Vasoactive use in early goal-directed therapy in dogs with severe sepsis and septic shock

Havva SÜLEYMANOĞLU[1,a,✉], Kürşad TURGUT[1,b], Merve ERTAN[1,c], Mehmet Ege İNCE[1,d], Amir NASERI[2,e]

[1]Near East University, Faculty of Veterinary Medicine, Department of Internal Medicine, 99280, Nicosia, North Cyprus; [2]Selçuk University, Faculty of Veterinary Medicine, Department of Internal Medicine, TR-42003, Konya, Türkiye

[a]ORCID: 0000-0002-6681-0212; [b]ORCID: 0000-0001-8725-8044; [c]ORCID: 0000-0003-3436-4817; [d]ORCID: 0000-0002-1859-1449
[e]ORCID: 0000-0001-9140-5879

ARTICLE INFO

Article History
Received : 26.11.2021
Accepted : 10.06.2022
DOI: 10.33988/auvfd.1028816

Keywords
Dobutamine
Early goal-directed therapy
Norepinephrine
Septic shock
Severe sepsis

✉Corresponding author
havva.suleymanoglu@neu.edu.tr

How to cite this article: Süleymanoğlu H, Turgut K, Ertan M, İnce ME, Naseri A (2023): Vasoactive use in early goal-directed therapy in dogs with severe sepsis and septic shock. Ankara Univ Vet Fak Derg, 70 (3), 327-335. DOI: 10.33988/auvfd.1028816.

ABSTRACT

The goal of this study was to see how to evaluate the changes in macrovascularand microvascular parameters in survivors (Sv) and non-survivors (non-Sv) dogs with severe sepsis and septic shock (SEVS & SEPS) in response to goal-directed hemodynamic optimization at the intensive care unit (ICU), and to evaluate norepinephrine (NE) and dobutamine (DT) ICU applications, and their effectiveness for predicting death. Thirty-five dogs with SEVS & SEPS were used. NE was given to 10 hypotensive dogs, despite receiving a single bolus of fluid therapy, at a constant infusion rate of 1.5 µg/kg/min for 2 h. The rate of NE infusion was doubled (3.0 µg/kg/min) if the clinical response was insufficient after 2 hours. DT was administered to 5 dogs with left ventricular systolic dysfunction (LVSD) (LVS'<7.5 cm/s) at a constant infusion rate of 5 µg/kg/min for 2 h. The Sv and non-Sv groups had no major differences in macrovascular and microvascular characteristics, PW-TDI septal mitral annulus systolic (S') and early diastolic (E') velocities, or DT applications. The only difference was the use of NE applications. non-Sv received a greater amount of NE, while Sv received a smaller amount of NE. In contrast, more Sv received a greater amount of DT applications. Total mortality rate was 25.7%. In conclusion, the effects of DT and NE in dogs with SEVS & SEPS are limited. To provide evidence-based guidelines for dogs with SEVS & SEPS, more research is needed.

Introduction

In both veterinary and human medicine, sepsis generates a high rate of morbidity and mortality (38). When the immune system overreacts to an infection, organ failure results. In dogs, sepsis-induced myocardial dysfunction (SiMD) is caused by canine parvovirus infection (CPVI) (22).

The basic pathologic developments resulting in SEVS & SEPS are absolute or relative dehydration, LVSD and left ventricular diastolic dysfunction (LVDD) (24), and right ventricular (RV) dysfunction, Chan and Klinger (12) marked peripheral vasodilation and vasoplegia. Even following the fluid balance correction, microcirculatory abnormalities may be constant and lead to the maldistribution of cardiac output (CO) (21) multiple organ dysfunction syndromes (MODS), and death (13). The incidence levels of SEVS & SEPS is unreported in veterinary medicine. SEVS & SEPS is observed in five percent to nineteen percent of human ICU admissions (1). The mortality rate in dogs and cats with SEVS & SEPS has been reported to range from 20% to 68% (37).

Early goal-directed therapy (EGDT) protocols have been developed to normalise irregular measurable indices of tissue perfusion and oxygenation (32). Macrovascular parameters such as SBP and MAP, together with microvascular parameters such as oxygen saturation (SpO2), lactate and base deficit (BE), which are used to reflect tissue perfusion and organ dysfunction, are often used to monitor patients with SEVS & SEPS because of their good prognostic value (11).

Vasoactive agents have both vasopressor and inotropic effects, however, vasopressor actions increase

blood pressure, whereas inotropic actions increase CO in EGDT (20). NE is a sympathetic catecholamine with mixed alpha and beta adrenergic effects. Its primary site of activity is the alpha 1 receptor (35). NE should be used in all hypotensive septic patients following adequate fluid replacement therapy (2, 14). In septic patients with hypotension unresponsive to other vasopressors, Jhanji et al. (23) discovered that NE was an effective rescue medication. DT has inotropic and vasodilatory properties, potentially improving oxygen delivery and tissue perfusion (13). Therefore, current guidelines recommend the use of DT for septic patients with low CO after appropriate fluid replacement therapy (5, 14). However, the optimal treatment of hypotension with NE and low CO with DT in volume-replete patients is debatable (38). Despite its extensive use, veterinary research on the effects of DT in LVSD and NE in hypotensive dogs with SEVS & SEPS is sparse (11). We expected that improvements in EGDT would be linked to higher survival rates in dogs with SEVS & SEPS. In veterinary medicine, the value of these macrovascular and microvascular monitoring metrics, as well as the effect of NE and DT in dogs with SEVS & SEPS, has not been widely examined. Therefore, the first purpose of this study was to evaluate the changes in the monitored parameters (SBP and MAP, lactate, SpO2, BE) in canine patients with SEVS & SEPS in response to goal-directed hemodynamic optimization. The second purpose was to evaluate NE and DT applications in ICU and their effectiveness in predicting death.

Materials and Methods

Ethics committee approval for this study was obtained from Local Ethics Committee of the Near East University (permit number: 2019/03). From January 2019 to September 2020 the records of dogs that were admitted to Near East University's Animal Hospital were evaluated.

Animals: The study included 35 dogs which are 16 female and 19 male sexes and different mix breeds who were 6 months old and suffering from CPVI with SEVS & SEPS. Clinical symptoms (vomiting and/or bloody diarrhoea) and test findings (leukopenia) were consistent with CPVI in all dogs with SEVS & SEPS. None of the dogs had been inoculated with a commercial parvovirus vaccine, and all SNAP CPV antigen tests (IDEXX, SNAPshot Dx) were positive. SBP, MAP, lactate, SpO2, BE and HR, LVSD, LVDD, and cardiac troponin I (cTnI) were measured at admission, as well as after one bolus fluid therapy, low dosage vasoactive medication, double dose vasoactive medication, and recurrent double dose vasoactive medication for dogs with SEVS & SEPS. The detection of systemic inflammatory response syndrome (SIRS) and SEVS & SEPS were the inclusion criteria in the dogs with SEVS & SEPS. Any dogs who had previously undergone other therapies and had congenital heart disease or inadequate echocardiographic images/measurements were eliminated.

Definitions of sepsis: To diagnose sepsis, researchers used SIRS and a positive SNAP CPV antigen test (IDEXX, SNAPshot Dx). Case definitions for SIRS in adults (25) and children (18), as well as established reference intervals for dogs (38) were used to determine whether the dogs had SIRS if they had two or more of the following abnormalities: leukopenia (5000 cells/L), hypothermia or hyperthermia (reference interval; 37.5–39.3 °C), tachycardia (>120 beats per minute), or tachypnea (>35 breaths per minute). Severe sepsis is characterized as sepsis accompanied by organ failure, hypoperfusion, or hypotension. Septic shock was described as a case of severe sepsis that did not respond to a single bolus of IV fluid. Hypotension was defined as SBP 90 mmHg and MBP 65 mmHg (34).

Blood pressure measurement: An oscillometric approach was used to assess systolic blood pressure and MAP indirectly (Compact 7, Medical Econet, Oberhausen, Germany). After the patient had had time to acclimate to their circumstances, BP readings were taken in a quiet, secluded area. The cuff was 40 percent of the circumference of the limb. The dogs were confined to a lateral recumbency position. The initial reading was eliminated, and the average of the next five readings was calculated (11).

Echocardiographic evaluation: An echocardiograph was used to perform transthoracic echocardiography (TTE) in the ICU (GE LOGIQ e R7 CONSOLE). All dogs with SEVS & SEPS had comprehensive PW-TDI echocardiographic exams (apical 4-chamber view). All measures were taken from three cardiac cycles in dogs with sinus rhythm, and mean values were determined. Heart rate (HR) was assessed using a base-apex or lead II electrocardiogram at the same time as echocardiographic procedures (40). Two investigators (ICU staff) performed all echocardiographic measurements, and one investigator (non-certified cardiologists) analysed the videotape recorded examinations. The systolic (S') and early diastolic (E') velocities of the PW-TDI septal mitral annulus were determined (8). When the S' was less than 7.5 cm/s, LVSD was diagnosed. When the E' was less than 8 cm/s, LVDD was determined (15).

Pulse oximetry: The clamp probe of a pulse oximeter (Compact 7, Medical Econet, Germany) was placed on the dog's buccal mucosa to detect tissue oxygenation. Pulse oximetry was used to determine the buccal mucosa's SpO2.

DOI: 10.33988/auvfd.1028816

Blood gas analysis and cTnI: Peripheral venous blood samples were collected for blood gas analysis to determine BE and lactate concentrations (GEM Premier Plus). Commercial ELISA tests (MyBioSource, USA) were used to measure cTnI.

Treatment Protocol: We used a standardized EGDT procedure that included fluid therapy, vasoactive medicine, antimicrobial therapy, blood products, anticoagulants, venous thromboembolism prophylaxis, stress ulcer prophylaxis, and nourishment after taking blood samples and measurements. Lactate, glucose, SBP and MBP, SpO2, BE, and ECG recordings were used to guide shock treatment in dogs with SEVS & SEPS, according to current understanding of EGDT protocols for SEVS & SEPS (31).

For the initial 30 minutes of treatment, intravenous fluid delivery was started with a 0.9 % NaCl solution at 30 ml/kg BW. SBP, MAP, and S' were assessed after one bolus of fluid therapy, and NE and DT administration were used, respectively. The effect on clinical indicators (e.g., HR, respiration rate, mucous membrane colour, and pulse quality) was then examined after multiple (up to four) boluses of 10–20 ml/kg were given over 10–15 minutes. Following that, 0.9 percent NaCl was given at a rate of 20 ml/kg/day as fluid maintenance therapy. Intravascular volume, hypoglycaemia, and continuing fluid losses were all monitored in the dogs. If hypoglycaemia was observed, dextrose (5%) was added to the intravenous fluids. A colloid solution (hydroxyethyl starch 6 percent, 10 ml/kg/h, i.v) was administered to patients with LVDD to prevent the establishment of positive fluid balance because of the administration of massive volumes of crystalloid solution.

Ceftriaxone (Novosef®, Sanofi İlaç San. ve Tic. A.Ş., Türkiye, 30 mg/kg BW, i.v, every 8 h), enrofloxacin (Enrocure®, Türkiye, 5 mg/kg BW, i.m, every 12 h), metronidazole (Flagyl®, Aventis Pharma, Türkiye, 10 mg/kg BW, i.vevery 12 h), and meloxicam (Bavet Meloxicam®, Bavet İlaç San., Türkiye, 0.1 mg/kg BW, i.v, 24 h) were used as wide-spectrum antibiotics and anti-inflammatory treatments, respectively.

A nasal oxygen mask was used to administer oxygen (100 ml/kg, BW/min) to dogs with a SpO2 of less than 90%. Metoclopramide was given if needed for vomiting or nausea. Pantoprazole (Protaz®, HTA, Türkiye, 1 mg/kg BW, i.v, every 24 h), was applied daily for stress ulcer prophylaxis. Potassium was supplemented if K+ levels were below 3.5 mEq/l.

To provide external warmth, hypothermic dogs were placed under an infrared heat lamp. Dalteparin (FRAGMIN®, Pfizer, Belgium) was given as a venous thromboembolism prophylaxis dose of 100 IU/kg s.c every 8 to 12 hours. In dogs with a haematocrit of less than 20%, fresh complete blood was given at a dosage of 20 ml/kg (33).

Vasoactive therapy: Despite receiving a single bolus of fluid treatment, hypotensive dogs were given vasopressor therapy by delivering NE (1.5 µg/kg/min in 0.9 percent NaCl solution) without a loading dose. If an acceptable clinical reply was not obtained after 2 hours, the dosage of NE administration in 0.9 percent NaCl solution was increased to 3.0 µg/kg/min (22, 41). DT was administered to dogs with LVS'<7.5 cm/s at a constant infusion for 2 h of 5 µg/kg/min in 0.9% NaCl solution. In cases which do not result in an adequate clinical response in 2 h a doubling of the DT infusion (10 µg/kg/min) was administered (40, 41).

Small amounts of food were introduced once feeding did not majorly exacerbate the levels of vomiting. We administered parenteral nutrition if prolonged anorexia occurred. For this reason, dogs received a 10 ml/kg i.v infusion of a solution (Duphalyte® solution, Zoetis, London, United Kingdom) each day. Before infusion, intravenous fluids were warmed to 38°C in a hot water bath.

Patient follow-up: The dogs were observed for 28 days to see if they died. According to their treatment response, the dogs were classified into two groups: survivors (Sv) and non-survivors (non-Sv). Dogs alive at discharge were considered Sv, and dogs that died were considered non-Sv.

Statistical analysis: Statistical software was used to analyse the data (SPSS 25.00 for windows). The Shapiro-Wilk test was done to see if the variables had a normal distribution. The independent samples t-test was used to examine the parametric data, and the results were provided as mean standard deviation (SD). The Mann Whitney U test was used to examine non-parametric data, and the median (min/max) was provided. Fisher Exact test was used to examine categorical variables. For NE and DT - treated pups, a Kaplan–Meier analysis and log-rank tests were utilized to assess survival probability. $P<0.05$ was used to determine statistical significance.

Results

Animals: Age, body weight, and sex differences were not significantly the distinction between Sv and non-Sv groups. The differences in macrovascular (SBP and MAP) and microvascular parameters (lactate, SpO2, BE), S' and E', and DT applications were also not significantly distinction between the two groups (Tables 1 and 2). The only the distinction between the Sv and non-Sv groups was the use of NE applications (Table 2).

Table 1. Base excess (mean ± standard deviation), lactate (mean ± standard deviation), SpO2 (%) (mean ± standard deviation), SBP and MAP (mean ± standard deviation), norepinephrine application, and Dobutamine application compared between survivors (n = 25) and non-survivors (n = 10) among the dogs treated for SS/SS.

Parameters	Non-Survivor	Survivor	P value
SBP (mmHg)	115.18±33.69	110.62±29.66	0.705
MAP (mmHg)	81.18±28.72	82.54±21.60	0.891
SpO_2 (%)	64 (19-91)	64.50 (20-99)	0.563
Lactate (mmol/L)	1.60 (0.70-31.00)	3.37 (0.80-26.00)	0.124
BE (mmol/L)	-5.60 (-17.90-1.90)	-6.35 (-17.90-12.80)	0.713
Norepinephrine (n)	**8 (72%)**	**2 (8%)**	**0.000**
Dobutamine (n)	1 (%9)	4 (%16)	0.491

SpO_2: oxygen saturation, SBP: systolic blood pressure, MBP: mean blood pressure, BE: base excess

Table 2. Heart rate (mean ± standard deviation), echocardiographic parameters (mean ± standard deviation) and cTnI (mid) compared between survivors (n = 25) and non-survivors (n = 10) among dogs treated for SS/SS.

Parameters	Non-Survivor	Survivor	P value
HR (bpm)	185.18±30.19	189.83±29.42	0.675
cTnI(pg/ml)	251 (57-920)	414 (57-1000)	0.211
S' (cm/s)	8.65±2.35	9.54±2.88	0.357
E' (cm/s)	6.99±2.31	5.41±1.36	0.054

HR: heart rate, cTnI: cardiac troponin I, S': septal mitral annulus systolic, E': early diastolic

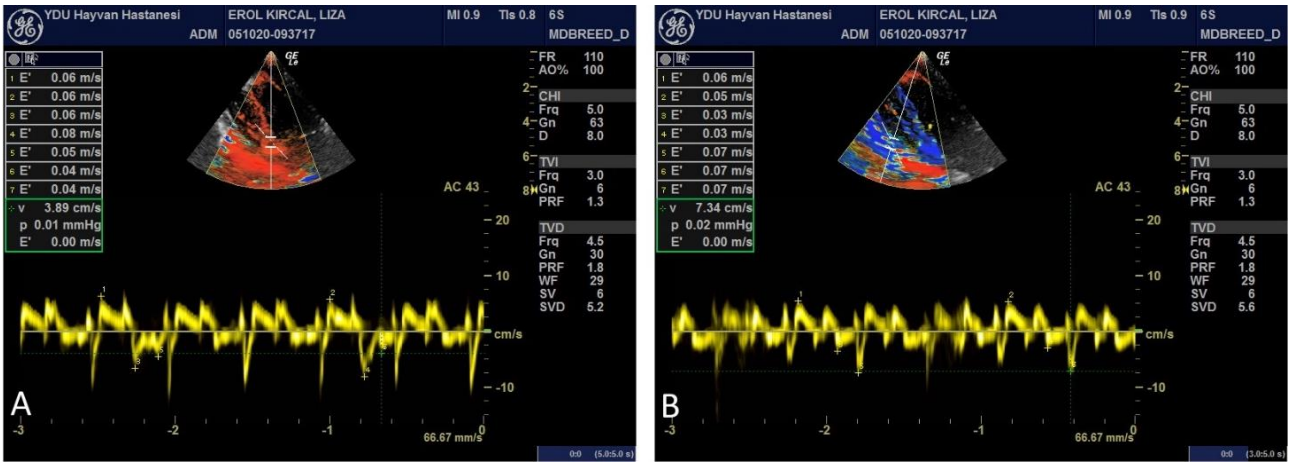

Figure 1. Left apical 4 chamber view in a dog for measurement of PW – Tissue Doppler Imagining mitral annulus systolic (Sm), early (Em) and late (Am) diastolic pick velocities. The Sm is less than 10cm/s and Em is less than 8 cm/s (A). No change was observed in the echo data and they died despite the administration of norepinephrine (B).

Systolic and diastolic dysfunctions: At the time of admission, 26 of the SEVS & SEPS dogs (74 percent) at least one type of myocardial dysfunction was present. LVSD (LVS' 7.5 cm/s) and LVDD (E' 8 cm/s) were both present in 7 (20%) of the participants, while both forms of dysfunction were present in 5 (14%), while 19 (60%) patients had both types of dysfunction. Isolated LVDD (E' <8cm/s) (Table 2) was more common type of dysfunction (16/35 46%). Neither LVSD nor LVDD were found in 9 dogs with SEVS & SEPS. A total of eight dogs with LVDD and one dog with LVSD died.

Response to vasoactive treatment: The NE group. At the time of admission, 12 of 35 dogs with SEVS & SEPS had hypotension. One SEVS & SEPS hypotensive dog had normal blood pressure after one bolus of fluid treatment. One hypotensive dog with SEVS & SEPS died during one bolus of fluid therapy. 10 of which still had low BP after one bolus fluid therapy (septic shock). 2 of which, were in the survivor group, responded to treatment with NE at the dose of 1.5 µg/kg/min. Five hypotensive dogs with SEVS & SEPS, which were in the non-Sv group, not responded to treatment with NE at the dose of 3.0 µg/kg/min (Figure 1).

The rest of 3 dogs with SEVS & SEPS, which were in the non-Sv group, not responded to treatment with repeated NE at the dose of 3.0 µg/kg/min. After one bolus of fluid therapy, the average rate of Sv for the NE group was 91 percent, according to Kaplan-Meier analysis. The average rate of the Sv was 82% after 1.5 µg/kg/min. The average rate of the Sv was 35% after 3.0 µg/kg/min. The average rate of the Sv was 0% after repeated 3.0 µg/kg/ (P<0.05) (Figure 2).

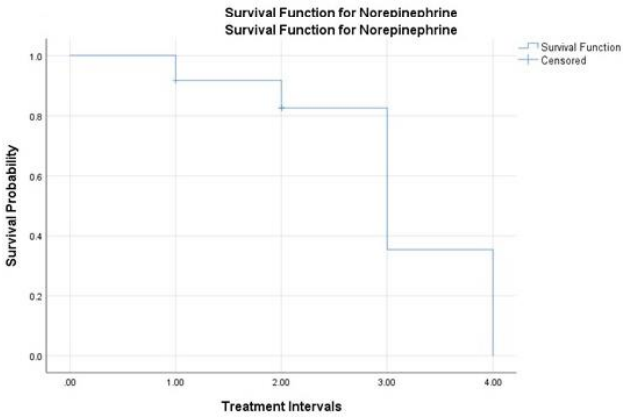

Figure 2. Kaplan-Meier's analysis showed that the average rate of the Sv was 91% after one bolus of fluid therapy for the NE group. The average rate of the Sv was 82% after 1.5 µg/kg/min. The average rate of the Sv was 35% after 3.0 µg/kg/min. The average rate of the Sv was 0% after repeated 3.0 µg/kg/ (p<0.05).
Description of treatment intervals for Norepinephrine
0: Hypotensive
1: One bolus fluid
2: Administration of norepinephrine 1.5 µg/kg/min in 2 h
3: Administration of norepinephrine 3.0 µg/kg/min, CRI in 24h
4: Administration of repeated norepinephrine 3.0 µg/kg/min, CRI in 24h

More non-Sv received a greater amount of NE, while more Sv received a smaller amount of NE.3 of 12 (25%) Sv received either no (one bolus fluid) or a single NE (1.5 µg/kg/min), while 8 of 12 (67%) non-Sv received at least 1 NE (P<0.000). The only dogs that received more than 1 NE consisted of 7 non-Sv.

DT group, 7 of 35 dogs with SEVS & SEPS had systolic dysfunction (S' 7.5 cm/s) at admission. Two of which responded to the one bolus fluid therapy and had normal systolic function (S' ≥ 7.5 cm/s). 5 of which still had S' < 7.5 cm/s after one bolus fluid therapy. All the dogs did not respond to the treatment with DT at the dose of 5µg/kg/min. 1 dog died despite the treatment with DT at the dose of 10 µg/kg/min. 1 dog responded to the treatment with DT at the dose of 10 µg/kg/min (Figure 3). 3 dogs did not respond to the treatment with DT at the dose of 10 µg/kg/min. The rest of 3 dogs with SEVS & SEPS, which were in the survivor group, responded to treatment with repeated DT at the dose of 10 µg/kg/min. The average rate of Sv for the DT group was 100 percent following one bolus of fluid treatment, according to Kaplan-Meier analysis. The average rate of the Sv was 100% after 5 µg/kg/min. The average rate of the Sv was 80% after 10 µg/kg/min. The average rate of the Sv was 100% after repeated 10 µg/kg/min (P<0.05) (Figure 4).

In contrast, more Sv received a greater amount of DT applications. While 1 (20%) non-Sv received 2 DT (5 µg/kg/min in 2 h + 10 µg/kg/min in 24 h), the 4 Sv dogs received 3 DT (5 µg/kg/min in 2 h, 10 µg/kg/min in 24 h, repeated 10 µg/kg/min in 24 h).

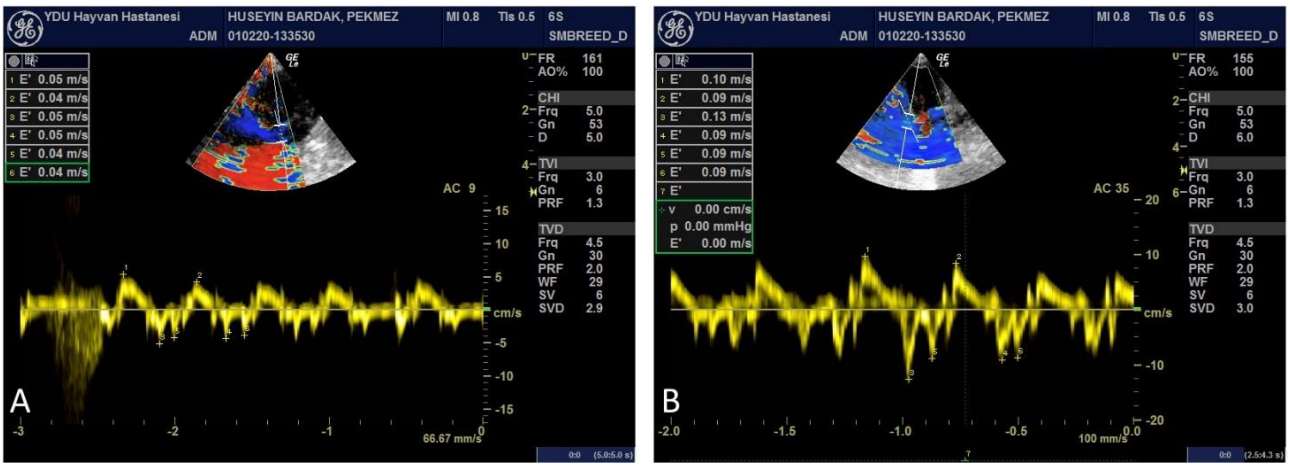

Figure 3. Left apical 4 chamber view in a dog for measurement of PW – (A). Tissue Doppler Imagining mitral annulus systolic (Sm), early (Em) and late (Am) diastolic pick velocities. (B) Normal systolic function was observed (S' ≥ 7.5 cm/s) responded to the treatment with dobutamine.

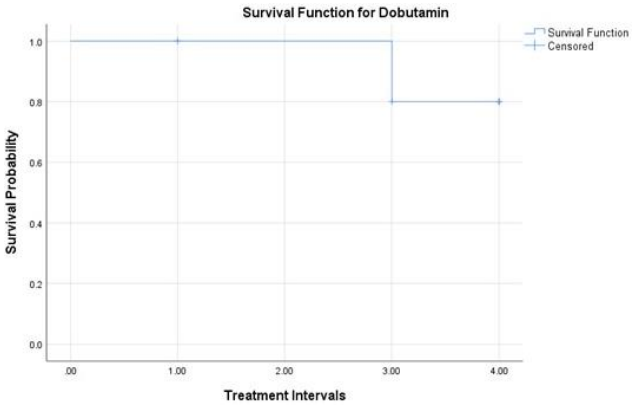

Figure 4. Kaplan-Meier's analysis showed that the average rate of the Sv was 100% after one bolus of fluid therapy for the DT group. The average rate of the Sv was 100% after 5 µg/kg/min. The average rate of the Sv was 80% after 10 µg/kg/min. The average rate of the Sv was 100% after repeated 10 µg/kg/min (P<0.05).
Description of treatment intervals for Dobutamine
0: Hypotensive
1: One bolus fluid
2: Administration of dobutamine 5 µg/kg/min, CRI in 2h
3: Administration of dobutamine 10 µg/kg/min in 24 h
4: Administration of repeated dobutamine 10 µg/kg/min in 24 h.

Mortality rate: Thirty-five dogs matched the criteria for inclusion, with 26 (74%) of those with SEVS & SEPS surviving and being discharged from the ICU (Sv). Nine individuals died, for a total mortality rate of 25.7 percent (non-Sv). The canines with LVDD (E'8 cm/s) (8 cases) and those who had NE applications (8 cases) had the lowest survival rates.

Discussion and Conclusion

Sepsis is a complex clinical syndrome, and can be complicated by tissue hypoperfusion. Septic shock is a life-threatening condition that arises when sepsis causes life-threatening hypotension (25). Septic shock death rates in dogs and cats have been found to range from 20% to 68 percent (37). LVSD and LVDD both developed in humans with SEVS & SEPS, according to studies (9). LVSD was present at admission in 7 of 35 (20%) dogs with SEVS & SEPS in our research. Two of them responded to the one bolus fluid therapy and had a normal systolic function. 1 dog died despite the treatment with DT. The rest of 4 dogs with SEVS & SEPS, which were in the Sv group, responded to treatment with DT. The patients with LVSD (7 cases) had a better survival outcome. Very high prevalence rates (60–84%) of LVDD with increased mortality have also been found in human with sepsis (24). M. E. Ince et al. (22) found that the E', an LVDD index, had the best sensitivity and specificity to distinguish Sv and non-Sv dogs, with values of 100 percent (95 percent CI: 55.2–100) and 100 percent (95 percent CI: 78.9–100), respectively, at an ideal cut-off point of 6.50. Therefore, LVDD was a good independent outcome predictor. Although there was no statistical difference (P <0.054) for E' between Sv and non-Sv dogs with SEVS & SEPS in this study, isolated LVDD (Table 2) was more common (16/35 46%), and the patients with LVDD (8 cases) had the worse survival outcome. The mitral annulus E' can be used with PW-TDI to properly quantify LV relaxation (40). E' does not alter much in response to diverse loading situations, according to several research (42). The lateral E'<10 and septal E'<8 cm/s have been observed to be highly indicative of LVDD and increased LA pressures (LAP) (17). By inhibiting LV dilation, LVDD may prevent stroke volume augmentation in response to fluid load. Lung congestion may be exacerbated by LVDD. Pulmonary hypertension and RV dysfunction might develop as a result of non-cardiogenic pulmonary oedema.

The EGDT protocols have been developed to normalise irregular measurable indices of tissue perfusion and oxygenation (32). There are two broad groups of monitoring parameters: macrovascular and microvascular. Macrovascular parameters, which are also referred to as upstream parameters, deal with systemic measures of cardiopulmonary status, such as SBP and MAP, central venous pressure, and urine output. Microvascular parameters, which are also referred to as the downstream parameters, are related to tissue oxygenation and include lactate and lactate clearance, ScvO2, and BE (30). Therefore, monitoring both macrocirculation and microcirculation parameters provide a broader picture which is required to enable informed clinical decisions (11). Our macrovascular (SBP and MAP) and microvascular (lactate, SpO2, and BE) measures did not differ significantly between the Sv and non-Sv groups (Table 1). This means that SBP and MAP, lactate concentration, SpO2, and BE were not correlated with the severity of dogs with SEVS & SEPS. These parameters can be useful, but flawed as a goal for the treatment of shock (4).

Hypotension, on the other hand, was present as a macrovascular measure in 12 of 35 dogs with SEVS & SEPS at admission. 8 of them did not respond to fluid resuscitation and NE applications. All of them were in the non-Sv group. A MAP of less than 60 to 65 mm Hg is considered hypotension (38). Restoration of systemic blood pressure to a MAP between 65-70 mm Hg is a good initial goal in EGDT (2). Hypotension is a common consequence in those suffering from septic shock, and it can be caused by hypovolemia, low CO, or improper vasodilation (11). Between Sv and non-Sv groups, there was no difference in SBP and MAP (Table 1). Hypotension could be explained in our investigation by the emergence of distributive shock. In sepsis or SIRS, the release of inflammatory mediators causes distributed shock. Septic shock is a type of shock that is classified as

a subtype of distributive shock (22). Different processes, including as hypovolemia, vasoplegia, and septic cardiomyopathy, are frequently found simultaneously or separately in this complex process.

Vasopressors raise circulatory system tone and, as a result, MAP (26, 37). If patients do not respond to fluid resuscitation, vasopressor medications are used as the next step in treating hypotension (14). As suggested by the sepsis surviving campaign (SSC), In a patient with septic shock, the initial vasopressor that should be given is NE (31). NE and its vasoconstricting effects move blood from the general circulation to increase the preload. This is essential in the early stages of septic shock because it can result in a positive fluid balance (29). In the early stages of septic shock, a MAP of >65 mmHg is the resuscitation aim to enhance the perfusion of important organs such as the brain and kidney (23, 31). NE has been used in dogs with endotoxic shock, (5) septic shock, (27) tamponade-induced stagnant hypoxia, (44) and haemorrhagic shock (16). Despite one bolus of fluid treatment, NE was given to the 10 hypotensive dogs in our trial. Dogs being treated with NE generally had no increase in their blood pressure, with 2 of 10 dogs achieving normotension. Persistent hypotension in dogs and cats has previously been associated with a poor outcome (36). All of the dogs that were perceived to be fluid tolerant in this study received one bolus of fluid therapy consisting of crystalloids before vasopressor initiation. Blood pressure measurements were consistently low in the non-Sv group despite fluid resuscitation. As in humans, it is difficult to determine at times if an adequate fluid challenge has been administered before starting vasopressors, (6) but there is growing evidence that a positive fluid balance is linked to an increase in mortality (10). Whether the non-Sv dogs died due to positive fluid balance or hypotension is unknown in this study.

In humans, unresolved hypotension and inadequate tissue perfusion are recognized as precursors to MODS and death and are important and tangible targets for intervention (3, 39). Evidence-based guidelines advocate the use of vasopressors in hypotensive humans who are adequately volume resuscitated and are therefore considered to have refractory hypotension, (31) but evidence-based guidelines do not exist for dogs surrounding the optimal use of vasopressors. We used NE as a vasopressor in dogs with SEVS & SEPS. The only difference between Sv and non-Sv was the use of NE (Table 1). 10 dogs with SEVS & SEPS were started on NE, 8 of which did not respond to NE applications and all of them were in the non-Sv group. This could be the result of distributive shock, vasopressor failure, hypotension, MODS, and LVDD or a combination of all these reasons. In this study, the patients received NE applications (8 cases) that had a worse survival outcome.

In dogs with SEVS & SEPS, the use of multiple vasopressors is linked to a poor prognosis. It has been found that dogs with septic peritonitis who were hypotensive due to surgery and dogs who received more than one vasopressor were less likely to survive (7). This implies that dogs with SEVS & SEPS requiring vasopressor therapy had higher levels of mortality. In addition to the maladaptive inflammatory responses that occur during sepsis and their impact on cardiovascular tone, (19) there may be a reduced reactivity due to long-term use of catecholamine medications and consequent down regulation of α-adrenergic receptors in the arterial smooth muscle (43). In our study, a proportionally higher number of non-Sv received a greater amount of NE, whilst more survivors received a smaller amount of NE. Kaplan-Meier's analysis supported this conclusion. The survivorship rate was 91% after one bolus of fluid therapy for the NE group. This rate was 82% after 1.5 µg/kg/min in 0.9% NaCl solution, CRI in 2h and 35% after 3.0 µg/kg/min in 0.9% NaCl solution, CRI in 24h; with 0% after repeated 3.0 µg/kg/min in 0.9% NaCl solution, CRI in 24h ($P<0.05$) (Figure 2).

Increased oxygen delivery may have enhanced tissue perfusion with inotropic treatment (14, 19). DT is used as part of standard care in clinical trials of EGDT (28). In dogs, the use of DT has been infrequently reported. In dogs with tamponade-induced stationary hypoxia, it enhanced oxygen availability to the tissues (44). In a dog model of endotoxic shock, Bakker and Vincent (5) reported that DT had a favourable effect on oxygen transport and consumption. In our study, although it was not significantly different for DT use between Sv and non-Sv, a larger number Sv received a greater amount of DT applications. Kaplan-Meier's analysis support this conclusion. The average rate of the survivor was 100% after one bolus of fluid therapy for the DT group. The average rate of the survivor was 100% after 5 µg/kg/min. The average rate of the survivor was 80% after 10 µg/kg/min. The average rate of the survivor was 100% after repeated 10 µg/kg/min ($P<0.05$) (Figure 2). We may suggest that DT can be used in cases of LVSD at the dose of 10 µg/kg/min.

In our research, 26 of 35 dogs with SEVS & SEPS survived and were released from the ICU (Sv). Nine patients died, resulting in a 25.7 percent total mortality rate (non-Sv). This relatively low mortality rate could be the result of the use of EGDT protocols in our study.

There is one more flaw in our research. The study's sample size was limited, but it was comparable to early echocardiographic studies in septic individuals. The specific rationale behind vasoactive decisions was to only use NE and DT, which may have affected the overall outcome.

In dogs with SEVS & SEPS, tissue perfusion is inadequate. Therefore, oxygen and nutrient delivery is impaired. EGDT is a protocol for the monitoring and management of hemodynamic in dogs with SEVS & SEPS. In dogs with SEVS & SEPS, therapy with NE and DT can be started if fluid administration fails to restore appropriate arterial pressure and organ perfusion. NE and DT can be used for patients with persistent hypotension and LVSD, respectively. In dogs with SEVS & SEPS, the ultimate goals of EGDT procedures are to increase effective tissue perfusion and regulate cellular metabolism. DT and NE in dogs with SEVS & SEPS can be used to improve outcomes. The use of NE applications was the only the distinction between the Sv and non-Sv groups. The dogs with an LVDD and the dogs received NE applications had the worse survival outcome. Veterinary medicine's evidence foundation for the use of DT and NE in dogs with SEVS & SEPS is inadequate, despite their frequent use. In order to produce evidence-based guidelines for dogs, more study is required.

Financial Support

This research received no grant from any funding agency/sector.

Conflict of Interest

The authors declared that there is no conflict of interest.

Author Contributions

KT, conceptualization, methodology, writing-review & editing. AN, HS, ME and MEI, writing-review & editing.

Data Availability Statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Ethical Statement

Ethics committee approval for this study was obtained from Local Ethics Committee of the Near East University (permit number: 2019/03).

Animal Welfare

The authors confirm that they have adhered to ARRIVE Guidelines to protect animals used for scientific purposes.

References

1. **Angus DC, Linde-Zwirble WT, Lidicker J, et al** (2001): *Epidemiology of Severe Sepsis in the United States: Analysis of Incidence, Outcome, and Associated Costs of Care.* Critical Care Medicine, **29,** 1303–1310.
2. **Antonucci E, Fiaccadori E, Donadello K, et al** (2014): *Myocardial depression in sepsis: from pathogenesis to clinical manifestations and treatment.* J Crit, **29**, 500-511.
3. **Asfar P, Hauser B, Radermacher P** (2006): *Catecholamines and vasopressin during critical illness.* Crit Care Clin, **22**, 131-149.
4. **Bakker J, Gris P, Coffernils M, et al** (1996): *Serial blood lactate levels can predict the development of multiple organ failure following septic shock.* Am J Surg, **171**, 221-226.
5. **Bakker J, Vincent JL** (1993): *Effects of norepinephrine and dobutamine on oxygen transport and consumption in a dog model of endotoxic shock.* Crit Care Med, **21**, 425-432.
6. **Bednarczyk JM, Fridfinnson JA, Kumar A, et al** (2017): *Incorporating Dynamic Assessment of Fluid Responsiveness Into Goal-Directed Therapy: A Systematic Review and Meta-Analysis.* Crit Care Med, **45**,1538-1545.
7. **Bentley AM, Otto CM, Shofer FS** (2007): *Comparison of dogs with septic peritonitis: 1988–1993 versus 1999–2003.* Journal of Veterinary Emergency and Critical Care, **17**, 391-398.
8. **Boon JA** (2011): Veterinary Echocardiography. Wiley-Blackwell, USA.
9. **Bouhemad B, Nicolas-Robin A, Arbelot C, et al** (2008): *Isolated and reversible impairment of ventricular relaxation in patients with septic shock.* Crit Care Med, **36**, 766-774.
10. **Boyd JH, Forbes J, Nakada TA, et al** (2011): *Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality.* Crit Care Med, **39,** 259-265.
11. **Butler AL** (2011): *Goal-directed therapy in small animal critical illness.* Vet Clin North Am Small Anim Pract, **41,** 817-838.
12. **Chan CM, Klinger JR** (2008): *The right ventricle in sepsis.* Clin Chest Med, **29,** 661-676.
13. **De Backer D, Scolletta S** (2013): *Clinical management of the cardiovascular failure in sepsis.* Curr Vasc Pharmacol, **11**, 222-242.
14. **Dellinger RP, Levy MM, Rhodes A, et al** (2013): *Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012.* Crit Care Med, **41,** 580-637.
15. **Dickson D, Shave R, Rishniw M, et al** (2017): *Echocardiographic assessments of longitudinal left ventricular function in healthy English Springer spaniels.* J Vet Cardiol, **19,** 339-350.
16. **Fine J, Frank ED, Frank HA, et al** (1956): *Effect of norepinephrine on circulation of the dog in hemorrhagic shock.* Am J Physiol, **186,** 74-78.
17. **Flachskampf FA, Biering-Sørensen T, Solomon SD, et al** (2015): *Cardiac Imaging to Evaluate Left Ventricular Diastolic Function.* JACC Cardiovasc Imaging, **8,** 1071-1093.
18. **Goldstein B, Giroir B, Randolph A** (2005): *International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics*. Pediatr Crit Care Med, **6,** 2-8.
19. **Hollenberg SM, Cunnion RE, Zimmerberg J** (1993): *Nitric oxide synthase inhibition reverses arteriolar hyporesponsiveness to catecholamines in septic rats.* Am J Physiol, **264,** H660-H663.
20. **Hollenberg SM** (2009): *Inotrope and vasopressor therapy of septic shock.* Crit Care Clin, **25,** 781-802.

21. **Ince C, Sinaasappel M** (1999): *Microcirculatory oxygenation and shunting in sepsis and shock.* Crit Care Med, **27,** 1369-1377.
22. **Ince ME, Turgut K, Akar A, et al** (2019): *Prognostic importance of tissue Doppler imaging of systolic and diastolic functions in dogs with severe sepsis and septic shock.* Acta Vet Hung, **67,** 517-528.
23. **Jhanji S, Stirling S, Patel N, et al** (2009): *The effect of increasing doses of norepinephrine on tissue oxygenation and microvascular flow in patients with septic shock.* Crit Care Med, **37,** 1961-1966.
24. **Landesberg G, Gilon D, Meroz Y, et al** (2012): *Diastolic dysfunction and mortality in severe sepsis and septic shock.* Eur Heart J, **33,** 895-903.
25. **Levy MM, Fink MP, Marshall JC, et al** (2003): *2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference.* Crit Care Med, **31,** 1250-1256.
26. **Manolopoulos PP, Boutsikos I, Boutsikos P, et al** (2020): *Current use and advances in vasopressors and inotropes support in shock. J Emerg Crit Care Med*, **4**, 20.
27. **Minneci PC, Deans KJ, Banks SM, et al** (2004): *Differing effects of epinephrine, norepinephrine, and vasopressin on survival in a canine model of septic shock.* Am J Physiol Heart Circ Physiol, **287,** H2545-H2554.
28. **Mouncey PR, Osborn TM, Power GS, et al** (2015): *Trial of early, goal-directed resuscitation for septic shock.* N Engl J Med, **372,** 1301-1311.
29. **Persichini R, Silva S, Teboul JL, et al** (2012): *Effects of norepinephrine on mean systemic pressure and venous return in human septic shock.* Crit Care Med, **40,** 3146-3153.
30. **Prittie J** (2006): *Optimal Endpoints of Resuscitation and Early Goal-Directed Therapy.* Journal of Veterinary Emergency and Critical Care, **16,** 329-339.
31. **Rhodes A, Evans LE, Alhazzani W, et al** (2017): *Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016.* Intensive Care Med, **43,** 304-377.
32. **Rivers EP, Katranji M, Jaehne KA, et al** (2012): *Early interventions in severe sepsis and septic shock: a review of the evidence one decade later.* Minerva Anestesiol, **78,** 712-724.
33. **Rozanski E, Chan DL** (2009): Anticoagulants. 797–800. In: DC Silverstein and K Hopper (Eds), Small Animal Critical Care Medicine, Elsevier, USA.
34. **Shankar-Hari M, Phillips GS, Levy ML, et al** (2016): *Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).* JAMA, **315,** 775-787.
35. **Shapiro DS, Loiacono LA** (2010): *Mean arterial pressure: therapeutic goals and pharmacologic support.* Crit Care Clin, **26**, 285-293.
36. **Shea EK, Dombrowski SC, Silverstein DC** (2017): *Survival analysis of hypotensive cats admitted to an intensive care unit with or without hyperlactatemia: 39 cases (2005-2011).* J Am Vet Med Assoc, **250**, 887-893.
37. **Silverstein DC, Beer KA** (2015): *Controversies regarding choice of vasopressor therapy for management of septic shock in animals.* J Vet Emerg Crit Care (San Antonio), **25,** 48-54.
38. **Silverstein DC, Hopper K** (2015): Small Animal Critical Care Medicine. Elseiver Saunders, USA.
39. **Silverstein DC, Wininger FA, Shofer FS, et al** (2008): *Relationship between Doppler blood pressure and survival or response to treatment in critically ill cats: 83 cases (2003-2004).* J Am Vet Med Assoc, **232,** 893-897.
40. **Turgut K** (2017): Klinik Kedi ve Köpek Kardiyolojisi. Nobel Tıp Kitabevleri, İstanbul.
41. **Turgut K** (2020): Manual of Heart Failure; Recommendations for Diagnosis and Treatment in Dogs and Cats. Near East University Press, Nicosia.
42. **Vignon P, Allot V, Lesage J, et al** (2007): *Diagnosis of left ventricular diastolic dysfunction in the setting of acute changes in loading conditions.* Crit Care, **11,** R43.
43. **Wakabayashi I, Hatake K, Kakishita E, et al** (1986): *Desensitization of alpha-1 adrenergic receptor mediated smooth muscle contraction in aorta from endotoxic rats.* Life Sci, **45,** 509-515.
44. **Zhang H, Spapen H, Vincent JL** (1994): *Effects of dobutamine and norepinephrine on oxygen availability in tamponade-induced stagnant hypoxia: a prospective, randomized, controlled study.* Crit Care Med, **22,** 299-305.