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Evaluation of micro vascular and macro vascular monitoring parameters in canine sepsis

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Abstract
Sepsis is an important cause of mortality in the human beings as well as dogs treated in the intensive care units. Monitoring of patient with sepsis is an essential part of patient care. The various monitoring parameters during sepsis were evaluated in this study for prognosis and to achieve maximum chance for survival of dogs with sepsis. The study was conducted on the dogs admitted in Critical Care Unit of the Madras Veterinary College Teaching Hospital (MVCTH) with sepsis. In the present study, the diagnosis of sepsis was made by using 16S rRNA gene PCR sequencing and blood culture. The monitoring parameters assessed in selected septic patients *viz*., blood pressure (BP), central venous pressure (CVP), urine output (UOP), blood lactate, central venous oxygen saturation ($S_{cv}O_2$) and base excess (BE). The present study revealed hypotension, hypovolemia, hyperlactatemia, decreased urine output, decreased base excess and decreased central venous oxygen saturation in the canine patients with sepsis. The results of the study were critically analyzed and discussed.

Keywords: Sepsis, SIRS, monitoring, lactate, CVP, BP, BE, $S_{cv}O_2$, dogs

Introduction
Monitoring of septic patients plays crucial role in reducing the percentage of mortality in Intensive and Critical Care Unit settings. Trzeciak and Rivers (2005) divided monitoring parameters into two broad categories: macro-vascular and micro-vascular parameters [1]. Macro-vascular parameters are related to systemic measures of cardiopulmonary status such as blood pressure (BP), central venous pressure (CVP), and urine output (UOP). Micro-vascular parameters are related to tissue oxygenation and include lactate and lactate clearance, central venous oxygen saturation ($S_{cv}O_2$), and base excess (BE) [2]. With this background, the present clinical study was conducted with the objective to monitor macro-vascular and micro-vascular parameters in all the selected septic animals [3].

Materials and Methods
Design of study
The canine patients presented with two or more than two SIRS criteria were assessed by thorough clinical examination. Criteria used for clinical diagnosis of SIRS in dogs [4] were,

Temperature	:	<37.2 °C or >39.4 °C
Heart Rate (beats/min)	:	>150/minute
Respiratory Rate (breaths/min)	:	>40/minute
WBC count (cells/cmm)	:	<5000 or >19000 or >5% bands

Evaluation for Sepsis
Animals fulfilling the SIRS criteria were evaluated for the possibility of an underlying causative septic focus. All the selected SIRS positive animals blood sample were subjected to 16S rRNA gene PCR sequencing and blood culture for diagnosis of sepsis [5]. Based on the results of above tests diagnosis of sepsis was made in the present study.
Based on the SIRS criteria, microbial source in blood, organ dysfunction and hemodynamic response the septic patients were classified into the following groups.

	Description	Number of cases	Selection criteria
Group 1	Sepsis	36	Confirmed microbial source in blood
Group 1I	Severe sepsis	57	Confirmed microbial source in blood + One or more organ failure
Group 1II	Septic shock	10	Confirmed microbial source in blood + One or more organ failure + Persistent hypotension
Group 1V	Healthy Dogs	10	Normal vital signs

Evaluation of Macro-vascular monitoring parameters

Central Venous Pressure (CVP): The dogs were placed on right lateral recumbency and catheter was introduced percutaneously into the jugular vein. Central venous pressure was estimated in cm H_2O using CVP manometer with accessory manometer tube attached to 3 way tap and extension line (Romsons, GS-3008) (Plate. 1) as per recommended protocols [6].

Doppler Blood Pressure: Non-invasive blood pressure measurements were done using Doppler BP apparatus (Vet Dop Blood Pressure System, USA) as per standard protocol [7] (Plate. 2). The dogs were placed on right lateral recumbency and an appropriate sized cuff was placed proximal to the carpal region and the probe was placed on the median artery. Three subsequent measurements were taken for analysis.

Urine Output: An appropriate sized urinary catheter was introduced and secured by using non absorbable suture material and attached with urine collecting bag fitted with non-return valve (Urobag- Romo 10, DB1070-10, India) (Plate. 3). The urine output volume was measured for every hour as per standard protocol [8].

Evaluation of Micro-vascular monitoring parameters

Blood Lactate: Serum samples were run in a fully automated biochemical analyser (A-15 Biosystem Random Access Analyzer, Biosystems, Barcelona, Spain). Quantitative estimation of lactate was carried out by using diagnostic kit (Plate. 4) (Lactate oxidase/ peroxidase method/ Lactate 11736-Biosystems, Spain) following the manufacturer's recommendations.

Central Venous Oxygen Saturation ($S_{cv}O_2$): A central jugular venous catheter was placed without sedation and the placement of catheter tip was confirmed via radiography. Approximately 1 ml of blood was collected in a syringe coated with heparin. $S_{cv}O_2$ measured using automated blood gas analyzer (Siemens 0L085-RAPIDLAB 348) as per standard protocol [9].

Base Excess (BE): An automated blood gas analyzer (Siemens 0L085-RAPIDLAB 348) was used to assess the base excess.

Results

Among monitoring parameters, the mean ± S.E, median, minimum and maximum values for BP, lactate and BE values in dogs under various groups were compared with the Group IV (Table. 1).

Table 1: Blood Pressure, Lactate and Base Excess in dogs with sepsis

Parameter		Group I Sepsis	Group II Severe sepsis	Group III Septic shock	Group 1V Control	F Value
Blood Pressure (mm Hg)	N	36	57	10	10	11.8**
	Mean ± S.E	94.9^{b}±5.8	80.1^{b}±3.7	48^{a}±3.18	116^{c}±4.5	
	Median	90	70	50	120	
	Minimum	50	40	20	90	
	Maximum	210	180	55	140	
Lactate (mmol/L)	N	15	17	18	10	8.19**
	Mean ± S.E	4.14^{b}±0.6	2.9^{b}±0.6	4.5^{b}±0.6	0.4^{a}±0.0	
	Median	3.89	2.32	4.40	0.42	
	Minimum	0.22	0.55	2.80	0.23	
	Maximum	7.79	8.64	7.30	0.68	
BE (mmol/L)	N	10	13	10	6	10.2**
	Mean ± S.E	-9.3^{a}±0.9	-13.2^{a}±1.2	-13.2^{a}±1.9	-2.5^{b}±0.5	
	Median	-9.1	-11.80	-11.65	-2.45	
	Minimum	-14.7	-23.10	-23.10	-4.10	
	Maximum	-5.6	-7.10	-5.60	-1.00	

The values bearing same superscript did not differ significantly.

*p<0.05-significant, **p<0.01-highly significant and ^{NS} p>0.05-non-significant.

The mean ±S.E values of BP (mmHg) in dogs under Group I, Group II, Group III and Group IV were 94.86±5.76, 80.09±3.65, 48.00±3.18 and 116.00±4.52 respectively. A highly significant (p<0.01) decrease in the BP levels of the various sepsis groups were observed compared with the group IV.

The mean ±S.E values of lactate (mmol/L) in dogs under Group I, Group II, Group III and Group IV were 4.14±0.6, 2.89±0.59, 4.49±0.55 and 0.44±0.045 respectively. A highly significant (p<0.01) increase in the lactate levels of the various sepsis groups were observed compared to Group IV.

The mean ±S.E values of BE (mmol/L) in dogs under Group I, Group II, Group III and Group IV were -9.3 ± 0.9, -13.2 ± 1.2, -13.2±1.9 and -2.5±0.5 respectively. A highly significant (p<0.01) decrease in base excess level was observed in the sepsis groups compared to the control group (Table. 1).

Among monitoring parameters, the mean ± S.E, median, minimum and maximum values for CVP, urine output and $S_{cv}O_2$ in dogs under various groups were compared within the septic groups not with the group IV (Table. 2), since measuring CVP, urine output and $S_{cv}O_2$ are invasive procedures.

Table 2: Central Venous Pressure, Urine Output and Central Venous Oxygen Saturation in septic dogs

Parameter		Group I Sepsis	Group II Severe sepsis	Group III Septic shock	F Value
CVP (cm H_2O)	N	5	5	6	19.68**
	Mean ± S.E	$3.4^{c} \pm 0.37$	$-0.2^{b} \pm 1.37$	$-3.33^{a} \pm 0.17$	
	Median	3	70	50	
	Minimum	2.50	-2.5	-4.0	
	Maximum	4.5	5	-3.0	
Urine Output (ml/kg/hr)	N	5	5	6	11.898**
	Mean ± S.E	$1.44^{b} \pm 0.19$	$0.98^{b} \pm 0.28$	$0.18^{a} \pm 0.07$	
	Median	1.50	0.9	0.2	
	Minimum	0.8	0.3	0	
	Maximum	2	2	0.4	
$S_{cv}O_2$ (%)	N	5	5	6	10.671**
	Mean ± S.E	$72.48^{c} \pm 0.7$	$65.9^{b} \pm 1.79$	$58.9^{a} \pm 2.78$	
	Median	72.9	67.9	59.3	
	Minimum	70	59.8	51	
	Maximum	74	69.5	66.1	

The values bearing same superscript did not differ significantly.
*p<0.05-significant, **p<0.01-highly significant and ^{NS} p>0.05-non-significant.

The mean ± S.E values of CVP (cm H_2O) in dogs under Group I, Group II and Group III were 3.4±0.37, -0.2±1.37 and -3.33±0.17, respectively. A highly significant (p<0.01) difference in the CVP levels was observed among sepsis groups with a significantly lowest CVP in septic shock group.

The mean ± S.E values of urine output (ml/kg/hr) in dogs under Group I, Group II and Group III were 1.44±0.19, 0.98 ± 0.28 and 0.18±0.07, respectively. A highly significant (p<0.01) difference in the urine output was observed among sepsis groups with a significantly lowest urine output in septic shock group.

The mean ± S.E values of $S_{cv}O_2$ (%) in dogs under Group I, Group II and Group III were 72.48±0.73, 65.9±1.79 and 58.9±2.78, respectively. A highly significant (p<0.01) difference in the $S_{cv}O_2$ levels was observed in among sepsis groups with a significantly lowest level in septic shock.

Discussion

The findings of this study is accordance to the sequence of hypotension in critically ill dogs with an initial phase of circulatory shock with overwhelming compensatory response and tissue hypoxemia resulted in refractory shock [10]. In addition, the baroreceptor dysfunction and neurohormonal changes paved way to hyperdynamic shock and vasoplegia in dogs with severe sepsis and septic shock conditions. Earlier studies observed hypovolemic shock and hypo-perfusion as a result of severe dehydration and also a decrease in vascular resistance in SIRS/sepsis, electrolyte imbalance and in metabolic acidosis/alkalosis [2. 11]. The high-risk patient had a systolic blood pressure of less than 90mm Hg even after a fluid challenge at the rate from 20-ml/kg to 40-ml/kg body weight [3]. It was described that the potential causes of hypotension included reduction in preload (Hypovolemia and obstructive), reduction in cardiac function and reduction in systemic vascular resistance (SIRS/sepsis, electrolyte abnormalities, severe hypoxia, severe acidosis or alkalosis and drug or toxins) [12]. In the present study, a highly significant (p<0.01) decrease in blood pressure was observed in the septic dogs of all groups when compared with the control group (Table. 1 and Plate. 2). The significant hypotension observed in this study is attributable to the above changes.

Lactate level has been used as a prognostic marker in human being and also in dogs admitted in the intensive care units. In the present study, a highly significant (p<0.01) increase in lactate level was observed in the septic dogs of all groups when compared with the control group (Table. 1 and Plate. 4). The earlier report suggested that in patients with septic shock, serial determinations of blood lactate levels were good predictors of the development of multiple system organ failure and death [13]. There are two primary types of hyperlactatemia have been described to occur in sepsis *viz*., type A and type B [14]. Type A hyperlactatemia occurs when tissue oxygen delivery is insufficient to meet tissue demand. Type B hyperlactatemia is associated with insufficient lactate clearance (liver failure), abnormal oxygen utilization (sepsis, SIRS, etc.) and certain drugs or toxins. Evaluation of serial blood lactate concentrations in systemically ill dogs showed a lactate concentration higher than the reference interval at 6 hours after initiation of treatment were more likely not to survive [15]. The lactate levels of dogs with SIRS were found significantly increased compared with the healthy control [16]. The plasma lactate concentration at the time of admission and lactate clearance were reported to be a reliable prognostic indicator in dogs with septic peritonitis [17]. The hyperlactatemia observed in the canine patients with sepsis in the present study were in agreement with the earlier findings.

A significant differences in BE were documented between SIRS positive and SIRS negative pyometra cases in bitches [18]. A strongly negative BE was found associated with higher mortality in critically ill patients [19]. A base deficit of less than -14.5 mmol/L was found associated with higher mortality in critically ill dogs due to severe sepsis and septic shock conditions, however, lower values of base excess at the levels less than -7.5mmol/L were found to have lower probability of death [20]. The present study revealed a highly significant (p<0.01) decrease in base excess level in the septic dogs of all groups compared with the control group (Table. 1). The findings of the present study were in agreement with the earlier findings observed in canine patient with sepsis [18, 19, 20].

The central venous pressure is a reliable indicator of patients hydration status and significantly low CVP has been recorded in the patients with shock. Among all septic patients, a highly significant (p<0.01) decrease in the CVP was observed in the group II and group III when compared with the group I (Table. 2). In the present study significantly low CVP in

severe septic and septic shock patients might be attributable to hypovolemia due to fluid loss or vasodilatation secondary to decreased peripheral vascular resistance [21].

The present study showed a highly significant decrease (p<0.01) in the urine output in the group II and group III compared with the group I (Table. 2) and this could be due to increased evidence of renal dysfunction and/or decreased renal perfusion in severe septic and septic shock patients. In the present study, a significantly low UOP in severe septic and septic shock patients might be attributable to inadequate renal perfusion as a sequel to reduced cardiac output or hypotension [22, 23].

A highly significant (p<0.01) difference in the $S_{cv}O_2$ levels was observed between all groups of septic patients. $S_{cv}O_2$ levels was very low in severe septic and septic shock patients compared to septic patients (Table. 2) which might be due to decreased oxygen content (anemia or hypoxemia), decreased cardiac output, and inappropriate vasodilation[3]. $S_{cv}O_2$ levels documented in survivors and non survivors of canine sepsis were 69·4% and 60·2% respectively [24]. A study on canine sepsis reported that animals with a higher $S_{cv}O_2$ at the time of admission to the ICU have a lower probability of death [20].

Conclusion

This study found that animals with sepsis had hypotension, hypovolemia, hyperlactatemia, decreased urine output, decreased base excess and decreased central venous oxygen saturation. Measuring of the above macro and micro vascular monitoring parameters in critically ill patients are effective and valuable tools to predict the severity of sepsis such as sepsis induced organ dysfunction and septic shock. This study suggested that the monitoring parameters such as blood pressure, central venous pressure, urine output, blood lactate, central venous oxygen saturation and base excess were highly useful for prognostication and for implementing goal directed therapy to reduce mortality in canine sepsis.

Plate 1: Central Venous Pressure measurement

Plate 2: Doppler systolic BP measurement

Plate 3: Urine output measurement

Plate 4: Serum lactate measurement by using kit method

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