Assessment of oxygen transport and utilization in dogs with naturally occurring sepsis

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Objective—To compare cardiac index (CI), oxygen delivery index ($\dot{D}o_2I$), oxygen extraction ratio (O_2ER), oxygen consumption index ($\dot{V}o_2I$), and systemic vascular resistance index (SVRI) in dogs with naturally occurring sepsis with published values for healthy dogs; compare those variables in dogs with sepsis that did or did not survive; and compare CI and $\dot{D}o_2I$ in dogs with sepsis with values in dogs with nonseptic systemic inflammatory response syndrome (nSIRS).

Design—Cohort study.

Animals—10 dogs with naturally occurring sepsis and 11 dogs with nSIRS.

Procedures—Over 24 hours, CI, $\dot{D}o_2I$, O_2ER, $\dot{V}o_2I$, and SVRI were measured 4 and 5 times in dogs with sepsis and with nSIRS, respectively. The mean values of each variable in each group were compared over time and between groups; data for dogs with sepsis that did or did not survive were also compared.

Results—Mean $\dot{D}o_2I$ was significantly decreased, and mean CI, O_2ER, $\dot{V}o_2I$, and SVRI were not significantly different in dogs with sepsis, compared with published values for healthy dogs. Mean CI and $\dot{D}o_2I$ in dogs with sepsis were significantly greater than values in dogs with nSIRS. Among dogs with sepsis that did or did not survive, values of CI, $\dot{D}o_2I$, O_2ER, $\dot{V}o_2I$, and SVRI did not differ significantly.

Conclusions and Clinical Relevance—Compared with values in healthy dogs, only $\dot{D}o_2I$ was significantly lower in dogs with sepsis. Values of CI and $\dot{D}o_2I$ were significantly higher in dogs with sepsis than in dogs with nSIRS, suggesting differing degrees of myocardial dysfunction between these groups. (*J Am Vet Med Assoc* 2010;237:167–173)

Sepsis is a systemic inflammatory response to infection with bacterial, viral, protozoal, or fungal organisms. This inflammatory response is mediated by cytokines released from macrophages in response to tissue injury or bacterial invasion.[1] The development of sepsis is associated with cardiovascular derangements and microcirculatory disturbances that lead to local tissue hypoperfusion.[2] Tissue oxygen extraction and utilization may be impaired, leading to development of tissue hypoxia and, ultimately, multiorgan dysfunction and death.[3]

Sepsis in volume-resuscitated humans is a hyperdynamic state characterized by normal to high CO despite impaired cardiac contractility.[4] Cardiac output is maintained through reversible biventricular dilatation and tachycardia.[2,5] Both survivors and nonsurvivors of sepsis appear to maintain this hyperdynamic state.[2,5] Low SVR, with or without decreases in mean arterial blood pressure, is also detected.[3] Oxygen delivery, which is the amount of oxygen (mL) delivered to the tissues per minute, is increased along with CO.[3]

In experimental studies,[6–12] dogs with sepsis have a similar hemodynamic profile to that of humans with sepsis. In conscious dogs that have clots containing *Escherichia coli* implanted IP, CO and mean arterial blood pressure values are initially low. Following administration of 80 mL of isotonic crystalloid fluid/kg (36.4 mL of isotonic crystalloid fluid/lb), those dogs develop increased CO and decreased SVR, comparable to findings in humans receiving fluid therapy for sepsis. Similar hemodynamic changes have been detected in dogs experimentally infused with *E coli* endotoxin[7] or live *E coli*[8] and dogs implanted IP with endotoxin-containing clots.[9] It is not known whether experimentally induced sepsis in dogs is associated with the same degree of myocardial depression as that which develops in humans with sepsis. One study[10] involving anesthe-

Abbreviations

Cao_2	Arterial oxygen content
CI	Cardiac index
CO	Cardiac output
CVP	Central venous pressure
$\dot{D}o_2$	Oxygen delivery
$\dot{D}o_2I$	Oxygen delivery index
nSIRS	Nonseptic systemic inflammatory response syndrome
O_2ER	Oxygen extraction ratio
SIRS	Systemic inflammatory response syndrome
SVR	Systemic vascular resistance
SVRI	Systemic vascular resistance index
$\dot{V}o_2$	Oxygen consumption
$\dot{V}o_2I$	Oxygen consumption index

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tized dogs revealed no changes in myocardial contractility for 4 hours following endotoxin infusion, whereas considerable myocardial depression has been detected following IV administration of endotoxin[11] or tumor necrosis factor-α.[12]

Despite sufficient $\dot{D}O_2$, metabolic dysfunction and signs of tissue hypoxia persist in sepsis.[13] The underlying cause of persistent tissue hypoxia is an area of debate[13,14] and is thought to be related to insufficient oxygen extraction. The O_2ER is the percentage of oxygen removed by the tissues.[15,16] Decreases in O_2ER in association with sepsis can occur as a result of microcirculatory dysoxia, an inability of the tissues to use oxygen, or more likely, some combination of these.[17] Microcirculatory dysoxia occurs secondary to abnormal blood flow patterns at the tissue level caused by endothelial dysfunction, microthrombosis, and functional shunting.[18] Microcirculatory flow derangements are associated with reduced tissue oxygen extraction,[18] and both have been identified in humans with sepsis.[19] Sepsis is also thought to decrease the ability of tissue to consume oxygen via mitochondrial dysfunction or cytopathic hypoxia, thereby creating a state of improper oxygen utilization.[20] Regardless of the underlying cause, O_2ER is decreased in dogs and humans with sepsis despite adequate $\dot{D}O_2$.[3,13,20,21]

Oxygen consumption is the total amount of oxygen consumed by the tissues.[15] In healthy animals, $\dot{V}O_2$ is independent of $\dot{D}O_2$ because oxygen is delivered far in excess of tissue requirements. Once $\dot{D}O_2$ decreases to less than a critical level, $\dot{V}O_2$ becomes directly dependent on the amount of oxygen delivered.[15] In a healthy animal, the amount of oxygen delivered is matched to oxygen demand. In septic states, inefficient matching of blood flow to oxygen demand creates a pathological oxygen supply dependency; despite increases in $\dot{D}O_2$, decreased O_2ER causes $\dot{V}O_2$ to become supply dependent.[22] Although it seems logical that $\dot{V}O_2$ should be decreased in septic states, $\dot{V}O_2$ is apparently normal to increased in both humans[3,14,21] and dogs with sepsis.[23] Alterations in $\dot{V}O_2$ may be a result of heterogeneous blood supply at the microcirculatory level, wherein low flow rates in some tissues increase the amount of oxygen consumed yet other tissues become unable to extract oxygen.[21]

To the authors' knowledge, there have been no previous studies of oxygen transport and utilization variables in dogs with naturally occurring sepsis. Studies[9,21] have been performed in anesthetized research dogs with experimentally induced sepsis, but the hemodynamic profile of clinically ill dogs is unknown. In another study[24] of dogs with SIRS, CO and $\dot{D}O_2$ were decreased, compared with findings in healthy dogs. The purpose of the study reported here was to compare CI, $\dot{D}O_2I$, O_2ER, $\dot{V}O_2I$, and SVRI in dogs with naturally occurring sepsis with published values for healthy dogs; compare those variables in dogs with sepsis that did or did not survive; and compare CI and $\dot{D}O_2I$ in dogs with sepsis with values in dogs with nSIRS. We hypothesized that dogs with naturally occurring sepsis have significantly higher values of CO, $\dot{D}O_2$, and $\dot{V}O_2$ and significantly lower values of O_2ER and SVRI, compared with values in healthy dogs; that dogs with sepsis that do not survive have significant alterations in CO, $\dot{D}O_2$, O_2ER, $\dot{V}O_2$, and SVRI over time, compared with surviving dogs with sepsis that do survive; and that dogs with sepsis have significantly higher CO and $\dot{D}O_2$ than dogs with nSIRS.

Materials and Methods

Dogs that were evaluated in the critical care unit at a veterinary teaching hospital were considered for inclusion in the study. Informed client consent was obtained prior to study enrollment of any dog, and the study was approved by the Colorado State University Animal Care and Use Committee. Data were collected from January 2005 through April 2007.

Inclusion criteria—A dog was eligible for inclusion in the study if it weighed > 10 kg (22 lb), had both an arterial catheter and central (jugular) venous catheter in place, and had evidence of SIRS (determined on the basis of 3 or more findings as follows: respiratory rate > 40 breaths/min or $PaCO_2$ < 30 mm Hg; heart rate > 120 beats/min; rectal temperature < 100.4°F [38°C] or > 104°F [40°C]; WBC count < 5,000 cells/mm^3 or > 18,000 cells/mm^3; and proportion of band neutrophils > 10%). Sepsis was initially diagnosed cytologically (ie, bacteria detected during microscopic examinations of samples of effusions or swabs) and subsequently confirmed on the basis of positive results of bacterial culture of samples. Negative results of bacterial culture or lack of underlying septic disease process (ie, secondary to gastric dilatation-volvulus, hemoabdomen, or polytrauma or following cardiac arrest and cardiopulmonary-cerebral resuscitation) were used to classify eligible dogs as dogs with nSIRS. Ten dogs with naturally occurring sepsis and 11 dogs with nSIRS were included in the study. Seven dogs with sepsis were excluded because only CO and $\dot{D}O_2I$ measurements were obtained in those patients.

Procedures—Lithium dilution CO measurements were performed by use of hemodynamic monitor[a] in accordance with the manufacturer's specifications. Lithium dilution CO measurements were performed at 0, 8, 16, and 24 hours in the dogs with sepsis and at 0, 4, 8, 16, and 24 hours in the dogs with nSIRS. At the predetermined time points, dogs in each group also underwent arterial blood gas analyses,[b] hemoximetry,[c] and measurements of direct mean arterial blood pressure. Venous blood gas analyses[b] and measurement of CVP were performed at each time point only in dogs with sepsis. Treatments were not standardized for either the nSIRS or sepsis groups; the primary clinician was free to use any treatment indicated by the patient's clinical condition.

Cardiac output was adjusted to patient body surface area (ie, calculation of CI) to allow comparisons among dogs of different size. Body surface area was calculated by use of an equation[25] as follows: body surface area (m^2) = 0.101 × body weight (kg)$^{0.67}$. Other formulas were used to calculate hemodynamic and oxygen transport variables ($\dot{D}O_2I$, CaO_2, O_2ER, $\dot{V}O_2I$, and SVRI; **Appendix**). For calculation of $\dot{D}O_2I$, CO was obtained from the lithium dilution CO measurement. Arterial and venous oxygen saturations and total hemoglobin concentrations were obtained from the hemoximeter readings. Arterial and venous PO_2 were obtained from the respective blood gas analyses.

Previously published values[26] for hemodynamic variables in conscious healthy dogs were used for comparison with data obtained from the dogs with sepsis. Some data from dogs with nSIRS have been published previously[24]; any dogs with sepsis included in that publication were omitted from analysis in this study. Because venous blood gas analysis and CVP assessments were not performed during investigation of the dogs with nSIRS, values of O_2ER, $\dot{V}O_2I$, and SVRI were not calculated for that group.

Statistical analysis—All statistical analyses were performed by a university statistician using computer software.[d] Data are reported as mean ± SD. For dogs with sepsis, values of CI, $\dot{D}O_2I$, O_2ER, $\dot{V}O_2I$, and SVRI at the various time periods were compared by use of a repeated-measures ANOVA to test for differences over time. For dogs with nSIRS, CI and $\dot{D}O_2I$ were compared with a repeated-measures ANOVA similarly to dogs with sepsis. Mean values of CI, $\dot{D}O_2I$, O_2ER, $\dot{V}O_2I$, SVRI, mean arterial blood pressure, heart rate, total hemoglobin concentration, arterial oxygen saturation, and CVP over all time points for dogs with sepsis were compared with values for healthy dogs[26] by use of a Student *t* test of unequal variance; the mean values of CI, $\dot{D}O_2I$, heart rate, total hemoglobin concentration, and arterial oxygen saturation in dogs with sepsis were similarly compared with values in dogs with nSIRS.[24] The effect of time on CI, $\dot{D}O_2I$, O_2ER, SVRI, or $\dot{V}O_2I$ in dogs with sepsis that did or did not survive to discharge from the hospital was analyzed by use of a repeated-measures ANOVA. Correlations among CI, $\dot{D}O_2I$, O_2ER, $\dot{V}O_2I$, and SVRI in dogs with sepsis were determined by calculation of Pearson correlation coefficients; values are reported as an adjusted R^2 value. For all comparisons, a value of $P < 0.05$ was considered significant.

Results

Dogs with sepsis—Ten dogs with naturally occurring sepsis were included in the study. Mean ± SD age of the dogs was 6.3 ± 3.2 years (range, 1 to 14 years), and mean weight was 33.5 ± 10.8 kg (73.7 ± 23.8 lb [range, 20.0 to 54.2 kg {44.0 to 119.2 lb}]). Labrador Retrievers were the most common breed represented (n = 4), followed by mixed-breed dogs (2) and Mastiff, Golden Retriever, Bloodhound, and English Setter (1 each). Causes of sepsis were septic peritonitis (n = 6), pneumonia (3), and nonhealing skin wounds (1). Bacterial culture of samples from all 10 dogs yielded growth of at least 1 organism; multiple types of bacteria were detected in samples from 8 dogs. The most common organisms isolated were *E coli* (n = 5 *dogs*), *Staphylococcus intermedius* (4), *Enterococcus* spp (4), and β-hemolytic *Streptococcus* spp (2). *Clostridium perfringens*, *Lactobacillus* sp, *Proteus mirabilis*, and methicillin-resistant *Staphylococcus aureus* were each isolated once.

A total of 32 lithium dilution CO measurements were obtained from the 10 dogs with sepsis over the 24-hour period. Five dogs survived to discharge from the hospital, and all were still alive 28 days later. Among the 5 surviving dogs, a 24-hour measurement was not completed in 1 dog because of dislodgement of the arterial catheter. Four dogs were euthanatized (3 during the 24-hour study period and 1 immediately following the study period) because of their deteriorating condition, including development of severe hypotension, multiorgan dysfunction, and disseminated intravascular coagulation. One dog was euthanatized after it survived the initial episode of septic pneumonia but failed to recover neurologically following craniotomy for cerebral mass removal. Data were obtained from the 2 euthanatized dogs surviving the study period at all time points and included in the analyses; data were available from the 3 dogs euthanatized during the study period at time points 0 (n = 3), 8 (1), and 16 (1) hours.

In the dogs with sepsis, values of CI, $\dot{D}O_2I$, O_2ER, $\dot{V}O_2I$, and SVRI did not significantly change over time within individuals; thus, values for each variable at the 4 time points were averaged for each dog with sepsis. These mean values of CI, $\dot{D}O_2I$, O_2ER, $\dot{V}O_2I$, and SVRI were compared with previously published values for healthy dogs. Mean values of CI and DO_2I were also compared with values in the dogs with nSIRS.

Dogs with nSIRS—Eleven dogs with nSIRS were included in the study. Mean age of the dogs was 8.4 ± 3.6 years (range, 0.3 to 13 years), and mean weight was 34.3 ± 19.9 kg (75.5 ± 43.8 lb [range, 14.8 to 86.8 kg {32.6 to 191.0 lb}]). Most dogs were mixed breeds (n = 5); the other 6 dogs included a Collie, Irish Wolfhound, Australian Cattle Dog, Rottweiler, Labrador Retriever, and Golden Retriever. Causes of nSIRS in these dogs included hemoabdomen (n = 5), nonseptic peritonitis (2), polytrauma (2), resuscitation from cardiopulmonary arrest (1), and intestinal foreign body (1).

A total of 53 lithium dilution CO measurements were obtained from the 11 dogs with nSIRS over the 24-hour period. Nine dogs survived to discharge from the hospital, and 7 of these were alive 28 days after discharge. One dog died as a result of ventricular fibrillation associated with norepinephrine administration, and another was euthanatized after developing acute renal failure; both events occurred after the 24-hour study period had ended. Among the 11 dogs, 24-hour CO measurement was not completed in 2 dogs because of dislodgement of the arterial catheter. For these 2 dogs, CO measurements were obtained at 0, 4, 8, and 16 hours; measurements at all time points were available for the remainder of the dogs. There was no effect of time on CI or $\dot{D}O_2I$ in the dogs with nSIRS; thus, values for each variable at the 5 time points were averaged for each dog with nSIRS.

Dogs with sepsis versus healthy dogs—Data obtained from dogs with sepsis were compared with previously published data[26] for conscious healthy dogs (**Table 1**). Mean values of CI, O_2ER, $\dot{V}O_2I$, and SVRI in dogs with sepsis did not differ significantly from values in healthy dogs. Values of $\dot{D}O_2I$, total hemoglobin concentration, arterial and venous oxygen saturations, and mean arterial blood pressure were significantly lower in dogs with sepsis, compared with values for healthy dogs.

Dogs with sepsis versus dogs with nSIRS—Data obtained from dogs with sepsis were compared with data obtained from dogs with nSIRS (**Table 2**). Dogs with sepsis had significantly higher CI and $\dot{D}O_2I$, com-

Table 1—Comparison of mean ± SD hemodynamic and oxygen transport and utilization variables in healthy dogs[26] (n = 97) and dogs with naturally occurring sepsis (10).

Variable	Healthy dogs	Dogs with sepsis*	*P* value†
CI (L/min/m²)	4.4 ± 1.2	4.2 ± 0.4	0.19
$\dot{D}O_2I$ (mL of O_2/min/m²)	790 ± 259	560 ± 129	< 0.001
O_2ER (%)	20.5 ± 5.7	28.0 ± 10.8	0.06
$\dot{V}O_2I$ (mL of O_2/min/m²)	164 ± 71	141 ± 37	0.36
SVRI (dynes•s/cm⁻⁵•m²)	1,931 ± 572	1,648 ± 534	0.14
Mean arterial pressure (mm Hg)	103 ± 15	87.5 ± 24.7	0.001
Heart rate (beats/min)	87 ± 22	135.5 ± 31.3	0.01
Total hemoglobin (g/dL)	13.6 ± 1.8	10.0 ± 1.7	< 0.001
Arterial oxygen saturation (%)	96.3 ± 0.9	92.6 ± 2.4	< 0.001
Venous oxygen saturation (%)	77.1 ± 5.5‡	67.8 ± 9.9§	0.01
CVP (mm Hg)	3.1 ± 4.1	5.5 ± 3.2	0.06

*Each variable was assessed in each dog at 4 time points (at 0, 8, 16, and 24 hours after admission to hospital), unless the dog was euthanized. For each dog, a mean value for each variable was calculated from the available measurements. A total of 32 measurements were taken (at 0 hours, n = 10 dogs; at 8 hours, 8; at 16 hours, 8; and at 24 hours, 6). Values in the table represent the mean of mean values for each variable. †A value of $P < 0.05$ was considered significant. ‡Mixed venous sample. §Central venous sample.

Table 2—Comparison of mean ± SD hemodynamic and oxygen transport and utilization variables in dogs with naturally occurring sepsis (n = 10) and dogs with nSIRS.[24]

Variable	Dogs with sepsis*	Dogs with nSIRS‡	*P* value†
CI (L/min/m²)	4.2 ± 0.4	3.3 ± 0.7	0.002
$\dot{D}O_2I$ (mL of O_2/min/m²)	560 ± 129	400 ± 156	0.02
Heart rate (beats/min)	135.5 ± 31.3	114.3 ± 25.0	0.11
Total hemoglobin (g/dL)	10.0 ± 1.7	8.9 ± 2.4	0.22
Arterial oxygen saturation (%)	92.6 ± 2.4	93.6 ± 1.7	0.30

‡Each variable was assessed in each dog at 5 time points (at 0, 4, 8, 16, and 24 hours after admission to hospital), unless the dog had died or was euthanized or the arterial catheter was dislodged. A total of 53 measurements were taken (at 0 hours, n = 11 dogs; at 4 hours, 11; at 8 hours, 11; at 16 hours, 11; and at 24 hours, 9). For each dog, a mean value for each variable was calculated from the available measurements. Values in the table represent the mean of mean values for each variable.
See Table 1 for remainder of key.

Table 3—Correlations among CI, $\dot{D}O_2I$, O_2ER, $\dot{V}O_2I$, and SVRI in 10 dogs with naturally occurring sepsis.

Comparison	Adjusted R^2	*P* value
CI vs $\dot{D}O_2I$	0.74	< 0.001
CI vs O_2ER	–0.03	0.42
CI vs $\dot{V}O_2I$	0.37	0.04
CI vs SVRI	0.61	0.01
$\dot{D}O_2I$ vs O_2ER	0.11	0.18
$\dot{D}O_2I$ vs $\dot{V}O_2I$	0.33	0.04
$\dot{D}O_2I$ vs SVRI	0.36	0.04
O_2ER vs $\dot{V}O_2I$	0.01	0.33
O_2ER vs SVRI	0.11	0.19
$\dot{V}O_2I$ vs SVRI	0.05	0.26

Data for analysis were obtained at admission from dogs with sepsis. Correlations were based on 10 measurements for each variable.

pared with dogs with nSIRS. Oxygen extraction ratio, $\dot{V}O_2I$, SVRI, and CVP were not assessed in the dogs with nSIRS; thus, comparisons of those variables between the 2 groups could not be made. Mean heart rate, total hemoglobin concentration, and arterial oxygen saturation in dogs with sepsis and dogs with nSIRS did not differ significantly.

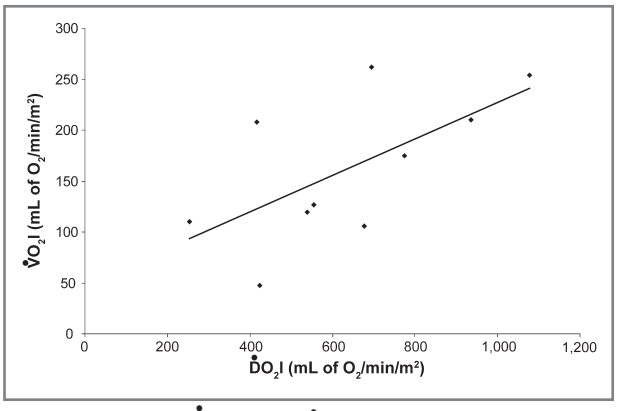

Figure 1—Graph of $\dot{D}O_2I$ versus $\dot{V}O_2I$ in 10 dogs with naturally occurring sepsis at admission to hospital. Data points represent the measurement for each dog. A significant relationship was found between $\dot{D}O_2I$ and $\dot{V}O_2I$ ($R^2 = 0.34$; $P = 0.04$).

Oxygen transport and utilization variables and survival of dogs with sepsis—Cardiac index, $\dot{D}O_2I$, O_2ER, $\dot{V}O_2I$, and SVRI were analyzed over time among dogs with sepsis that did or did not survive to discharge from the hospital. There did not appear to be a significant effect of CI ($P = 0.42$), $\dot{D}O_2I$ ($P = 0.85$), O_2ER ($P = 0.55$), $\dot{V}O_2I$ ($P = 0.18$), or SVRI ($P = 0.66$) on survival at any time point or over time.

Correlations between oxygen transport and utilization variables in dogs with sepsis at admission—In the dogs with sepsis, correlations between pairs of hemodynamic and oxygen transport variables were assessed (**Table 3**). Significant correlations between CI and $\dot{D}O_2I$, CI and $\dot{V}O_2I$, CI and SVRI, $\dot{D}O_2I$ and $\dot{V}O_2I$, and $\dot{D}O_2I$ and SVRI were identified. The relationship between $\dot{D}O_2I$ and $\dot{V}O_2I$ was expressed graphically (**Figure 1**).

Discussion

The goal of the present study was to determine whether oxygen transport and utilization variables differ among healthy dogs, dogs with sepsis, and dogs with nSIRS. Results indicated that there were few differences between variables in healthy dogs and dogs with sepsis, but significant differences were detected between dogs with sepsis and dogs with nSIRS.

In previous studies[2,5,9,21] in humans and dogs, CO was increased in individuals with sepsis, compared with values in healthy individuals; however, a similar finding (based on CO values indexed to body surface area [CI]) was not a result of the present study. The dogs in our study had sepsis for an undetermined period prior to enrollment. Although humans with sepsis typically remain in a hyperdynamic phase for 7 to 10 days following initial diagnosis,[27] there is little information on the duration of changes in affected dogs. One study[6] revealed that increases in CO were present for 10 days following induction of sepsis but only after bolus fluid administration each day. Cardiac output was assessed only during the first 24 hours of hospitalization of dogs in the present study, so it is possible that an earlier or later change in CO may not have been detected.

It is also possible that biventricular dilatation, as identified in humans with sepsis,[27] does not develop to the same degree in dogs with naturally occurring sepsis. Following experimental induction of sepsis in dogs, reversible myocardial depression, decreased ejection fraction, and increased left ventricular end-diastolic volume are detected.[6] Compared with healthy dogs, dogs with sepsis in our study were significantly tachycardic. Lack of ventricular filling time may have resulted in decreased end-diastolic volume and consequently a lack of change in CO. Measurement of right and left end-diastolic volume and ejection fraction would be needed to investigate altered cardiac function; these assessments were not performed in our study.

Another reason for the lack of significant difference in CO between published values for healthy dogs and dogs with sepsis was that the dogs in our study may not have been adequately fluid resuscitated. Humans with sepsis typically have decreased CO but become hyperdynamic once intravascular volume is restored.[4] In 1 study,[6] fluid administration was required to induce increases in CO. Although the dogs in the present study had a mean CVP of 5.5 mm Hg and clinical evidence of euvolemia, fluid resuscitation may have been inadequate. However, apparently normal values of CVP—although a reflection of right atrial filling pressure—do not necessarily imply adequate intravascular volume. Factors that can falsely increase CVP include venoconstriction, elevated intrathoracic pressure (as develops during positive-pressure ventilation), decreased CO, elevated intra-abdominal pressure, pericardial effusion, and changes in head and body position.[28] Despite the inherent limitations in CVP measurement, one would expect CI to increase over the 24-hour study period as the dogs were appropriately volume resuscitated, but there was no significant effect of time on CI.

Cardiac index in dogs with sepsis was significantly higher than it was in dogs with nSIRS. This is particularly interesting given that evidence of SIRS was part of the inclusion criteria for the dogs with sepsis. Therefore, one might expect dogs with sepsis to develop the same hemodynamic changes as dogs with nSIRS. The etiopathogenesis of myocardial depression, ventricular dilatation, and increased CO in humans with sepsis is not clear,[27] but those abnormalities are thought to be related to derangements in calcium handling by myocytes.[29] Increased concentrations of circulating cytokines (eg, tumor necrosis factor-α, interleukin-1β, and interleukin-6), increased nitric oxide production, and myocardial apoptosis have all been implicated in the development of myocardial depression.[30] These biochemical and cytokine alterations are associated with both sepsis and SIRS, but in humans, SIRS is associated with myocardial depression and decreased CO.[31] Most of the research on SIRS-related myocardial depression has been conducted in patients with sepsis or following cardiopulmonary bypass. There are isolated reports of myocardial depression with and without decreased CO in humans with nSIRS, which can develop secondary to chemotherapy administration[32] and renal necrosis.[33] However, there has been no further research into the reason why sepsis results in a high-CO state, whereas SIRS alone does not.

Of the oxygen transport and utilization variables that were investigated in our study, only $\dot{D}O_2I$ was significantly different between dogs with sepsis and healthy dogs. Given that mean total hemoglobin concentration and mean arterial oxygen saturation (components of the $\dot{D}O_2$ equation) were significantly lower in dogs with sepsis, it is not surprising that $\dot{D}O_2I$ was significantly lower in that group. Total hemoglobin concentration may be lower in dogs with sepsis as a result of loss via hemorrhage or cavitary effusions, hemodilution subsequent to fluid therapy, erythrolysis due to immune-mediated processes, or decreased production secondary to chronic disease. Arterial oxygen saturation may be lower in dogs with sepsis because of impaired gas exchange associated with primary pulmonary diseases (eg, pneumonia or cardiogenic edema) or pulmonary diseases that develop secondary to the septic process (eg, acute respiratory distress syndrome or pulmonary thromboembolism resulting from activation of the coagulation system).

Values of $\dot{D}O_2I$ in the dogs with sepsis were lower than values for healthy dogs but significantly greater than values in dogs with nSIRS. The latter finding was likely attributable to higher CI in the dogs with sepsis because values for the other components of the $\dot{D}O_2$ equation were not significantly different between dogs with sepsis and those with nSIRS.

Oxygen extraction ratio, $\dot{V}O_2I$, and SVRI were also not significantly different between dogs with sepsis and healthy dogs. Although decreased O_2ER is largely associated with sepsis, 1 study[34] in pigs revealed increased O_2ER in response to infusion of *Pseudomonas aeruginosa*. The authors hypothesized that the increase was a response to maintain $\dot{V}O_2$ in the face of decreasing $\dot{D}O_2$.[34] It is possible that the significant decrease in $\dot{D}O_2I$ in dogs with sepsis caused a nonsignificant increase in O_2ER to maintain $\dot{V}O_2I$.

Among the dogs with sepsis, there was no significant difference in CI, $\dot{D}O_2I$, O_2ER, or $\dot{V}O_2I$ between nonsurvivors and survivors. Results of a previous study[24] of dogs with SIRS also indicated that CI and $\dot{D}O_2I$ did not change significantly over time between survivors and nonsurvivors. This is similar to findings in humans with sepsis, in whom CI and $\dot{D}O_2I$ are maintained even prior to death in nonsurvivors.[2,5] Overall, $\dot{V}O_2$ has not been shown to have an effect on survival in critically ill humans,[35] but no similar information is available for veterinary patients, to our knowledge. Nonsurvival in critically ill humans is more strongly associated with an inability to increase $\dot{D}O_2$ and $\dot{V}O_2$,[36] even with pressor or inotropic support, despite increases in CI. Significantly lower O_2ER also appears to be predictive of death.[37] These findings imply that critically ill humans who lack the physiologic reserves to optimize hemodynamic variables are more likely to die[36,37] and that measurements at a single time point do not predict survival. The present study was considerably underpowered because of the small sample size, and it is possible that assessment of a larger number of dogs with sepsis might reveal a significant difference between survivors and nonsurvivors. Another possible cause for lack of differences between survivors and nonsurvivors is that oxygen transport and utilization variables do not pro-

vide adequate information regarding what is happening at the cellular level.

Significant correlations between CI and $\dot{D}O_2I$, CI and $\dot{V}O_2I$, CI and SVRI, $\dot{D}O_2I$ and $\dot{V}O_2I$, and $\dot{D}O_2I$ and SVRI in septic dogs at admission were identified in the present study. Given that CI is an important component of the equations for calculation of the other 3 variables, these correlations are not surprising. However, a significant linear correlation between $\dot{D}O_2I$ and $\dot{V}O_2I$ was found, indicating that the dogs with sepsis were in the supply-dependent portion of the oxygen delivery-consumption curve. At values less than the critical $\dot{D}O_2$, $\dot{V}O_2$ becomes directly dependent on delivery of oxygen. In previous studies of whole-body $\dot{D}O_2I$ in dogs with sepsis induced experimentally via endotoxin infusion, the critical $\dot{D}O_2I$ was 10.4 ± 0.7 mL of O_2/kg/min (4.7 ± 0.32 mL of O_2/lb/min)[7] to 12.1 ± 3.1 mL of O_2/kg/min (5.5 ± 1.41 mL of O_2/lb/min).[38] Mean $\dot{D}O_2I$ of the dogs with sepsis in our study was 560 ± 129 mL of O_2/min/m^2 or 18.2 ± 6.1 mL of O_2/kg/min (8.3 ± 2.8 mL of O_2/lb/min). Because mean $\dot{D}O_2I$ was greater than the reported values of critical $\dot{D}O_2$ in previous studies,[7,38] not all of the dogs with sepsis in our study should have been in the supply-dependent portion of the oxygen delivery-consumption curve. The relationship between $\dot{D}O_2I$ and $\dot{V}O_2I$ may be a result of unexplained shifting of the curve to the right and, with it, an increase in the critical $\dot{D}O_2$. One cause for right-shifting of the curve may be microcirculatory disturbances such as shunting or heterogeneous blood flow, where higher flow rates are necessary to meet tissue needs. Another possible cause is reduced oxygen extraction as a result of mitochondrial dysfunction.[20]

The supply dependence of $\dot{V}O_2I$ on $\dot{D}O_2I$ should be accompanied by an increase in O_2ER, but there was no significant relationship between $\dot{V}O_2I$ and O_2ER or between $\dot{D}O_2I$ and O_2ER in dogs with sepsis in our study. Oxygen extraction ratios should increase as $\dot{V}O_2$ becomes dependent on $\dot{D}O_2$, but that was not evident in the dogs with sepsis. However, that effect occurs in humans with sepsis,[3,13] has been detected in dogs with experimentally induced sepsis,[21] and has been hypothesized to occur for the same reasons that the oxygen delivery-consumption curve and critical $\dot{D}O_2$ shift to the right.

Limitations of the present study include the small number of dogs, inherent variations in treatment of clinical cases, and the short period over which measurements were made. Enrollment of more cases may have allowed detection of significant changes in CI, O_2ER, and $\dot{V}O_2$ in dogs with sepsis, compared with findings in healthy dogs. Treatment was not standardized for clinical cases, and each dog was treated at the discretion of the primary clinician. Many of these interventions can affect CO and oxygen transport. The lack of significant differences in hemodynamic and oxygen transport variables between dogs with sepsis and healthy dogs may be related to variations in treatment, but in a clinical study, withholding appropriate treatment would be unethical. The duration of sepsis in each dog prior to or after study enrollment may have also had a role in the lack of significant findings in our study. Performing CO measurements during the entire period of hospitalization would help elucidate the cardiovascular changes that can occur over time in dogs with sepsis.

Future research into the hemodynamic alterations that occur in dogs with sepsis or SIRS could include measurements of cardiac contractility and left ventricular preload. This would help to determine whether ventricular dilation develops in dogs with sepsis as it does in humans with sepsis.[2,5] Measurement of circulating cytokine concentrations in temporal relation to alterations in CI, $\dot{D}O_2I$, O_2ER, $\dot{V}O_2I$, and SVRI would also be beneficial for understanding how changes in the inflammatory system impact hemodynamics and oxygen utilization variables. Alterations in the microvasculature in relation to global hemodynamic indices could also be investigated.

Results of the present study indicated that dogs with sepsis do not have significantly different CI, O_2ER, $\dot{V}O_2I$, and SVRI, compared with values for healthy dogs; however, $\dot{D}O_2I$ was significantly decreased. This decrease in $\dot{D}O_2I$ may be attributable to lower total hemoglobin concentrations in dogs with sepsis. Dogs with sepsis had significantly higher CI and $\dot{D}O_2I$ than dogs with nSIRS, with values much closer to those in healthy dogs than to those in other critically ill patients. The mechanism for lower CO in dogs with nSIRS is currently unknown, but future research may elucidate mechanisms of cardiovascular dysfunction in SIRS and sepsis in this species.

a. LiDCO Plus hemodynamic monitor, LiDCO Plus Plc, London, England.
b. ABL 800 Flex blood gas analyzer, Radiometer Inc, Copenhagen, Denmark.
c. OSM-3 hemoximeter, Radiometer Inc, Copenhagen, Denmark.
d. SAS, version 9.2, SAS Institute Inc, Cary, NC.

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Appendix

Equations used in calculation of hemodynamic and oxygen transport and utilization variables in dogs.

Variable	Equation
$\dot{C}I$ (L/min/m^2)	$\dot{C}I = CO/BSA$
$\dot{D}o_2I$ (mL of O_2/min/m^2)	$\dot{D}o_2I = CI \times Cao_2 \times 10$
Cao_2 (mL of O_2/dL of blood)	$Cao_2 = (1.34 \times Sao_2 \times Hb) + (0.003 \times Pao_2)$
O_2ER (%)	$O_2ER = ([SaO_2 - Svo_2]/SaO_2) \times 100$
$\dot{V}o_2I$ (mL of O_2/min/m^2)	$\dot{V}o_2I = CI \times (CaO_2 - Cvo_2) \times 10$
SVRI (dynes•s/cm^{-5}•m^2)	$SVRI = ([MAP - CVP] \times 80)/CI$

BSA = Body surface area. Cvo_2 = Venous oxygen content. Hb = Total hemoglobin concentration. MAP = Mean arterial blood pressure. Sao_2 = Arterial oxygen saturation. Svo_2 = Venous oxygen saturation.