



# Changes in tissue perfusion parameters in dogs with severe sepsis/septic shock in response to goal-directed hemodynamic optimization at admission to ICU and the relation to outcome

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## Abstract

**Objective** – To evaluate the changes in tissue perfusion parameters in dogs with severe sepsis/septic shock in response to goal-directed hemodynamic optimization in the ICU and their relation to outcome.

**Design** – Prospective observational study.

**Setting** – ICU of a veterinary university medical center.

**Animals** – Thirty dogs with severe sepsis or septic shock caused by pyometra who underwent surgery and were admitted to the ICU.

**Measurements and Main Results** – Severe sepsis was defined as the presence of sepsis and sepsis-induced dysfunction of one or more organs. Septic shock was defined as the presence of severe sepsis plus hypotension not reversed with fluid resuscitation. After the presumptive diagnosis of sepsis secondary to pyometra, blood samples were collected and clinical findings were recorded. Volume resuscitation with 0.9% saline solution and antimicrobial therapy were initiated. Following abdominal ultrasonography and confirmation of increased uterine volume, dogs underwent corrective surgery. After surgery, the animals were admitted to the ICU, where resuscitation was guided by the clinical parameters, central venous oxygen saturation (ScvO<sub>2</sub>), lactate, and base deficit. Between survivors and nonsurvivors it was observed that the ScvO<sub>2</sub>, lactate, and base deficit on ICU admission were each related independently to death ( $P = 0.001$ ,  $P = 0.030$ , and  $P < 0.001$ , respectively). ScvO<sub>2</sub> and base deficit were found to be the best discriminators between survivors and nonsurvivors as assessed via receiver operator characteristic curve analysis.

**Conclusion** – Our study suggests that ScvO<sub>2</sub> and base deficit are useful in predicting the prognosis of dogs with severe sepsis and septic shock; animals with a higher ScvO<sub>2</sub> and lower base deficit at admission to the ICU have a lower probability of death.

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**Keywords:** base deficit, central venous oxygen saturation, lactate, septicemia

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## Abbreviations

CI	confidence interval
CO	cardiac output
CVP	central venous pressure

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DBP	Doppler blood pressure
NOS	nitric oxide synthase
ROC	receiver operator characteristic
SIRS	systemic inflammatory response syndrome
ScvO <sub>2</sub>	central venous oxygen saturation
SvO <sub>2</sub>	mixed venous oxygen saturation

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## Introduction

Sepsis is a clinical syndrome associated with the systemic inflammatory response syndrome (SIRS) evoked by invading microorganisms or their toxins in the blood stream.<sup>1</sup> Severe sepsis is defined as the presence of sepsis concomitant with dysfunction of one or more organs. Septic shock is defined as the presence of severe sepsis plus hypotension despite fluid resuscitation.<sup>2</sup> In veterinary medicine, the incidence of sepsis is unknown; however, the mortality ranges between 20% and 68%.<sup>3</sup>

Patients with severe sepsis display absolute hypovolemia and relative hypovolemia as a result of systemic vasodilation, decreased venous return and arterial hypotension, all of which compromise the microcirculation and oxygen delivery, hence promoting multiple organ failure.<sup>4,5</sup> Moreover, sepsis promotes endothelial dysfunction, which undermines the control of vascular tone, coagulation and the immune response.<sup>6</sup> The cytokines released during SIRS act on the endothelium and promote an increase in nitric oxide synthase (NOS) expression and nitric oxide production in septic shock.<sup>6,7</sup> Nitric oxide promotes intense arterial vasodilation, which is considered an important component of refractory arterial hypotension in patients with septic shock. In turn, arterial vasodilation activates the neurohumoral axis and increases cardiac output (CO) secondary to afterload reduction, characterizing the hyperdynamic phase of septic shock.<sup>8</sup> In the hypodynamic phase, inflammatory mediators promote myocardial depression, decreased CO, increased vascular permeability,<sup>9,10</sup> decreased preload, loss of vascular tone control, vasopressin deficiency, and changes in the microcirculation.<sup>11,12</sup> Systemic and regional tissue hypoperfusion with normal or above normal CO characterize the distributive shock.<sup>6</sup>

Clinical findings related to severe sepsis can be vague and include altered level of consciousness, pale mucous membranes, arterial hypotension, leukocytosis or leukopenia, and hyperglycemia.<sup>13</sup> Patients with vague clinical signs, when not treated early, may progress rapidly to septic shock.<sup>14</sup> Recognizing these patients at an early stage when there may be tissue hypoxemia despite normal clinical parameters such as CO, arterial pressure and body temperature may be vital for successful early volume resuscitation. The aim of volume resus-

citation is to restore the balance between tissue oxygen consumption and supply.<sup>4,5,13,14</sup>

Based on a prospective and randomized study, the Surviving Sepsis Campaign recommends the use of central venous oxygen saturation (ScvO<sub>2</sub>) or mixed venous oxygen saturation (SvO<sub>2</sub>) to assess the supply and consumption of oxygen in the tissues.<sup>15</sup> In this human study, reduced mortality was observed in patients who underwent early volume resuscitation with the goal of maintaining ScvO<sub>2</sub> above 70%, compared to another group that received the same protocol without monitoring of ScvO<sub>2</sub>.<sup>16</sup>

SvO<sub>2</sub> reflects the proper ratio between oxygen supply and consumption; its value is decreased when there is increased consumption or reduced supply of oxygen to the tissues.<sup>17</sup> However, collection of mixed venous blood requires passing a pulmonary artery catheter, making it an invasive method,<sup>18</sup> and is rarely used in veterinary medicine.<sup>19</sup> Alternatively, ScvO<sub>2</sub> has been used to monitor critically ill human patients as this technique is less invasive because the blood sample is collected from a central venous catheter.<sup>17</sup>

During tissue hypoperfusion, the oxygen supply becomes insufficient and tissue hypoxia leads to anaerobic metabolism, which produces lactate.<sup>20</sup> If hypoxia persists, lactic acidosis is observed, which can be quantified by blood gas analysis and measurement of the base deficit and lactate concentrations.<sup>21</sup> The literature suggests that mild systemic hypoperfusion is associated with plasma lactate concentrations of 2.5–4.9 mmol/L and moderate hypoperfusion with 5–7 mmol/L whereas in cases of severe hypoperfusion, lactate concentrations can exceed 7 mmol/L.<sup>19</sup> Serial assessments of lactate during resuscitation may be helpful in assessing treatment response.<sup>22</sup>

In people, the base deficit can also be used to monitor critically ill patients<sup>23</sup> because it provides an indirect estimate of tissue hypoperfusion.<sup>24</sup> The base deficit is the amount of base in millimoles required to titrate 1 L of blood to a pH of 7.40 at 37°C and a partial pressure of carbon dioxide of 40 mm Hg.<sup>25</sup> In veterinary medicine, no clinical studies have evaluated changes of base deficit in dogs with severe sepsis and septic shock.

The identification and monitoring of parameters that reflect tissue perfusion are essential for the correction of tissue hypoperfusion and the prevention of organ dysfunction. Parameters such as ScvO<sub>2</sub>, lactate, and base deficit are often used to monitor septic human patients because they are considered to possess good prognostic value.<sup>18</sup> However, the importance of these parameters, pertinent cut-off values and their applicability are unknown in dogs with severe sepsis and septic shock admitted to the ICU for postoperative and intensive care. Thus, the first aim of this study was to evaluate the

changes in ScvO<sub>2</sub>, lactate, and base deficit levels in canine patients with severe sepsis/septic shock in response to goal-directed hemodynamic optimization at admission to the ICU. The second goal was to correlate values obtained at ICU admission to mortality and to determine cut-off values and their sensitivity and specificity for predicting death.

### Materials and Methods

This prospective study was conducted from October 2008 to October 2009. Only female dogs with severe sepsis or septic shock secondary to pyometra and subjected to ovariohysterectomy were included. The study design was assessed and approved by the Bioethics Committee of our institution and the animals were included after obtaining client consent.

The diagnosis of severe sepsis was based on meeting criteria of at least 2 variables compatible with SIRS and dysfunction of no less than one organ or have evidence of tissue hypoperfusion.<sup>2</sup> SIRS variables considered were: hypo- or hyperthermia (<38.1°C [100.6°F] or >39.2°C [102.6°F]), tachycardia (heart rate >120/min), tachypnea (respiratory rate >20/min), increased leukocytes (>16 × 10<sup>9</sup> cells/L [16 × 10<sup>3</sup> cells/μL]) or leukopenia (<6 × 10<sup>9</sup> cells/L [ $<6 \times 10^3$  cells/μL]), and >3% band forms in the WBC count.<sup>26</sup>

The variables associated with organ dysfunction included arterial hypotension (Doppler blood pressure <90 mm Hg), PaO<sub>2</sub>/FIO<sub>2</sub> < 300, acute oliguria (urine output <2 mL/kg/h), increased serum creatinine (>159 μmol/L [>1.8 mg/dL]), thrombocytopenia (<200 × 10<sup>9</sup> platelets/L [ $<200 \times 10^3$  platelets/μL]), hyperbilirubinemia (>4.3 μmol/L [>0.25 mg/dL]), and plasma lactate concentrations > 2.5 mmol/L. The diagnosis of septic shock was based on the presence of severe sepsis plus hypotension not reversed with fluid resuscitation.<sup>2</sup>

Animals with a history of comorbidities such as hepatic dysfunction, heart disease, chronic kidney disease, or neoplasia were excluded.

### Clinical procedures

Once the dogs had been admitted to the emergency room, and the presumptive diagnosis of sepsis secondary to pyometra made based on the history and physical examination, blood samples were collected and clinical findings were recorded at time point M0 (Figure 1). Arterial blood samples were collected for blood gas analysis, pH<sup>a</sup> and lactate,<sup>b</sup> and peripheral venous blood samples were collected for measurement of glucose,<sup>c</sup> complete blood count, platelet count, and serum biochemistry, including urea, creatinine, alkaline phosphatase, alanine aminotransferase, total bilirubin, total

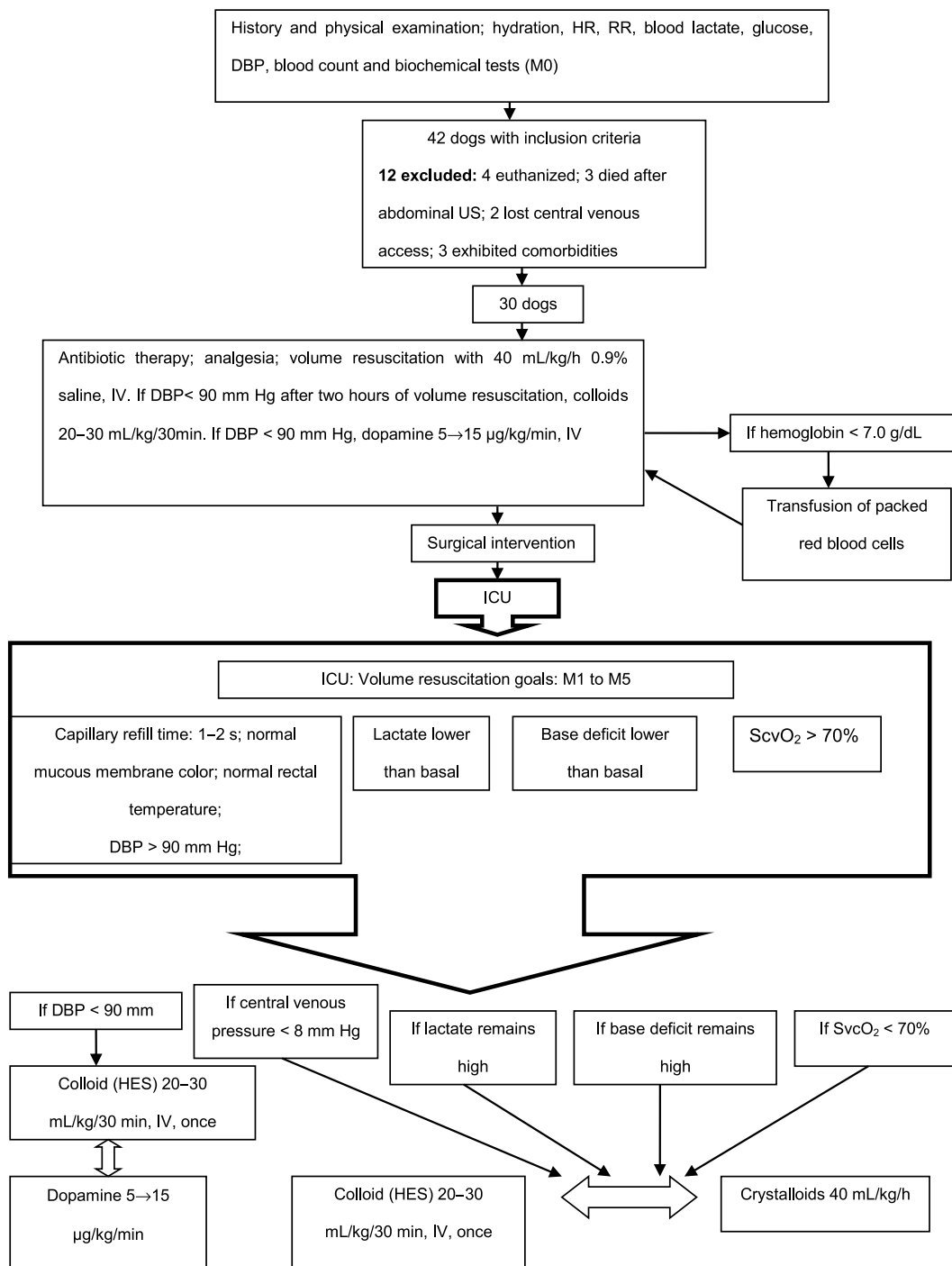
serum protein, and albumin. The clinical evaluation included heart rate, systolic arterial pressure by Doppler flow monitoring<sup>d</sup> (DBP), capillary refill time, and estimation of the degree of hydration by means of skin turgor, mucous membrane dryness, and urine output, as well as rectal temperature, respiratory rate, and mucous membrane color. The classification of sepsis was done at M0.

Volume resuscitation was then initiated using 0.9% saline solution<sup>e</sup> (40 mL/kg/h) by peripheral venous access, to improve the clinical parameters and decrease lactate concentrations. At the same time, antimicrobial therapy with cephalothin<sup>f</sup> (22 mg/kg, IV, q8h) and metronidazole<sup>g</sup> (15 mg/kg, IV, q12h) was initiated. After 2 hours of volume resuscitation with saline solution, animals not exhibiting improved parameters were administered colloid HES 130/0.4<sup>h</sup> (20–30 mL/kg/30 min) once. When hypotension (SAP < 90 mm Hg) persisted after 2 hours of fluid resuscitation, vasopressor therapy with dopamine<sup>i</sup> (5–15 μg/kg/min, IV) was initiated. For analgesia, tramadol hydrochloride<sup>j</sup> (3 mg/kg, IV) was administered. After abdominal ultrasonography and confirmation of increased uterine volume, the dogs underwent surgery. Transfusion of packed red blood cells (10 mL/kg) was provided as needed whenever hemoglobin was below 70 g/L [7.0 g/dL], to achieve a 10% increase in the amount of hemoglobin. The hemoglobin was rechecked after surgery and at the end of fluid resuscitation (time point M5, 6 h after ICU admission). All animals underwent surgery by the same surgeon 2 hours after the initial treatment began. Approximately 20 minutes before the end of surgery, central venous access was obtained by the passage of a catheter into the intrathoracic vena cava, via the jugular vein. Immediately after tracheal extubation, the animals were admitted to the ICU. The catheter tip was visualized by thoracic radiography and confirmed to be cranial to the right atrium.

### Monitoring and treatment after ICU admission

During the first 6 hours after admission to the ICU, volume resuscitation was continued to maintain the Doppler blood pressure > 90 mm Hg, central venous pressure (CVP) between 8 and 12 mm Hg, urine output above 2 mL/kg/h and ScvO<sub>2</sub> above 70%, and to reduce lactate and the base deficit from their baseline concentrations. The animals were monitored every 90 minutes (time points M1, M2, M3, M4, and M5) from the time of ICU admission after surgery (M1) to the end of volume resuscitation (M5). The variables monitored included heart rate, systolic blood pressure by means of vascular Doppler, capillary refill time, rectal temperature, respiratory rate, mucous membrane color, degree of hydration, urine output, glucose, central venous blood gas analysis, plasma lactate (from central venous blood), base deficit

### Protocol during intensive treatment



**Figure 1:** Treatment protocol for dogs with septic shock. The dogs received antibiotic therapy with cephalothin<sup>f</sup> (22 mg/kg, IV, q8h) and metronidazole<sup>g</sup> (15 mg/kg, IV, q12h), analgesia and volume resuscitation with 40 mL/kg/h 0.9% saline, IV. After 2 hours of volume resuscitation with saline solution, animals not exhibiting improved parameters were administered colloid HES 130/0.4<sup>i</sup> (20–30 mL/kg/30 min) once. When hypotension (DBP <90 mm Hg) persisted, vasopressor therapy with dopamine<sup>i</sup> was initiated. After admission to the ICU, volume resuscitation was continued to maintain the DBP > 90 mm Hg, CVP between 8 and 12 mm Hg, urine output above 2 mL/kg/h and ScvO<sub>2</sub> above 70%, and to reduce lactate and the base deficit from their baseline concentrations.

(central venous blood), and ScvO<sub>2</sub>. The central venous blood samples were collected into heparinized syringes (liquid heparin) and analyzed immediately. The blood sample temperature was corrected to patient temperature at the moment of gasometry. After time point M5, the monitoring was recorded every 3 hours until the treatment outcome.

Analgesia was achieved with tramadol hydrochloride (2.0–4.0 mg/kg, IV, q8h), morphine<sup>k</sup> (0.1–0.5 mg/kg, IV, q4–6h), or fentanyl<sup>l</sup> by continuous infusion (0.02–0.05 µg/kg/min, IV). Animals with emesis were treated with metoclopramide<sup>m</sup> (0.5 mg/kg, SC, q8h) and ranitidine hydrochloride<sup>n</sup> (2 mg/kg, SC, q12h). Sodium bicarbonate<sup>o</sup> was administered only to animals with low bicarbonate (<14 mmol/L [ $<14$  mEq/L]) and metabolic acidosis concomitant to renal dysfunction.<sup>21</sup> Sodium bicarbonate was replaced according to the formula: sodium bicarbonate (mmol [mEq]) =  $0.3 \times$  bicarbonate deficit  $\times$  weight (kg). Infusion was conducted for 1 hour.

### Statistical analysis

At the end of the study, the animals were divided into survivor and nonsurvivor groups. The Kolmogorov-Smirnov statistical test for normality was used to determine whether the data were normally distributed. Statistical significance was set at  $P < 0.05$  and a statistical software package<sup>p</sup> was used to analyze the data.

The use of vasoactive drugs in both groups was analyzed by the chi-square or Fisher's exact test when appropriate. ScvO<sub>2</sub>, lactate, and base deficit were assessed during the intensive treatment and were compared between the survivors and nonsurvivors using a 2-way analysis of variance model. When a significant change of the parameters evaluated over time was observed, Tukey's multiple comparison method was applied to see at which moments these variations occurred between M1 and M5.

The initial (M1) ScvO<sub>2</sub>, plasma lactate, and base deficit levels underwent univariate analysis using the *t*-test for independent samples, comparing survivors to nonsurvivors. Next, the data were subjected to logistic regression (multivariate analysis) to evaluate in the set the relevance of each variable to mortality.

Receiver operator characteristic (ROC) curves and the area under the curve were also calculated for the prognostic markers evaluated. Ninety-five percent confidence intervals (CIs) were reported for the area under the curve.

### Results

Forty-two animals met the inclusion criteria, but 12 were later excluded. Of the excluded animals, 4 were eutha-

nized at the request of the owner, 3 died after abdominal ultrasonography, 2 animals removed the central venous access, and 3 animals exhibited comorbidities such as neoplasia or chronic kidney disease. Thirty dogs of various breeds with an average age of 9 years (range, 6–15 y) were included in the study, of which 17 (54%) had severe sepsis and 13 (46%) had septic shock (Table 1). Their physical examination and tissue perfusion parameters on ICU admission are shown in Table 2.

Survivors were defined as patients that were alive at the time of discharge (19/30). Nonsurvivors were patients that died while in the ICU. None were euthanized. The mortality was 36.7% (11/30). Fifty-four percent (17/30) had severe sepsis; 46% (13/30) had septic shock, with persistent arterial hypotension after volume resuscitation. Out of the survivors, only one animal had septic shock and 18 animals had severe sepsis. Most of the nonsurvivors (90.9%) had septic shock. Four of these animals had persisting arterial hypotension despite treatment with crystalloids, colloids, and dopamine, and died during the first 6 hours of intensive care.

The need for vasoactive drugs was significantly higher among the animals that did not survive ( $P < 0.001$ ). All of the nonsurvivors needed vasoactive drugs. This group received an average of 9.6 (range, 6.6–13) µg/kg/min of dopamine, whereas only 4 of the survivors needed dopamine (7–10 µg/kg/min). Among the survivors, the average volume of crystalloid infused from M0 to M5 was 27.0 mL/kg/h, whereas the nonsurvivors received an average of 38.2 mL/kg/h ( $P < 0.001$ ).

In the analysis of variance of the ScvO<sub>2</sub> and base deficit, there were no significant changes over time ( $P = 0.258$ ,  $P = 0.909$ , respectively); however, both variables showed a significant difference between groups ( $P < 0.001$ ). The survivors demonstrated higher ScvO<sub>2</sub> than the nonsurvivors (Figure 2), and the nonsurvivors had higher base deficits than the survivors (Figure 3). In the analysis of variance of plasma lactate concentrations, there was significant change over time ( $P = 0.001$ ) as well as between the groups ( $P < 0.001$ ). The survivors showed lower lactate concentrations than nonsurvivors. In both groups, there were significant differences between the measurements taken at the end of resuscitation (M5) and those obtained during the initial evaluation (M0). The lactate concentrations at M5 were lower than those at M0 ( $P = 0.001$ ) (Figure 4). The analysis of variance showed no significant effect between measurements over time and death for ScvO<sub>2</sub>, base deficit, and lactate ( $P = 0.889$ ,  $P = 0.744$ ,  $P = 0.443$ , respectively).

The univariate analysis demonstrated that the ScvO<sub>2</sub>, lactate, and base deficit values obtained on ICU admission (M1) were independently related to death. The surviving animals had average values of 74.6% ScvO<sub>2</sub> (SD, 7.23),  $-7.7$  mmol/L base deficit (SD, 6.1), and

**Table 1:** Parameters of physical examination and laboratory data at admission in the emergency room

Parameters	Survivors (19) mean ± SD		Nonsurvivors (11) mean ± SD	
	Severe sepsis (16)	Septic shock (3)	Severe sepsis (1)	Septic shock (10)
Age (years)	8.9 ± 2.2	8.7 ± 1.2	11	11.3 ± 3.0
Body weight (kg)	17.3 ± 14.5	17.2 ± 9.4	8	9.6 ± 6.8
Heart rate (beats/min)	130 ± 22	145 ± 22	120	132 ± 28
Respiratory rate (breaths/min)	34 ± 9	32 ± 12	36	37 ± 14
Rectal temperature (°C)	38.0 ± 1	36.5 ± 3.0	37.2	37.3 ± 1.0
SAP (mm Hg)	117.0 ± 28.3	56.7 ± 5.8	120	54.0 ± 7.0
Urine output (mL/kg/h)	2.0 ± 2.6	0.3 ± 0.6	2.0	0.8 ± 1.6
Lactate (mmol/L)	2.7 ± 1.4	4.7 ± 2.1	2.1	4.8 ± 2.0
WBC count × 10 <sup>9</sup> /L	34.2 ± 26.3	23.9 ± 22.0	67.1	37.0 ± 55.5
Hemoglobin (g/L)	121.1 ± 28.7	137.3 ± 31.0	125.0	119.8 ± 36.6
Platelets × 10 <sup>9</sup> /L	176.250 ± 135.308	139.333 ± 3.215	109.000	257.600 ± 147.975
Total bilirubin (μmol/L)[mg/dL]	21.5 ± 30.8	14.9 ± 10.9	18.0	26.3 ± 32.5
ALP (U/L)	[1.26 ± 1.80]	[0.87 ± 0.64]	[1.05]	1.54 ± 1.91
ALT (U/L)	289 ± 246	367 ± 424	204.8	230 ± 244
ALT (U/L)	18.0 ± 10.5	22.1 ± 19.6	25.3	46.8 ± 39.3
Creatinine (μmol/L) [mg/dL]	230.7 ± 146.7	199.0 ± 76.0	716.0	271.4 ± 145.0
Glucose (mmol/L) (mg/dL)	[2.6 ± 1.7]	[2.3 ± 0.9]	[8.1]	[3.1 ± 1.6]
Glucose (mmol/L) (mg/dL)	5.5 ± 2.2	2.9 ± 0.9	7.2	4.0 ± 0.3
	[99 ± 39]	[53 ± 16]	[129.0]	[72 ± 48]

ALP = alkaline phosphatase; ALT = alanine transaminase.

**Table 2:** Physical examination and tissue perfusion parameters upon ICU admission

Parameters	Survivors (19) mean ± SD		Nonsurvivors (11) mean ± SD	
	Severe sepsis (16)	Septic shock (3)	Severe sepsis (1)	Septic shock (10)
Heart rate (beats/min)	121 ± 22	126 ± 26	140	130 ± 30
Respiratory rate (breaths/min)	29 ± 10	32 ± 7	44	44 ± 12
Rectal temperature (°C)	36.1 ± 0.8	35.7 ± 0.3	34.0	35.7 ± 1.1
SAP (mm Hg)	139.0 ± 23.0	90.0 ± 10.0	150.0	88.0 ± 27.0
Urine output (mL/kg/h)	3.2 ± 3.6	3.5 ± 3.5	2.0	3.6 ± 6.5
Lactate (mmol/L)	2.31 ± 1.35	2.57 ± 0.67	3.3	3.8 ± 2.3
ScvO <sub>2</sub> (%)	74.1 ± 7.6	77.3 ± 4.9	71.0	61.5 ± 10.7
Base deficit (mmol/L)	-6.2 ± 5.3	-15.7 ± 3.5	-19.0	-16.1 ± 4.0

2.35 mmol/L lactate (SD, 1.2). The nonsurvivors had averages of 62.4% ScvO<sub>2</sub> (SD, 10.5), -16.4 mmol/L base deficit (SD, 3.91), and 3.8 mmol/L lactate (SD, 2.2). The difference between groups at this time point (M1) was statistically significant for all 3 parameters, respectively,  $P < 0.001$ ,  $P < 0.001$ , and  $P = 0.034$  (Figures 5–7).

In the initial model of multiple logistic regression with ScvO<sub>2</sub>, lactate, and base deficit, lactate lost significance in the set with the other variables, with an odds ratio of 0.89 ( $P = 0.799$ ). Therefore, the final logistic regression modeling was performed using ScvO<sub>2</sub> and base deficit, which together showed statistical significance, with an odds ratio of 0.76 for every 1% increase in ScvO<sub>2</sub> ( $P = 0.033$ , 95% CI) and an odds ratio of 0.55 for every 1% decrease in base deficit ( $P = 0.032$ , 95% CI).

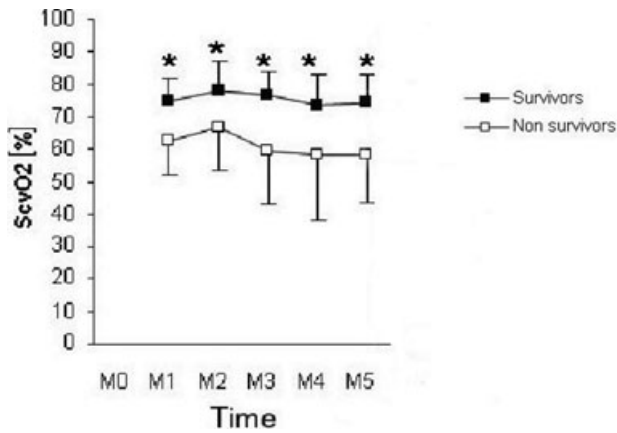
In the ROC curve analysis with death as the outcome, the following area under the curve values were calculated: ScvO<sub>2</sub>, 0.804 (95% CI, 0.633–0.975); base

deficit, 0.895 (95% CI, 0.785–1.005); and lactate, 0.689 (95% CI, 0.468–0.910). ScvO<sub>2</sub> and base deficit were the best discriminators between survivors and nonsurvivors (Figure 8). Cut-off points and their sensitivity, specificity, and accuracy are listed in Table 3.

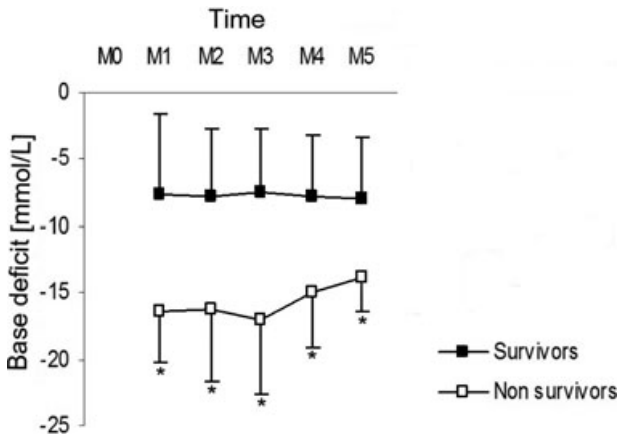
## Discussion

In people, the first 6 hours after the diagnosis of severe sepsis are known as the “golden hours,” because volume resuscitation performed within these 6 hours is associated with reduced organ dysfunction and mortality.<sup>16</sup>

In our study, following diagnosis in the emergency room, all of the animals were resuscitated to restore the clinical parameters of tissue perfusion and reduce lactate concentrations until the end of surgery. After central venous access had been obtained, the ScvO<sub>2</sub> and base



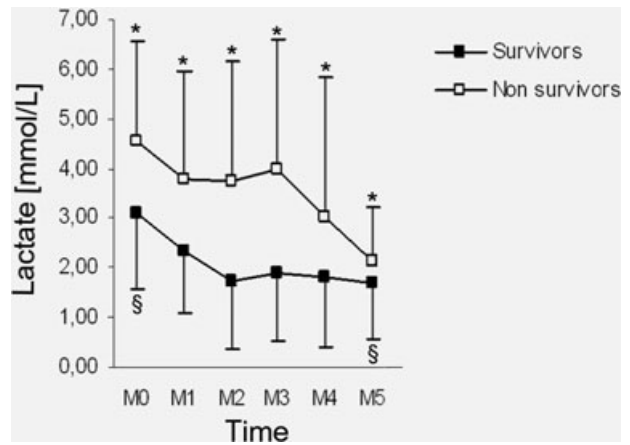
**Figure 2:** Changes in ScvO<sub>2</sub> from ICU admission to death or discharge. Mean ScvO<sub>2</sub> values (%) and standard deviations in survivors and nonsurvivors. Two of 11 animals died before M4 and two before M5. (\*) There was a significant difference between the groups ( $P < 0.001$ ).



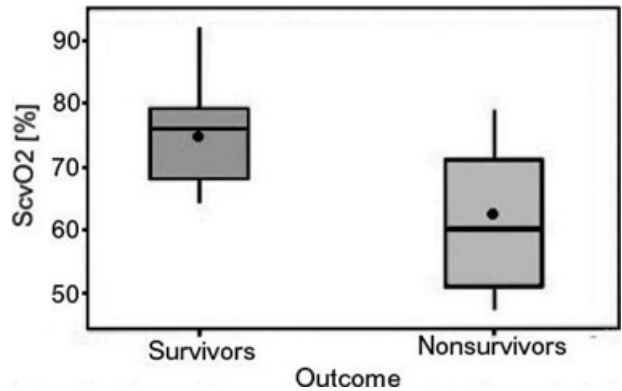
**Figure 3:** Changes in base deficit from ICU admission to death or discharge. Mean base deficits (mmol/L) and standard deviations in survivors and nonsurvivors. Two of 11 animals died before M4 and two before M5. (\*) There was a significant difference between the groups ( $P < 0.001$ ).

deficit were also used as resuscitation goals until the end of the resuscitation period (M5).

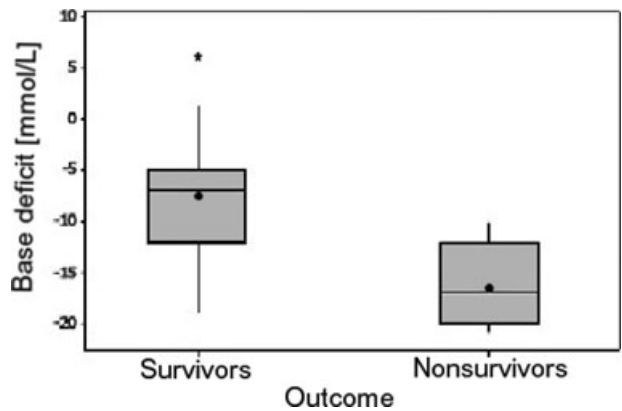
In people, a prospective randomized study involving patients with sepsis concluded that patients who were treated with early fluid resuscitation, aiming to reach values of ScvO<sub>2</sub>  $\geq 70\%$ , resulted in decreased mortality. In this study, the incidence of death from cardiovascular collapse was twice as high in the group receiving conventional treatment, suggesting that when resuscitation is not instituted early, septic shock develops abruptly.<sup>16</sup> Recognition of patients at this early stage, when there is tissue hypoxia despite normal vital signs, early resuscitation is vital to restore the balance between tissue oxygen demand and consumption. Early reversal of severe



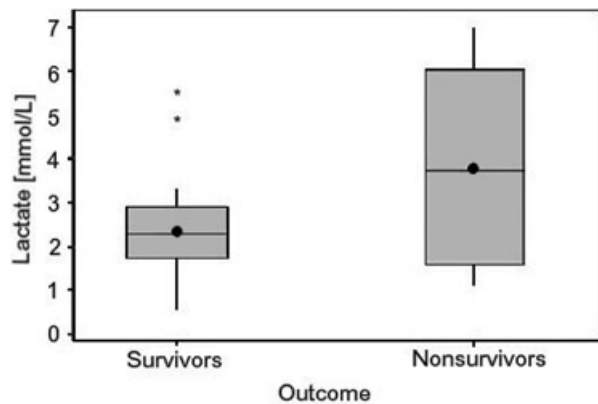
**Figure 4:** Changes in lactate from emergency room admission to death or discharge. Mean lactate levels (mmol/L) and standard deviations in survivors and nonsurvivors. Two of 11 animals died before M4 and two before M5. There was a significant variation over time (§) ( $P = 0.001$ ) as well as between the groups (\*) ( $P < 0.001$ ).



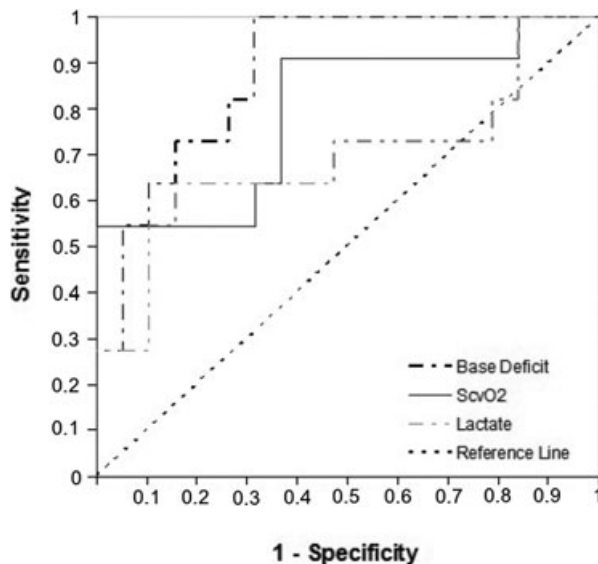
**Figure 5:** ScvO<sub>2</sub>. This box plot shows ScvO<sub>2</sub> at ICU admission (M1), comparing survivors to nonsurvivors ( $P < 0.001$ ). •, mean; central black line is the median. The whiskers represent the range.



**Figure 6:** Base deficit. This box plot shows base deficit at ICU admission (M1), comparing survivors to nonsurvivors ( $P < 0.001$ ). •, mean; central black line is the median. \*, individual patient data point. The whiskers represent the range.



**Figure 7:** Lactate. This box plot shows lactate levels at ICU admission (M1), comparing survivors to nonsurvivors ( $P = 0.034$ ). ●, mean; central black line is the median. \*, individual patient data point. The whiskers represent the range.



**Figure 8:** ROC curves comparing the discriminating capabilities of prognostic markers between survivors and nonsurvivors.

sepsis is associated with improved prognosis and reduced mortality.<sup>14,16</sup>

During the development of hypoperfusion, there is a period in which the oxygen supply to tissues decreases, but the oxygen consumption is maintained because of increased oxygen extraction by the tissues. The oxygen extraction increases gradually, resulting in decreased mixed venous oxygen saturation (SvO<sub>2</sub>).<sup>17</sup> Sepsis also promotes cytopathic hypoxia, a condition in which there is mitochondrial dysfunction and the cells have difficulty extracting oxygen and using it for cellular respiration.<sup>12</sup> Thus, normal or high SvO<sub>2</sub> does not necessarily indicate adequate tissue perfusion, but low values of SvO<sub>2</sub> suggest the need for rapid intervention to increase oxy-

**Table 3:** List of cut-off points with the sensitivity, specificity, and accuracy for hospital mortality at ICU admission

Parameters upon ICU admission	Cut-off points	Sensitivity	Specificity	Accuracy
ScvO <sub>2</sub> (%)	52	64.5%	100%	83.3%
Lactate (mmol/L)	3.15	63.6%	84.2%	76.7%
	3.50	54.5%	89.5%	76.7%
Base deficit (mmol/L)	-9.5	100%	68.4%	80%
	-14.5	72.7%	84.2%	80%
	-15.5	63.6%	89.5%	80%
	-16.5	54.5%	94.7%	80%

gen delivery to the tissues. Decreased SvO<sub>2</sub> is associated with poor prognosis in patients with septic shock or heart failure. The disadvantage is the need for placement of a pulmonary artery catheter, which is invasive and requires expensive equipment.

ScvO<sub>2</sub> is an excellent tool for patient assessment during the resuscitation for shock, but controversy remains regarding its use for monitoring in the ICU after this initial phase.<sup>27</sup> In a prospective study of septic humans patients, ScvO<sub>2</sub> was used as a guide to resuscitation, showing a reduction in mortality. The authors of this study suggest that the use of ScvO<sub>2</sub> reflects hypovolemia, besides being a less invasive method than SvO<sub>2</sub>.<sup>17</sup>

In people, a prospective observational study was conducted to compare ScvO<sub>2</sub> and SvO<sub>2</sub> in critically ill patients. The study included 53 patients monitored with a pulmonary artery catheter. The values of ScvO<sub>2</sub> and SvO<sub>2</sub> were equivalent because of their physiological relationship; however, the obtained values of ScvO<sub>2</sub> were higher than those of SvO<sub>2</sub>, with a standard deviation of 5.2%.<sup>28</sup>

At ICU admission, higher ScvO<sub>2</sub> was associated with a lower probability of death (odds ratio = 0.76,  $P = 0.033$ ), suggesting that ScvO<sub>2</sub> is an important independent surrogate marker for outcome, as well as in conjunction with the base deficit. Furthermore, the ROC curve analysis indicates that at ICU admission, patients with ScvO<sub>2</sub> below 52% have an increased risk of death (Table 3). ScvO<sub>2</sub> below 70% during the first 6 hours after admission to the ICU, as observed among the nonsurvivors, reflects the severity of macrocirculatory and microcirculatory dysfunction,<sup>9,29</sup> as well as the increase in cellular metabolism found in patients with severe sepsis or septic shock.<sup>13,30</sup> Considering the occurrence of cytopathic hypoxia, it is difficult to interpret these data; however, taking all of these quoted studies from human medicine into account suggests that higher values of ScvO<sub>2</sub> may be a better goal in dogs with severe sepsis and septic shock.



Throughout the postoperative resuscitation period (M1–M5), the animals that did not survive had a greater base deficit than the animals that survived. At ICU admission, lower base deficit was also associated with a lower probability of death (odds ratio = 0.55;  $P = 0.032$ ), characterizing the base deficit as a prognostic marker. In people, an observational study of critically ill patients indicated that base excess  $< -4$  mmol/L at admission identified patients at high risk of death when accompanied by lactate  $> 1.5$  mmol/L, highlighting the value of the base deficit obtained at admission as a prognostic marker.<sup>23</sup> This study suggests that base deficit  $< -14.5$  mmol/L on ICU admission identified animals at high risk of death (72.7% sensitivity and 84.2% specificity) (Table 3).

It should be noted that the literature suggests that volume resuscitation with 0.9% saline solution may increase metabolic acidosis<sup>31</sup> and consequently the base deficit.<sup>32</sup> The high chloride concentration and highly resorbable nature of chloride ions in the renal tubules contribute to a decrease in plasma bicarbonate concentration and an increase in chloride concentration.<sup>31</sup> In this study, saline solution was not compared to another crystalloid, but there was a decrease in base deficit during resuscitation in the nonsurvivors and no significant difference between time points in the survivors.

In human studies, persistence of increased lactate concentration during hospitalization is considered a predictor of mortality and organ failure,<sup>33</sup> in addition to the presence of increased lactate concentrations in critically ill patients at ICU admission,<sup>23</sup> as observed in our study. Elevated lactate at ICU admission of critically ill patients has been associated with increased mortality in studies performed on dogs<sup>34</sup> and children.<sup>35</sup> However, when the lactate concentrations measured in the emergency room underwent multivariate analysis together with ScvO<sub>2</sub> and base deficit, lactate lost significance ( $P = 0.799$ ). This is probably because of the small number of dogs included in this study. The literature reports limitations regarding the use of lactate as a tissue perfusion marker, because it rises slowly while tissue hypoxia continues after the maximization of oxygen extraction by the tissues.<sup>19,27</sup> In addition, based on the ROC curve analysis, lactate concentrations are a poor test for the identification of nonsurvivors compared to base deficit and ScvO<sub>2</sub>, which could be considered a good test. Thus, it is recommended that lactate should be evaluated along with other markers of tissue hypoperfusion, especially in septic patients with relative hypovolemia.<sup>19</sup>

### Study limitations

It is important to highlight that this study evaluated and compared variables measured during the postoperative

period. In addition to the depressant effects of anesthesia on the cardiovascular system, the surgical intervention is likely to have promoted the release of inflammatory mediators that might have exacerbated the systemic inflammatory response already present in the patients. Another limitation of our study was delayed insertion of the central venous catheter. The first evaluation of ScvO<sub>2</sub> occurred only 3 hours after the onset of volume resuscitation, because central venous access was obtained in the operating room. Passage of a central venous catheter is a less invasive procedure than that of a pulmonary artery catheter, but it should be performed with an appropriate aseptic technique to prevent infection.<sup>19</sup> Our study design could have been improved had central venous catheters been placed before surgery.

In conclusion, the initial values of ScvO<sub>2</sub>, lactate, and base deficit as well as their changes over time aided the recognition of more severely ill patients at risk of death. Moreover, our study provides preliminary evidence that these variables may be useful in predicting the prognosis of dogs with severe sepsis and septic shock, such that animals with a higher ScvO<sub>2</sub> and lower base deficit at admission to the ICU have a lower probability of death. Further evaluation and confirmation of the use of ScvO<sub>2</sub> and base deficit for prognostication, in addition to their known value for monitoring treatment, are warranted.

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### Footnotes

- <sup>a</sup> ABL5-Radiometer, Copenhagen, Denmark.
- <sup>b</sup> Accutrend Lactate® Roche, São Paulo, Brazil.
- <sup>c</sup> Aparelho Achu-check® portátil, Roche.
- <sup>d</sup> Parks Medical Electronic, Aloha, OR.
- <sup>e</sup> Solução fisiológica 0.9%, Baxter Hospitalar, São Paulo, Brazil.
- <sup>f</sup> Cefalotina sódica – genérico, São Paulo, Brazil.
- <sup>g</sup> Flagyl®, Sanofi-Aventis, São Paulo, Brazil.
- <sup>h</sup> Tramal, Pfizer, São Paulo, Brazil.
- <sup>i</sup> Cloridrato de dopamina – genérico, União Química, São Paulo, Brazil.
- <sup>j</sup> Voluven®, Fresenius Kabi Brasil Ltda, Campinas, Brazil.
- <sup>k</sup> Dimorf – Cristália – São Paulo, Brazil.
- <sup>l</sup> Fentanil – Cristália.
- <sup>m</sup> Metoclorpramida – Ariston – São Paulo, Brazil.
- <sup>n</sup> Cloridrato de ranitidina – Borges Sabará – Minas Gerais, Brazil.
- <sup>o</sup> Bicarbonato de sódio – Minas Gerais, Brazil.
- <sup>p</sup> Minitab, 15.1, Minitab Inc., State College, PA.

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