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RESEARCH ARTICLE

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Evaluation of the levels of cardiac troponin I as an end point in resuscitation of dogs with hemorrhagic shock

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ABSTRACT

This study sought to assess the levels of cardiac troponin I, as a resuscitation end point, along with oxygen delivery (DO_2) and oxygen consumption (VO_2) during resuscitation of dogs with experimental hemorrhagic shock using lactated Ringer's solution or 6% hydroxyethyl starch. After induction of anesthesia (control measurements), hemorrhagic shock was induced by rapid removal of blood to achieve a mean arterial pressure (MAP) of 40 to 50 mmHg within 30 minutes and then maintained in hypovolemic situation for additional 30 minutes (second and third stages of measurements). Afterward, the dogs were randomly assigned to two groups which received 20 ml/kg lactated Ringer's solution or 5 ml/kg Hydroxyethyl starch, in four consecutive 15 minutes intervals (forth stage of measurements). One hour after the last resuscitation step, final measurements were performed. Hemorrhagic shock caused marked elevation in the levels of cTnI and reduction in DO_2 and VO_2 ($p < 0.05$). Following resuscitation, a significant reduction was observed in the levels of cTnI and VO_2 but a significant elevation was seen in DO_2 levels ($p < 0.05$), without significant differences between the groups ($p > 0.05$). The results of this study proved that cTnI can be evaluated for better monitoring during fluid therapy in hemorrhagic shock, as a novel resuscitation end point.

Keywords

cardiac troponin I, dog, hemorrhagic shock

Abbreviations

cTnI: Cardiac Troponin I
DO_2: Oxygen Delivery
VO_2: Oxygen Consumption
MAP: Mean Arterial Pressure
CO: Cardiac Output

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Introduction

Hemorrhagic shock is characterized by decreased mean arterial pressure (MAP), cardiac output (CO), and tissue hypoxia [18]. Significant loss of intravascular volume may lead sequentially to a critical decrease in oxygen delivery (DO_2) and, in later stages, a decreased tissue oxygen consumption (VO_2), which results in altered cell metabolism, cell death, and multiorgan failure [17].

Cardiac Troponin I (cTnI) is a myocardial regulatory protein of the contractile apparatus that is released into the serum as a result of myocyte injury [23]. Due to its cardiac muscle specificity and very low concentrations in the serum of normal individuals [7], evaluation of cTnI is a highly sensitive and specific method for the detection of myocardial cell damage in dogs [9].

Previous studies have used cTnI concentration to assess healthy dogs and dogs with a variety of diseases such as gastric dilatation and volvulus, ehrlichiosis, pyometra, congestive heart failure or with experimentally induced myocardial infarction [20, 22]. In addition, hemorrhagic shock may cause myocardial ischemic injury and play an important role in the release of troponin from the cardiomyocytes [2, 3]. Fluid therapy is considered the first therapeutic strategy to resuscitation of most patients with hypotension and shock [16]. However, its effect on changes in the cTnI levels caused by probable myocardial ischemia during hemorrhagic shock is unclear. Also the solution to be infused into a hemodynamically unstable patient is still under debate [24].

Troponin I has not been previously evaluated in hemorrhagic shock as well as fluid resuscitation in dogs. Therefore, the aim of this study was to assess the effect of fluid therapy on the probable myocardial ischemia induced by severe hemorrhagic shock in dogs using evaluation of cTnI levels, as a resuscitation end point, along with DO_2 and VO_2 after induction of hemorrhagic shock and fluid resuscitation with lactated Ringer's solution and 6% hydroxyethyl starch.

Results

In this study, the average blood volume loss was 54 ± 4 ml/kg, which corresponded to approximately 62% ± 4% of the estimated circulating blood (88 ml/kg) volume; so that there were no significant differences between the groups ($p > 0.05$).

Serum cardiac troponin I, oxygen delivery and oxygen consumption levels are presented in Table 1. Evaluation of the cTnI, DO_2 and VO_2 levels demonstrate no considerable differences between the groups throughout the study stages ($p > 0.05$). After induction of hemorrhagic shock cTnI levels increased significantly in both groups compared to E1 ($p < 0.05$). Results revealed no statistically remarkable differences in cTnI levels between E2 and E3 ($p > 0.05$). Furthermore, during resuscitation steps there were no significant changes compared to hypovolemic stage (E3) in both groups ($p > 0.05$). Although cTnI levels in the last stage of evaluation elevated in comparison with all previous stages in both groups, but it was only statistically significant at E1 and resuscitation steps (E4 to E7) ($p < 0.05$).

After induction of hemorrhagic shock (E2) signs of tissue hypoperfusion were evident, so that in both groups a notable decrease in DO_2 and VO_2 were observed compared to E1 ($p < 0.05$), although there

Table 1
Mean ± SD of serum cardiac troponin I, oxygen delivery and oxygen consumption levels at the baseline, after induction of hemorrhagic shock, hypovolemia, resuscitation with LR and HES, and post resuscitation stages in dogs

Factors	cTnI (ng/ml)		DO_2 (ml/min/kg)		VO_2 (ml/min/kg)	
Steps	LR	HES	LR	HES	LR	HES
E1	0.49 ± 0.016^{c}	0.53 ± 0.11^{c}	34.20 ± 7.99^{a}	36.19 ± 8.17^{a}	8.87 ± 1.55^{a}	9.40 ± 1.25^{a}
E2	2.12 ± 0.89^{ab}	2.03 ± 0.88^{ab}	21.11 ± 3.36^{c}	23.89 ± 6.48^{c}	5.37 ± 1.29^{b}	5.17 ± 1.18^{b}
E3	1.97 ± 1.34^{ab}	1.71 ± 1.15^{ab}	19.98 ± 3.36^{c}	21.08 ± 4.95^{c}	4.88 ± 1.57^{b}	4.8 ± 1.09^{b}
E4	0.99 ± 0.56b^{c}	1.21 ± 0.11^{bc}	24.02 ± 2.54^{bc}	22.79 ± 4.51^{c}	3.07 ± 1.03^{c}	2.17 ± 0.55^{c}
E5	1.11 ± 0.43b^{c}	1.06 ± 0.64^{bc}	22.6 ± 1.49^{bc}	24.63 ± 5.75^{bc}	2.96 ± 0.47^{c}	2.44 ± 0.41^{c}
E6	0.58 ± 0.08b^{c}	1.29 ± 0.44^{bc}	24.10 ± 3.92^{bc}	29.66 ± 8.54^{b}	3.21 ± 0.39^{c}	2.78 ± 0.37^{c}
E7	0.82 ± 0.49b^{c}	0.83 ± 0.48^{bc}	24.62 ± 3.04^{b}	33.98 ± 9.35^{a}	3.54 ± 0.44^{bc}	3.06 ± 0.29^{c}
E8	6.93 ± 5.9^{a}	6.58 ± 4.29^{a}	30.8 ± 3.09^{a}	33.52 ± 9.26^{a}	7.17 ± 1.15^{a}	6.89 ± 1.07^{a}

LR: Lactated Ringer's solution, HES: 6% hydroxyethyl starch. Different letters in each column denote significant differences ($p < 0.05$).

were no significant differences with E3 ($p > 0.05$). Despite relative increase in the levels of DO_2 during resuscitation steps, there were statistically insignificant differences in E4 and E6 in groups B and A, respectively, and in E5 in both groups compared to hypovolemic stage (E3) ($p > 0.05$). In the Post-resuscitation stage (E8), only animals that were resuscitated with LR showed significant increase in DO_2 levels compared to E7 ($p < 0.05$). During the resuscitation stage, all steps demonstrated notable decrease in VO_2 compared to E3 ($p < 0.05$), except animals in group A at E7 that showed no change ($p > 0.05$). Also significant increase were observed in VO_2 levels between last step of resuscitation (E7) and post-resuscitation stage (E8) in both groups ($p < 0.05$).

Table 2 shows the changes of mean arterial pressure and blood lactate levels throughout the study. There was no considerable difference between the studied groups according to MAP ($p > 0.05$). Evaluation of the blood lactate levels demonstrated significant increase in group A compared to group B ($p < 0.05$). In the last stage of evaluation, MAP and blood lactate levels approximately returned to control values and showed no significant differences compared to E1 ($p > 0.05$).

Table 2
Mean ± SD of mean arterial pressure and blood lactate levels at the baseline, after induction of hemorrhagic shock, hypovolemia, resuscitation with LR and HES, and post resuscitation stages in dogs

Factors	MAP (mmHg)		Lactate (mmol/L)	
Steps	LR	HES	LR	HES
E1	76.8 ± 14.2^{a}	67.2 ± 10.5^{6a}	0.59 ± 0.23^{c}	0.41 ± 0.17^{c}
E2	45 ± 3^{b}	43 ± 2.12^{c}	2.52 ± 0.68^{a}	2.26 ± 0.5^{a}
E3	45.4 ± 4.33^{b}	47.4 ± 2.3^{bc}	2.93 ± 0.88^{a}	2.65 ± 0.67^{a}
E4	64 ± 9.27^{a}	62.2 ± 10.79^{abc}	2.11 ± 0.74^{ab}	1.48 ± 0.72^{a}
E5	66.4 ± 6.06^{a}	70.8 ± 9.81^{a}	1.76 ± 0.77^{b}	0.99 ± 0.41^{b}
E6	69.6 ± 8.38^{a}	75 ± 11.3^{a}	1.41 ± 0.58^{b}	0.81 ± 0.29^{b}
E7	68.4 ± 10.21^{a}	74 ± 11.4^{a}	1.19 ± 0.5^{4b}	0.57 ± 0.16^{b}
E8	61 ± 9.43^{a}	68.3 ± 10.48^{abc}	0.75 ± 0.47^{c}	0.61 ± 0.14^{c}

LR: Lactated Ringer's solution, HES: 6% hydroxyethyl starch. Different letters in each column denote significant differences ($p < 0.05$).

Discussion

In the present study, hemorrhagic shock caused significant elevation in cTnI levels, however, during fluid resuscitation cTnI levels almost returned to pre-shock values in both groups.

Cardiac troponin I was accepted by the Joint Committee of the European Society of Cardiology/American College of Cardiology as the preferred biomarker for the diagnosis of acute myocardial injury [1]. Damage and disintegration of the cardiac sarcomere causes release of cTnI, as a high sensitive and specific long-lived biomarker for myocardial damage, into the general circulation that is cleared by the liver, kidney, and reticuloendothelial system [12, 20]. Evaluation of cTnI is valuable for monitoring treatment response because its levels are directly related to the extent of damaged myocard [9].

In this study, because of a lower tendency to depress the cardiovascular system, propofol and isoflurane were used to induce and maintain anesthesia, respectively [6]. However, part of increased cTnI levels in dogs after induction of hemorrhagic shock and cessation of resuscitation may be due to anesthetic drugs. So that anesthesia may cause complex changes in cardiovascular function, such as cardiovascular depression with hypotension and decreased tissue perfusion, and in turn to decreased myocardial oxygen delivery and cellular injury. Cilli et al. (2010) suggested that minor myocardial cell damage may occur during routine anesthesia, because they observed increased cTnI after anesthesia compared to pre-anesthesia levels in 14% of apparently healthy dogs [7].

Hypovolemia induced by experimental hemorrhagic shock in dogs during this study may act an important role in releasing of troponin from the cardiomyocytes. Subendocardial hemorrhages and necrosis were demonstrated to occur in the myocardium of severely injured patients after fatal hypovolemic shock [3]. Arterial blood pressure is one of the most important determinants of myocardial blood flow. As a result of hypovolemia, mean arterial blood pressure was reduced to 40-50 mmHg. According to the results of Arlati et al. (2000), hypotension may cause cardiac damage in critically ill patients with acute non-cardiac diseases, as shown by abnormal levels of cTnI [3]. Thus, hypotension is another contributed factor that may be responsible of high cTnI levels in the present study.

Following the onset of hemorrhage, blood lactate levels were increased significantly, due to decreased blood flow that leads to a decreased supply in both oxygen and substrate to the organs involved in the lactate metabolism, especially the liver [25]. However, the lag phase in the reduction of lactate levels in group A can be related to the time interval required for the liver to handle a lactate load [4].

Post-hemorrhagic decrease in the DO_2 and VO_2 is

thought to be due to the decrease in the stroke volume [14]. The resulting imbalance of DO_2 and VO_2 can enhance the probability of myocardial ischemia [3]. In fact, myocardial oxygen supply was impaired by lowered arterial blood pressure, whereas increased heart rate resulted in an increased myocardial oxygen demand [12] and although not documented in dogs, these events are likely to also underlie canine myocardial injury. Therefore, part of the increased levels of cTnI in the current survey can be due to myocardial ischemia.

Noncardiac parameters can also affect cTnI, so that increased levels of this biomarker have been documented in azotemic cats and dogs [9]. In this study, after induction of hemorrhagic shock, urine output significantly decreased, probably due to the occurrence of pre-renal azotemia, which can cause transient elevation in serum cTnI levels.

In the current study, the end point resuscitation method was used. Therefore, traditional end point parameters such as heart rate, mucous membrane color and capillary refill time, urine output, peripheral pulse quality and blood pressure [13], were assessed routinely at the end of each steps. Most of the mentioned parameters almost returned to the resuscitation end point during the fluid therapy and maintained their stability until the last stage of the study. The cTnI levels showed a successful reduction, similar to other factors considered during the resuscitation stage, which may be due to increased intravascular volume and blood pressure, improved pre-renal azotemia as well as increased urinary output. But elevated cTnI levels in the eighth step of evaluation can be the result of defects in myocardial oxygen diffusion in the early post resuscitation period. Accordingly, the probable etiology is subendocardial ischemia during hemorrhagic shock with either post-resuscitation impairment of myocardial oxygen diffusion, or in cellular oxygen utilization, or both [2]. Due to the low interval of time after the last resuscitation step, this situation is probably temporary. It is worth noting that cTnI levels reduce to baseline within 5– 10 days of the initial injury [9].

The lack of significant differences in serum troponin I levels between the two types of solutions that were used, despite different dosage, probably is due to the discrepancy in mechanisms of action as well as the half-life of infused fluids.

All studied dogs were apparently normal up to one week after induction of shock. Thus, a high cTnI level is not always related to poor outcome. This confirms the data obtained by Hamacher et al. (2015) who reported that cTnI can be an additional tool for the evaluation of disease severity, but it is not reliable to distinguish between survival and nonsurvival ones [10].

Serum cTnI elevation in this study indicated that destruction of cardiomyocytes occurs during hemorrhagic shock in dogs. Based on the present study, cTnI as a novel resuscitation end point, can be evaluated for better monitoring during fluid therapy in hemorrhagic shock.

Materials and methods

Animal Preparation

Ten male mongrel dogs, aged 1.5 – 3.5 years and weighing 18.56 ± 4.80 kg, were included in the study. They were in good health according to clinical examination, hematological and biochemical parameters. Animals were excluded from the study if they had a relevant cardiac disease determined by the echocardiographic and electrocardiographic examinations.

All dogs were housed in single environmentally controlled cages. The animals were fasted for 12 hours prior to experiment but had free access to water. After blood cannulation with an 18-gauge catheter in the right cephalic vein (for drugs and fluid administration) and left jugular vein (for collection of blood samples), the anesthesia was induced with an intravenous bolus dose of propofol (Lipuro 1%, Braun, Melsungen, Germany) (6.0 mg/kg) and fentanyl (Caspian Tamin, Rasht, Iran) (5 µg/kg) [5]. The dogs were intubated with an 8.0 to 8.5 mm endotracheal tube and immobilized in right lateral recumbency on the operating table. Anesthesia was maintained with isoflurane (1.8%) in 100% oxygen [8]. A catheter was placed into the bladder for urinary volume measurement. In the medial right hindlimb of the animals, dissection of the femoral artery was performed and a 16-gauge catheter was inserted and connected to a 3-way stopcock for induction of bleeding and obtaining arterial blood samples.

By the electronic multi-parameter monitor (PM-9000Vet, Burtons, Kent, UK), vital signs such as heart rate, respiratory rate and blood pressure were monitored throughout the experiment. Body temperature was monitored by a rectal temperature probe and was maintained at 37°C to 38°C with a heating blanket [19]. Also, mucous membrane color, capillary refill time and peripheral pulse quality were assessed routinely at the end of each step.

Experimental Protocol

During this study eight steps of evaluation was performed in five distinct stages.

Control stage (E1): Baseline measurements were obtained after induction of anesthesia and instrumentation.

Hemorrhagic stage (E2): Each dog was hemorrhaged to a MAP ranging from 40 to 50 mmHg [5]. The procedure lasted approximately 30 min and blood was collected into sterile empty blood bags.

Hypovolemic stage (E3): The animals were left in shock state for an additional 30 min period during which no fluid was administered. If a physiologic compensatory mechanism developed and MAP increased above the purpose values, more blood was removed to restore the MAP back to 40 to 50 mmHg.

Resuscitation stage (E4 – E7): Animals were randomly allocated into two equal groups 30 minutes after induction of hemorrhagic shock, based on the type of infused fluids. Group A was resuscitated with lactated Ringer's solution (LR) (Iranian Parenteral and Pharmaceutical Co., Tehran, Iran) at 20 ml/kg in 15 min for four consecutive times. Group B was resuscitated with 6% hydroxyethyl Starch (HES) (Voluven, Fresenius Kabi, Homburg, Germany) at 5 ml/kg in a similar manner to group A.

Post-resuscitation stage (E8): The last stage of evaluation was performed one hour after termination of resuscitation. Then, animals were allowed to recover from anesthesia.

In each of the above-mentioned steps, whole blood samples were collected for measurements of cTnI. Samples were centrifugated for 5 minutes at 4,000 × g after being allowed to clot for 30 minutes [10]. Serum was separated and stored in Eppendorf tubes at -80°C. Serum cTnI concentrations were measured using the human Access AccuTnI assay (Monobind, Inc., Lake Forest, USA). The AccuTnI assay uses a chemiluminescent sandwich ELISA technique that previously has been shown to have great sensitivity and specificity for canine cTnI with an analytical sensitivity of 0.02 ng/mL [21]. In addition, arterial and mixed venous blood was collected in heparinized insulin syringe and immediately analyzed for Arterial oxygen tension (PaO_2), Mixed venous oxygen tension (PvO_2), Arterial hemoglobin saturation (SaO_2), Mixed venous hemoglobin saturation (SvO_2) and plasma lactate with a blood gas analyzer (Blood Gas and Chemistry Analyzer, i15Vet - Edan Instruments, Inc., Shenzhen, China). Arterial and mixed venous oxygen contents (CaO_2 and $CmvO_2$, respectively) were calculated as follows [11]:

$CaO_2 = (1.34 \times Hb \times SaO_2) + (0.003 \times PaO_2)$

$CmvO_2 = (1.34 \times Hb \times SvO_2) + (0.003 \times PvO_2)$

DO_2 and VO_2 were estimated as [11]:

$DO_2 = CaO_2 \times (CI\ (kg)/100)$

$VO_2 = (CaO_2 - CmvO_2) \times [CI\ (kg)/100]$, where CI (cardiac index) = Cardiac output/ kg body weight.

Also, to estimation of the stroke volume, transthoracic Doppler echocardiography (Digital Color Doppler Diagnostic Ultrasound, Model: Mirror 2, Landwind Medical, Shenzhen, China) using a 5.0 MHz phased array transducer was performed by evaluation of cross-sectional area of aorta and aortic flow. Then, CO was calculated as follow [15]:

CO = VTI × aortic cross-sectional area × heart rate, where VTI (Velocity-Time Integral) = area under the velocity spectrum.

Data analysis

Data of this study were evaluated by repeated measures analysis of variance and LSD post hoc using SPSS 16.0 statistical software (SPSS, Inc., Chicago, USA). All data are presented as mean ± SD. A *p* value of less than 0.05 was considered significant.

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Author Contributions

Conceived and designed the experiments: R.A., R.A., A.G. Performed the experiments: A.G., H.I, R.A. Analyzed the data: M.P. Research space and equipment: R.A, M.R. Contributed reagents/materials/ analysis tools: M.R., H.I. Wrote the paper: R.A.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined: A consensus document of the Joint European Society of Cardiology/ American College of Cardiology Committee for the Redefinition of Myocardial Infarction. J Am Coll Cardiol. 2000 Sep;36(3):959-69.

2. Archie JP, Mertz WR. Myocardial oxygen delivery after experimental hemorrhagic shock. Ann Surg. 1978 Feb;187(2):205-10.

3. Arlati S, Brenna S, Prencipe L, Marocchi A, Casella GP, Lanzani M, et al. Myocardial necrosis in ICU patients with acute non-cardiac disease: a prospective study. Intensive Care Med. 2000 Jan;26(1):31-7.

4. Baue AE, Tragus ET, Wolfson SK Jr, Cary AL, Parkins WM. Hemodynamic and metabolic effects of Ringer's lactate solution in hemorrhagic shock. Ann Surg. 1967 Jul;166(1):29-38.

5. Braz J, Nascimento P, Filho O, Braz L, Vane LA, Galva˜oVianna PT, et al. The early systemic and gastrointestinal oxygenation effects of hemorrhagic shock resuscitation with hypertonic saline and hypertonic saline 6% dextran-70: A comparative study in dogs. Anesth Analg. 2004 Aug;99(2):536-46.

6. Cheung AT, Driessen B, Jahr JS, Duong PL, Ramanujam S, Chen PC, et al. Blood substitute resuscitation as a treatment modality for moderate hypovolemia. Artif Cells Blood Substit Immobil Biotechnol. 2004 May;32(2):189-207.

7. Cilli F, Alibhai H, Armitage-Chan E, Boswood A, Hammond RA, Jasani S, et al. Incidence of elevation of cardiac troponin I prior to and following routine general anaesthesia in dogs. Vet Anaesth Analg. 2010 Sep;37(5):409-16.

8. Dyson D, Sinclair M. Impact of dopamine or dobutamine infusions on cardiovascular variables after rapid blood loss and volume replacement during isoflurane-induced anesthesia in dogs. Am J Vet Res. 2006 Jul;67(7):1121-30.

9. Hagman R, Lagerstedt AS, Fransson BA, Bergström A, Häggström J. Cardiac troponin I levels in canine pyometra. Acta Vet Scand. 2007 Feb 28;49:6.

10. Hamacher L, Dörfelt R, Müller M, Wess G. Serum cardiac troponin I concentrations in dogs with systemic inflammatory response syndrome. J Vet Intern Med. 2015 Jan;29(1):164-70.

11. Haskins S, Pascoe PJ, Ilkiw JE, Fudge J, Hopper K, Aldrich J. Reference cardiopulmonary values in normal dogs. Comp Med. 2005 Apr;55(2):156-61.

12. Karpati PC, Rossignol M, Pirot M, Cholley B, Vicaut E, Henry P, et al. High incidence of myocardial ischemia during postpartum hemorrhage. Anesthesiology. 2004 Jan;100(1):30-6. 13. Keefe J. Shock and Initial Stabilization. In: Norkus C, editor. Veterinary Technician's Manual for Small Animal Emergency and Critical Care. 1st ed. Iowa: Wiley-Blackwell; 2012.

14. Ko JJ, Alam R, Kim NS. Hemodynamic effects of fluid resuscitation with 6% hydroxyethyl starch and whole blood in experimental hypovolemic shock in Beagle dogs. Turk J Vet Anim Sci. 2012 Jan;36(4):416-23.

15. Lopes PC, Sousa MG, Camacho AA, Carareto R, Nishimori CT, Santos PS, et al. Comparison between two methods for cardiac output measurement in propofol-anesthetized dogs: thermodilution and Doppler. Vet Anaesth Analg. 2010 Sep;37(5):401-8.

16. Marik P. Hemodynamic parameters to guide fluid therapy. Transfus Altern Transfus Med. 2010 Sep;11(3):102-112.

17. Moore KE, Murtaugh RJ. Pathophysiologic characteristics of hypovolemic shock. Vet Clin North Am Small Anim Pract. 2001 Nov;31(6):1115-28.

18. Murakawa K, Kobayashi A. Effects of vasopressors on renal tissue gas tensions during hemorrhagic shock in dogs. Crit Care Med. 1988 Aug;16(8):789-92.

19. Nascimento P.Jr, De Paiva Filho O, de Carvalho LR, Braz JR. Early Hemodynamic and Renal Effects of Hemorrhagic Shock Resuscitation with Lactated Ringer's Solution, Hydroxyethyl Starch, and Hypertonic Saline with or without 6% Dextran-70. J Surg Res. 2006 Nov;136(1):98-105.

20. Oyama MA, Sisson DD. Cardiac troponin-I concentration in dogs with cardiac disease. J Vet Intern Med. 2004 Nov-Dec;18(6):831-9.

21. Oyama MA, Solter PF. Validation of an immunoassay for measurement of canine cardiac troponin-I. J Vet Cardiol. 2004 Nov;6(2):17-24.

22. Schober K, Cornand C, Kirbach B, Aupperle H, Oechtering G. Serum cardiac troponin I and cardiac troponin T concentrations in dogs with gastric dilatation-volvulus. J Am Vet Med Assoc. 2002 Aug 1;221(3):381-8.

23. Strickland KN. Pathophysiology and Therapy of Heart Failure. In: Smith FWK, Tilley LP, Oyama MA, Sleeper MM, editors. Manual of canine and feline cardiology. 5th ed. Missouri: Elsevier; 2016.

24. Udelsmann A, Bonfim MR, Silva WA, Moraes AC. Hemodynamic effects of volume replacement with saline solution and hypertonic hydroxyethyl starch in dogs. Acta Cir Bras. 2009 Mar-Apr;24(2):87-92.

25. Vincent JL, Dufaye P, Berré J, Leeman M, Degaute JP, Kahn RJ. Serial lactate determinations during circulatory shock. Crit Care Med. 1983 Jun;11(6):449-51.