distribution, linearity, and regression slopes were checked. In all tests, $p<0.05$ was taken as the criterion of significance, and analyses were performed in the SPSS v26 statistical program.

RESULTS

In CK-MB values measured after Sevoflurane and Isoflurane administrations, it was determined that the 0th-hour measurements did not cause a statistically significant increase on the 12th-hour post-anesthesia measurements ($p=0.465$) but a difference was observed in CK-MB values due to the use of different anesthetic agents ($p=0.002$) (Figure 1). On the other hand, in terms of troponin, it was observed that the zero-hour measurements did not cause a statistically significant difference in the 12th -hour post-anesthesia measurements ($p=0.811$) and no statistically significant difference was observed in troponin values due to the use of different anesthetic agents ($p=0.829$) (Figure 2). In Nt-ProBNB values measured after Sevoflurane and Isoflurane administrations, it was determined that the zero-hour measurements caused a statistically significant change on the 12th-hour post-anesthesia measurements ($p<0.001$), but Sevoflurane and Isoflurane administrations did not make a significant difference on this change ($p=0.198$) (Figure 3) (Table 1). Since serum D-Dimer values were measured within normal limits, they could not be included in statistical analysis.

Figure 1: Change of CK-MB level according to time and anesthetic agents

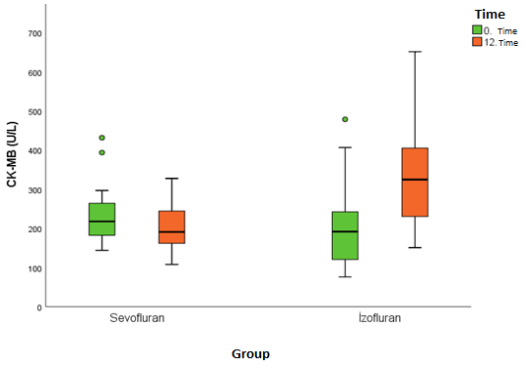

Figure 2: Change of troponin level according to time and anesthetic agents

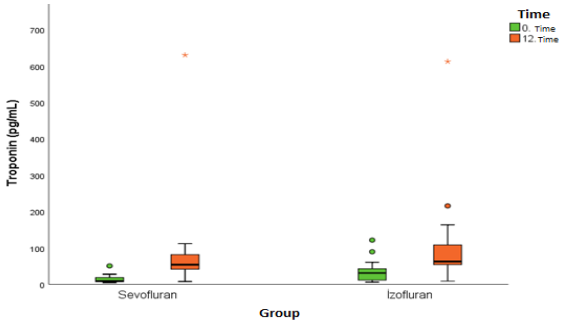

Figure 3: Change of NT-proBNP level according to time and anesthetic agents

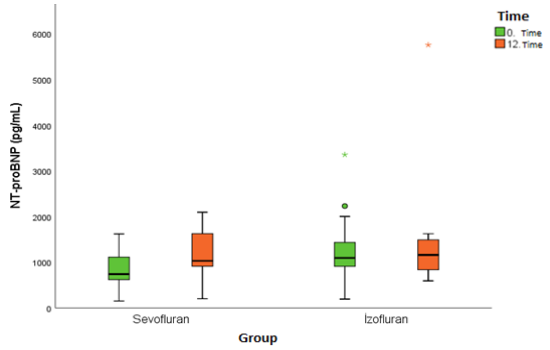

Table 1: Change of CK-MB, Troponin, and NT-proBNP levels according to time and anesthetic agents.

				p	
Parameter	Time	Sevoflurane	Isoflurane	Anesthetic Agent	Covariant (0th hour)
CK-MB	0th hour	236.7±21.6	207±31.6	0.002	0.465
	12th hour	301.1±15.6	344.8±39.3		
Troponin	0th hour	14.5±3.1	35.5±8.6	0.829	0.811
	12th hour	94.1±39.2	113.2±38.4		
NT-proBNP	0th hour	845.7±95.9	1255±206.8	0.198	<0.001
	12th hour	1203±141.2	1415.5±323.3		

DISCUSSION AND CONCLUSION

A careful evaluation including pre-intervention risk classification is of great importance for the selection of anesthetic agents to be administered with appropriate anesthesia management in patients who will undergo surgical intervention. The anesthesia management and agent chosen should be appropriate and within the limits that the patient and the surgical intervention can tolerate. There are many parameters to evaluate the level of known cardiovascular effects of general anesthesia. In our study, we aimed to evaluate the cardiovascular effects of anesthetic methods in castrated healthy noncardiac dogs based on troponin I, CK-MB, NT-proBNP, and D-dimer values.

Sevoflurane is a new inhalation anesthetic with a blood-gas solubility coefficient of 0.63. It was synthesized in the 1960s but entered clinical use in the 1990s. Since the blood-gas solubility coefficient is low, anesthesia induction and recovery from anesthesia are faster compared to isoflurane (Girard F *et al.,* 2002; Rossignol B *et al.,* 2003). Therefore, we aimed to evaluate Sevoflurane and Isoflurane as inhalation anesthetics in our study.

The two fractions of BNP and NT-proBNP have been successfully used to evaluate cardiac failure, acute coronary syndrome, or ischemic heart disease and also for monitoring of cardiac failure treatment in human medicine and have been reported to serve as a model for veterinary medicine (Maisel *et al.,* 2002; Braunwald, 2008; Liquori *et al.,* 2014). In dogs, an NT-proBNP concentration of less than 900 pmol/L is not compatible with increased myocardial damage and stress. On the other hand, it was reported that a concentration of more than 735 pmol/L indicates an increased risk for dilated cardiomyopathy in Doberman pinschers (Baisan *et al.,* 2016). Previous studies have shown that dogs with mitral valve disease and dilated cardiomyopathy have higher serum NT-proBNP concentrations allowing the evaluation of the degree of cardiac disease and its severity compared to healthy dogs. Furthermore, it has been reported that NT-proBNP concentrations correlate with heart rate, respiratory rate, echocardiographic changes, and renal function in dogs with cardiac disease and that NT-proBNP concentrations may be useful in the diagnosis of cardiac diseases as well as the assessment of severity (Oyama *et al.,* 2008; Baisan *et al.,* 2016). In a previous study, BNP concentration was evaluated in order to distinguish cardiac and non-cardiac dyspnea and 22 dogs with congestive heart failure-related dyspnea and 26 dogs with dyspnea of no cardiac origin. It was reported that dogs with congestive heart failure (a mean of 34.97 pg/mL) had higher BNP concentrations than dogs with non-cardiac dyspnea (a mean of 12.8 pg/mL) (Prosek *et al.,* 2007). It was reported that Golden

Retriever dogs with muscular dystrophy cardiomyopathy had higher (a mean±standard deviation of 117±92 pg/mL) BNP concentrations than healthy dogs (a mean±standard deviation of 46±22 pg/mL) (Chetboul *et al.,* 2004). Moreover, NT-proBNP has been evaluated in babesiosis at different concentrations and different degrees of severity between groups, and it was reported that NT-proBNP concentration may predict the severity of the disease and induced cardiac stress (Lobetti *et al.*, 2012). Likewise, in our study, it was determined that the 0th-hour measurements created a statistically significant change in the 12th-hour post-anesthesia measurements of Nt-ProBNB values obtained after Sevoflurane and Isoflurane administrations ($p<0.001$), but Sevoflurane and Isoflurane administrations did not make a significant difference on this change ($p=0.198$).

D-dimer is formed as a result of the activation of the coagulation system for any reason and the destruction of fibrin clot formed by plasmin cross-links (Blomback *et al.*, 1978). In the clinic, D-dimer is most frequently used in the diagnosis and follow-up of venous thromboembolism (VTE) and disseminated intravascular coagulation (DIC). In medicine, D-dimer levels may increase very rarely in healthy individuals. In addition, D-dimer levels have been reported to be elevated in all conditions that promote fibrin formation and destruction, such as acute coronary syndromes, peripheral vascular diseases, deep vein thrombosis, pulmonary embolism, acute stroke, pregnancy, hemolytic crises in sickle cell anemia, malignant diseases, post-surgery, congestive heart failure, and chronic renal failure (Hager and Platt, 1995; Chapman *et al.,* 1990). In our study, D-dimer levels were measured within normal limits in healthy noncardiac animals, supporting other studies, and could not be statistically evaluated.

In cardiac damage, levels of enzymes such as AST, CK, CK-MB, and LDH may increase (Burgener *et al.,* 2006; Gupta *et al.,* 2008). The best indicators of myocardial cell damage are CK-MB (Wells *et al.,* 2002), cTnI (Bader *et al.,* 2006; Diniz et al., 2007), and natriuretic peptides among neurohormonal markers (Oyama *et al.,* 2008; Boswood, 2009). The cardiac markers in humans, cTnI and CK-MB, are used in the diagnosis of ischemic, traumatic, and septic myocardial injury and necrosis. An important enzyme that indicates cardiac damage is CK-MB. In case of cardiac muscle damage, the level of this enzyme in the blood increases within 24 hours and decreases in a short time (La Vecchia *et al.,* 2000; Burgener *et al.,* 2006). It has been reported that the serum CK-MB level significantly increases in cardiac failure, aortic stenosis, and coronary diseases in humans and animals (Vartner and Ingwall, 1984). In myocardial damage, blood cTnI level increases in the first 4 hours and reaches its peak in 12 and 24 hours (Ooi *et al.,* 2000; Colantonio *et al.,* 2002; Diniz *et al.,* 2007). Similarly, in our study, we made our measurements at the 0th hour and 12th hour for better evaluation. Oyama and Sisson (2004) determined that cTnI levels increased in dogs with cardiomyopathy, heart valve insufficiency, and aortic stenosis. Çakıroğlu *et al.* (2009) reported that cTnI may be a candidate for an important cardiac determinant in animals. Burgener *et al.* (2006) reported that serum cTnI (>0.29 µg/L) and CK-MB (>2.2 µg/L) levels significantly increased with acute myocardial damage in dogs. Cummins and Cummins (1987) and rucchiuti *et al.* (1998) revealed that cTnI and cTnT markers are important indicators for the determination of myocardial damage in dogs. In the present study, in the CK-MB values measured after Sevoflurane and Isoflurane administrations, it was observed that the 0th-hour measurements did not cause a statistically significant change on the 12th-hour post-anesthesia measurements ($p=0.465$) but there was a difference in CK-MB values due to the use of different anesthetic agents ($p=0.00$). However, no statistical difference

was found in troponin values according to time and anesthetic agents (p=0.829).

Changes may occur in heart rate, heart rhythm, myocardial contractility, and vascular tonus through the autonomic nervous system in patients undergoing general anesthesia. In order to reduce possible events that may develop due to cardiovascular complications, the risks in patients should be determined in advance and measures should be taken. On such an important issue, it is important to determine the risks and benefits of anesthesia based on the anesthetic agents to be selected. Many studies have been conducted on the heart in veterinary medicine, however, the effects of different anesthesia protocols on the heart have not been examined before, as in the current study. The cardiac effects of two different anesthesia protocols were compared based on the troponin I, CK-MB, NT-proBNP, and D-dimer values in healthy noncardiac dogs, and the effects of anesthetic agents that are constantly used in veterinary medicine on the heart were revealed. With the present study, we can partially say that sevoflurane is safer than isoflurane, but we believe that more studies should be done with more samples.

ACKNOWLEDGE

This study was supported by Research Fund of the Siirt University. Project code: 2021-SİÜVET-039

REFERENCES

Abramov, Y.; Abramov, D.; Abrahamov, A.; Durst, R. and Schenker, J. (1996): Elevation of serum creatine phosphokinase and its MB isoenzyme during normal labor and early puerperium. Acta Obstet Gynecol Scand 75, 255-60.

Adams, J.E.; Bodor, G.S. and Roman, V.G. (1992): Cardiac Troponin I:A Marker with High Specifity for Cardiac Injury. Circulation 88, 101-106.

Bodor, G.S.; Porter, S. and Landt, Y. (1993): Development of Monoclonal Antibodies for an Assay of Cardiac Troponin I and Preliminary Results in Suspected Cases Of Myocardial Infarction. Clin. Chem 38, 2203-2214.

Aktas, M.; Auguste, D.; Concordet, D.; Vinclair, P.; Lefebvre, H.; Toutain, P.L. and Braun, J.P. (1994): Creatine kinase in dog plasma: preanalytical factors of variation, reference values and diagnostic significance. Res Vet Sci 56, 30-36.

Bader, D.; Kugelman, A.; Lanir, A.; Tamir, A.; Mula E. and Riskin, A. (2006): Cardiac troponin I serum concentrations in newborns: A study and review of the literature. Clin Chem Acta 371, 61–65.

Baisan, R.A.; Rosa, A.D.; Loria, A.D.; Vulpe, V. and Piantedosi D. (2016): Cardiac biomarkers in clinical practice of dog and cat-a review. HVM Bioflux 8, 50-58.

Braunwald, E. (2008): Biomarkers in heart failure. N Engl J Med 358, 2148-2159.

Blomback, B.; Hessel, B.; Hogg, D. and Therkildsen, L. (1978): A two-step fibrinogen-fibrin transition in blood coagulation. Nature 275, 501-505.

Boswood, A. (2009): Biomarkers in cardiovascular disease: Beyond natriuretic peptides. J Vet Cardiol 11, 23-32.

Boyd, J,W. (1983): The mechanisms relating to increases in plasma enzymes and isoenzymes in diseases of animals. Veterinary Clinical Pathology 12, 9-24.

Burgener, I.A.; Kovacevic, A.; Mauldin, N. and Lombard, C.W. (2006): Cardiac tropoins as indicators of acute myocardial damage in dogs. J Vet Intern Med 20, 277-283.

Chetboul, V.; Tessier-Vetzel, D.; Escriou, C.; Tissier, R.; Carlos, C. and Boussouf, M. (2004): Diagnostic potential of natriuretic peptides in the occult phase of golden retriever

muscular dystrophy cardiomyopathy. J Vet Intern Med 18, 845-850.

Ciaramella, P.; De Luna, R.; Cortese, L.; Oliva, G.; Galati, M.G. and Persechino, A. (1995): Comportamento dell'ormone natriuretico atriale in cani con scompenso cardiaco congestizio, sottoposti a trattamento terapeutico. Acta Med vet 41, 363-373.

Colantonio, D.A.; Pickett, W. and Brison, R.J. (2002): Detection of cardiac troponin I early after onset of chest pain in six patients. Clin Chem 48, 668-671.

Cummins, B. and Cummins, P. (1987): Cardiac specific troponin-I release in canine experimental myocardial infarction:development of a sensitive enzyme- linked immunoassay. Journal of Molecular and Cellular Cardiology 19, 999-1010.

Çakıroğlu, D.; Meral, Y.; Bakırel, U. and Kazancı, D. (2009): Cardiac troponin levels in dogs with dilate cardiomyopathy. Kafkas Üniv Vet Fak Derg 15, 13-17

Diniz, P.V.P.; Schwartz, D.S. and Collicchio-Zuanaze R.C. (2007): Cardiac trauma confirmed by cardiac markers in dogs: two case reports. Arq Bras Med Vet Zootec 59, 28-35.

Esener, Z. (2004): Klinik anestezi, 3. Baskı, İstanbul, Logos yayıncılık, pp,313-314.

Falk, T.; Ljungvall, I.; Zois, N.E.; Hoglund, K.; Olsen, L.H.; Pedersen, H.D. and Haggstrom, J. (2013): Cardiac troponin-I concentration, myocardial arteriosclerosis, and fibrosis in dogs with congestive heart failure because of myxomatous mitral valve disease. J Vet Intern Med 27, 500-506.

Fox, P.R.; Oyama, M.A.; Reynolds, C.; Rush, J.E.; DeFrancesco, T.C. and Keene, B.W. (2009): Utility of plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) to distinguish between congestive heart failure and non-cardiac causes of acute dyspnea in cats. J Vet Cardiol 11, 51-61.

Girard, F.; Boudreault, D.; Ruel, M. and Todorov A. (2002): Sevoflurane provides faster recovery and postoperative neurological assessment than isoflurane in long-duration neurosurgical cases. Anesth Analg 95, 1384-1388.

Gönül, R.; Koenhemsi, L.; Yıldız, K.; İskefli, O. and Or, E. (2017): Dispneli Köpeklerin Ayırıcı Tanısında Kullanılan Troponin I ve NT-proBNP Düzeylerinin Immuno Assay Rotatorik Test Kitleri ve Cihazı ile Belirlenebilirliğinin İncelenmesi. F.Ü.Sağ.Bil.Vet.Derg 31, 39-42.

Guan, X.; Mack, D.L.; Moreno, C.M. and Strande, J.L. (2014): Dystrophin-deficient cardiomyctes derived from human urine: New biologic reagents for dug discovery. Stemm Cell Research 12, 467-480.

Gupta, S.; Singh K.N.; Bapat, V.; Mishara, V.; Agarwal, D.K. and Gupta P. (2008): Diagnosis of acute myocardial infarction: CK-MB versus cTn-T in Indian patient. Ind J Clin Biochem 23, 89-91.

Hager, K. and Platt, D. (1995): Fibrin degeneration product concentrations (D-dimers) in the course of ageing. Gerontology 41,159-65.

Chapman, C.S.; Akhtar, N.; Campbell, S.; Miles, K.; O'Connor, J. and Mitchell, V.E. (1990): The use of D-Dimer assay by enzyme immunoassay and latex agglutination techniques in the diagnosis of deep vein thrombosis. Clin Lab Haematol 12, 37-42.

İçen, H.; Çelik, Ö.Y. and Şimşek, A. (2009): Köpeklerde Kardiyovasküler Hastalıkların Tanısında Natriüretik Peptidler'in Önemi. YYU Veteriner Fakultesi Dergisi 20, 85-89.

La Vecchia, L.; Mezzena, G.; Zanolla, L.; Paccanaro, M.; Varotto, L.; Bonanno, C. and Ometto, R. (2000): Cardiac troponin I as diagnostic and prognostic

marker in severe heart failure. J Heart Lung Transplant 19, 644-652.

Liquori, M.E.; Christenson, R.H.; Collinson, P.O. and Defilippi, C.R. (2014): Cardiac biomarkers in heart failure. Clinical Biochemistry 47, 327-337.

Lobetti, R.; Kirberger, R.; Keller, N.; Kettner, F. and Dvir, E. (2012): NT-ProBNP and cardiac troponin I in virulent canine babesiosis. Veterinary Parasitology 190, 333-339.

Maisel, A.S.; Krishnaswamy, P.; Nowak, R.M.; McCord, J.; Hollander, J.E. and Duc, P. (2002): Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. New England Journal of Medicine 347, 161-167.

Morgan, G.E. and Maget, S.M. (2008): Klinik anesteziyoloji, Lange, Güneş Tıp kitapevi 4, 155-175.

Ooi, D.; Isotalopa, S. and Veinot, J.P. (2000): Correlation of ante mortem serum creatine kinase, Creatine kinase-MB, Troponin I, and troponin T with cardiac pathology. Clin Chem 46, 38-344.

Oyama. M.A. and Sisson, D.D. (2004): Cardiac troponin-I concentration in dogs with cardiac diseases. J Vet Intern Med 18, 797-799.

Oyama, M.A.; Fox, P.R.; Rush, J.E.; Rozanski, E.A. and Lesser, M. (2008): Clinical utility of serum N-terminal pro-B-type natriuretic peptide concentration for identifying cardiac disease in dogs and assessing disease severity. Am Vet Med Assoc 232, 1496-1503.

Prosek, R.; Sisson, D.D.; Oyama, M.A. and Solter, P.F. (2007): Distinguishing cardiac and noncardiac dyspnea in 48 dogs using plasma atrial natriuretic factor, B-type natriuretic factor, endothelin, and cardiac troponin-I. J Vet Intern Med 21, 238-242.

Rossignol, B.; Gueret, G.; Gall, G.L. and Arvieux, C.C. (2003): A comparison of sevoflurane, target-controlled infusion propofol, anesthesia in patients undergoing elective brain tumor surgery: costs and recovery profile. ASA abstract number A280.

Rucchiuti, V.; Sharkey, S.W. and Murokami, M.M. (1998): Cardiac troponin I and T alterations in dogs with myocardial infarction: correlation with infarct size. Am J Clin Pathol 110, 241-247.

Slack, J.O.; McGuirk, S.M.; Erb, H.N.; Lien, L.; Coombs, D.; Semrad, S.D.; Riseberg, A.; Marques, F.; Darien, B.; Fallon, L.; Burns, P.; Murakami, M.A.; Apple, F,S. and Peek, S.F. (2005): Biochemical Markers of Cardiac Injury in Normal, Surviving Septic, or Nonsurviving Septic Neonatal Foals. J Vet Intern Med 19, 577–580.

Suzuki, K.; Uchida, E.; Schober, K.E.; Niehaus, A.; Rings, M.D. and Lakritz, J. (2012): Cardiac troponin I in calves with congenital heart disease. J Vet Intern Med 26, 1056-1060.

Uçar, F. and Turhan, S. (2005): Natriüretik Peptidler. Türk Hij Den Biyol Derg 62, 49- 54.

Vartner, D.E. and Ingwall, J.S. (1984): Effect of moderate pressure overload cardiac hypertrophy on the distribution of creatinin kinase isoenzymes. Proc Soc Exp Biol Med 175, 5-9.

Van, Kimmenade, R.R. and Januzzi, J.L. (2009): The evolution of the natriuretic peptides – Current applications in human and animal medicine. J Vet Cardiol 11, 9-21.

Wells, S.M. and Sleeper, M. (2008): Cardiac troponins. Vet Emerg Crit Care 18, 235-245.

Wells, T.M.; Kukes, G.D. and Sandwies, L.M. (2002): Differences of creatinin kinase MB and cardiac troponin I concentrations in normal and diseased human myocardium. Annals Clin Lab Sci 32,44-49