Original Study

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Lithium dilution cardiac output and oxygen delivery in conscious dogs with systemic inflammatory response syndrome

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Abstract

Objective: Compare cardiac index (CI) and oxygen delivery index (DO_2I) in conscious, critically ill dogs to control dogs; evaluate the association of CI and DO_2I with outcome.
Design: Prospective non-randomized clinical study.
Setting: Veterinary teaching hospital.
Animals: Eighteen client-owned dogs with systemic inflammatory response syndrome (SIRS) and 8 healthy control dogs.
Measurements and Main Results: CI of dogs with SIRS was measured using lithium dilution at times 0, 4, 8, 16, and 24 hours. Data collected included physical exam, arterial blood gas (ABG) and hemoximetry. CI of control dogs was measured 3 times with 1 measurement of ABG. Mean CI ± SE in SIRS patients was $3.32 \pm 0.95\,L/min/m^2$; lower than controls at $4.18 \pm 0.22\,L/min/m^2$ ($P < 0.001$). Mean $DO_2I \pm SE$ in SIRS patients was $412.91 \pm 156.67\,mL\ O_2/min/m^2$; lower than controls at $785.24 \pm 45.99\,mL\ O_2/min/m^2$ ($P < 0.001$). There was no difference in CI ($P = 0.49$) or DO_2I ($P = 0.51$) for dogs that survived to discharge *versus* those that did not. There was no difference in mean CI ($P = 0.97$) or DO_2I ($P = 0.50$) of survivors *versus* non-survivors for 28-day survival. Survivors had lower blood glucose ($P = 0.03$) and serum lactate concentrations ($P = 0.04$) than non-survivors.
Conclusions: CI and DO_2I in conscious dogs with SIRS were lower than control dogs, which differs from theories that dogs with SIRS are in a high cardiac output state. CI and DO_2I were not significantly different between survivors and non-survivors. Similar to previous studies, lactate and glucose concentrations of survivors were lower than non-survivors.

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Introduction

Oxygen delivery (DO_2) is defined as the amount of oxygen delivered to the tissues in mL O_2/min.[1] It is calculated as the product of cardiac output (CO) and arterial oxygen content (C_aO_2).[1–3] Arterial oxygen content (C_aO_2) is defined by the equation: $C_aO_2 =$ (1.34 × hemoglobin concentration × hemoglobin oxygen saturation (S_aO_2)) + (0.003 × P_aO_2).[1] Inadequate DO_2, whether from low blood flow or maldistribution of flow, can lead to local tissue hypoxia, organ dysfunction and ultimately may cause death.

In order to improve oxygen delivery, the abnormal components of the equation must be identified and corrected. Arterial oxygen content can usually be improved with either supplemental oxygen or blood transfusions, and represents only one part of the oxygen delivery equation. The other portion of the equation is CO, which is the amount of blood the heart pumps per minute and is an indicator of the volume of blood available for perfusion. In human studies published in the 1970s, low CO states are associated with increased morbidity and mortality.[4,5]

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If poor tissue perfusion must be corrected, then it seems logical that improving CO and DO_2 would improve outcome. Improving CO and DO_2 has received significant attention in the human literature; however, the benefits and even the definitions are not clear. While some studies have focused on supranormal DO_2, others have investigated optimization of DO_2. However, the goals of supranormal and optimal oxygen delivery are frequently the same.[6–10] Some studies showed improved survival with increasing oxygen delivery,[6,11] while others did not.[8,9,12] One study showed that increasing oxygen delivery may be detrimental.[10] More importantly, 2 studies found that those patients who were able to be optimized had a significantly better outcome than those who could not.[11,13] This suggests that possessing the physiologic reserves to achieve normal or even above normal CO and DO_2 is more a predictor of survival than an endpoint of resuscitation.[13]

For veterinarians, CO has been difficult to monitor in the clinical setting. Traditionally, measurement of CO in the clinical setting has been performed via the thermodilution method. This method requires that a catheter is placed into the pulmonary artery via the jugular vein.[14,15] However, this method carries inherent risks, including infection and fatal pulmonary artery rupture.[16–18] Other methods of CO measurement, including magnetic flowmetry,[19] indocyanine dilution,[20] partial CO_2 rebreathing,[21] transesophageal Doppler,[22] and transthoracic bioimpedance[20] have been described, but are too invasive, technically demanding, or impractical to perform on conscious patients.

Recently, a new method, lithium dilution cardiac output (LiDCO), has been validated for use in humans[23,24] and dogs.[25] In conscious patients LiDCO is safer, less invasive, or technically easier than other methods, and may be more accurate than thermodilution.[26] This technique allows CO to be measured using only a peripheral[27] or central venous catheter and a peripheral arterial catheter. LiDCO monitoring has been compared with other methods of CO measurement in dogs, and found to have good correlation in normotensive, hypotensive and hypertensive states under anesthesia.[25] Additional studies have found that background lithium concentrations do not interfere with repeated measurements[28] and that lithium is safe for use in dogs.[25,27,28]

In the clinical setting, CO and DO_2 are commonly estimated using a variety of parameters collected from physical examination, patient monitoring and laboratory values. These may include a combination of heart rate, rectal temperature, serum lactate concentrations, arterial blood pressure, urine output, acid–base status, and other information. Clinical experience would suggest that parameters of perfusion and blood pressure should correlate with measured CO. However, estimation of hemodynamic parameters based on clinical assessment may not be accurate. Wo et al. [29] demonstrated poor correlation between mean arterial pressure, heart rate, and measured CO except in extreme hypotensive states. Other human studies have found poor agreement between measured CO and estimated CO based on clinical assessment.[30,31] In one human study, therapeutic decisions for patients in circulatory shock based on measured CO rather than estimated CO led to improved survival.[32]

There are a number of therapeutic interventions used in the treatment of critically ill patients that can affect CO and DO_2. Inotropes such as dobutamine and dopamine have been used in human studies to increase CO and thus DO_2.[10–12] Acepromazine has been shown to decrease CO in clinically healthy dogs.[33] Blood transfusions are used to increase C_aO_2 and DO_2.[8,10,12] The use of IV magnesium supplementation,[34] hetastarch,[35,36] norepinephrine,[37] vasopressin,[38] and local anesthetics[39] have all been shown to alter CO. In a clinical study, one of or a combination of these drugs may be used. Therefore, knowledge of therapeutic interventions is important when comparing CO and DO_2 between patients.

To the authors' knowledge, there have not been any previous reports on CO and DO_2 in conscious critically ill dogs. All previous CO and DO_2 studies using the LiDCO technique in dogs have been performed in anesthetized patients.[25,27,28,33] Therefore, CO and DO_2 in conscious, critically ill dogs are currently unknown. The correlation of parameters used to estimate CO and DO_2 and measured CO and DO_2 in canine patients is also unknown. The objectives of this study were: (1) To compare CO and DO_2 in conscious, critically ill canine patients with healthy controls; (2) To investigate if any parameters used clinically to estimate CO and DO_2 are correlated with measured CO and DO_2; (3) To investigate if therapeutic interventions are associated with changes in CO and DO_2; and (4) To investigate if values of CO and DO_2 are associated with survival. We hypothesized that CO and DO_2 are lower in patients meeting criteria of SIRS compared with healthy controls; that parameters used clinically to estimate CO and DO_2 correlate well with measured CO and DO_2; that therapeutic interventions are associated with changes in CO and DO_2; and that non-survivors have lower CO and DO_2 than survivors.

Materials and Methods

The study protocol was approved by the Colorado State University Animal Care and Use Committee.

Study group

Eighteen client-owned dogs admitted to the Critical Care Unit (CCU) of the Colorado State University Veterinary Teaching Hospital were enrolled. Inclusion criteria were: weight >10 kg, the presence of a preexisting arterial and venous catheter (jugular or cephalic), and evidence of a systemic inflammatory response syndrome (SIRS), consisting of 3 or more of the following parameters: respiratory rate >40 breaths/min, heart rate >120 beats/min, rectal temperature <38 °C (100.4 °F) or >40 °C (104 °F), and WBC <5000 or >18,000 cells/μL, or band neutrophils >10%.[40] Informed client consent was obtained before study enrollment.

LiDCO[a] measurements were performed as described previously[25,27,41] and in accordance with the manufacturer's specifications. LiDCO measurements were performed at times 0, 4, 8, 16, and 24 hours after study enrollment. At the time of each measurement the following data was measured or assessed and recorded: rectal temperature, heart rate, respiratory rate, capillary refill time, mucous membrane color, direct arterial blood pressure (systolic, diastolic, and mean), and urine output (in mL/kg/hr). Arterial blood gas[b] analysis and hemoximetry[c] were performed at the time of each measurement. All therapeutic interventions were recorded. All data from the SIRS group was collected by a single researcher (A.B.). No changes in therapy were recommended as a result of the CO measurement. The results of blood gas analysis and hemoximetry were provided to the primary clinician, whereas CO and DO_2 results were blinded to the primary clinician.

Control group

Eight healthy dogs not meeting criteria of SIRS served as a control group. Inclusion criteria were: weight >10 kg, no history of systemic disease, and absence of SIRS criteria based on physical exam and complete blood count (CBC). Cephalic venous catheters were placed and the dogs were sedated with fentanyl[d] (5 μg/kg, IV) and midazolam[e] (0.5 mg/kg, IV) for placement of dorsal pedal arterial catheters. Six dogs also required propofol[f] (2–4.5 mg/kg, IV, mean dose 3.21 mg/kg) for arterial catheter placement. Following arterial catheter placement, sedation was reversed with naloxone[g] (0.04 mg/kg, IV) and flumazenil[h] (0.01 mg/kg, IV). Forty-five minutes to 1 hour elapsed between time of reversal to CO measurement in order to allow for complete recovery from sedation.[i] Arterial blood gas analysis, electrolytes, and hemoximetry were obtained immediately before measuring CO. Three LiDCO measurements were performed with 15 minutes between each measurement. One dog had only 2 measurements taken, and 1 dog had only 1 measurement taken, both due to poor patient cooperation. All data from the control group was collected by 2 researchers (A.B., C.S.). Cardiac index (CI) for the control group was averaged over the 3 readings to create a mean CI for each dog.

CO was indexed to patient body surface area for both control and study groups in order to allow for comparisons between dogs of different size. The equation: BSA (m^2) = 0.101 × body weight (kg)$^{0.67}$ was used to calculate body surface area.[42] Oxygen delivery index (DO_2I) was calculated using the equation: $DO_2I = CI \times ([1.34 \times \text{hemoglobin concentration} \times S_aO_2] + [0.003 \times \text{measured } P_aO_2])$. CI was obtained from the LiDCO measurement. The hemoglobin concentration and S_aO_2 were measured by the hemoximeter, and the $1.34 \times$ hemoglobin concentration $\times S_aO_2$ portion of the equation was calculated by the investigators. P_aO_2 was obtained from the arterial blood gas measurement.

Statistics

All statistics were performed using a commercially available computer statistical package.[d] Normality of the data was assessed using the Kolmogorov–Smirnov test. For nonsignificant results, a power analysis was performed. For statistical analysis of time-averaged variables (CI and DO_2I *versus* controls, CI and DO_2I *versus* outcome, and all laboratory data *versus* outcome), a $P < 0.05$ was considered significant. A $P < 0.01$ was chosen for non-averaged variables (laboratory data *versus* CI and DO_2I, therapeutic interventions *versus* CI and DO_2I) due to the large number of values being compared and the multiple significance tests. CI and DO_2I for the study group were compared between the different time periods using a repeated measures analysis of variance to test for differences over time. CI and DO_2I for the study group and control group averages over all time periods were compared using the Student's *t*-test of unequal variance with a $P < 0.05$ considered significant. Data is reported as the mean ± SE.

Spearman's correlation coefficients at each time point were calculated between CI, DO_2I, physical exam, and laboratory data including: rectal temperature, heart rate, respiratory rate, capillary refill time, mucous membrane color, direct arterial blood pressure (systolic, diastolic, and mean), urine output (in mL/kg/hr), pH, P_aCO_2, P_aO_2, bicarbonate concentration, packed cell volume, total protein, hemoglobin concentration, calculated oxygen content, electrolytes (sodium, potassium, chloride, and ionized calcium concentrations), blood glucose concentration, and serum lactate concentration. Correlations were reported as *r*-values, with a $P < 0.01$ considered significant.

A main effects repeated measures analysis of variance was used to determine the effect of medications on CI and DO_2I. The use of colloid infusions, colloid

boluses, acepromazine[j], inotropes, vasopressors, blood component therapy, antiarrhythmics, and magnesium supplementation was recorded as a yes or no answer for each time period.[k] A yes answer was recorded if the patient was receiving colloid infusion, inotropes, vasopressors, magnesium supplementation, or IV antiarrhythmics at the time of LiDCO measurement. Colloid boluses and blood component therapy were recorded as yes and in mL/kg if they were administered 4 hours or less before LiDCO measurement. Acepromazine and oral antiarrhythmics were recorded as yes if administered within that medication's half-life before LiDCO measurement. CI and DO_2I were reported as least square means, with a $P < 0.01$ considered significant.

CI and DO_2I for study group survivors and non-survivors were compared using the Student's *t*-test of unequal variance. Survival was assessed at both discharge and 28 days after admission. The effect of time on CI and DO_2I of survivors and non-survivors was analyzed using a repeated measures analysis of variance. Hospitalization time for survivors *versus* CI and DO_2I at study enrollment was computed using Spearman's correlation coefficient. The association of outcome and all physical exam and laboratory parameters averaged over all time periods was analyzed using a repeated measures analysis of variance. A $P < 0.05$ was chosen to be significant.

Results

Study group

Eighteen dogs meeting SIRS criteria were enrolled in the study. Eight were spayed females, 8 were castrated males and 2 were intact females. Breeds included: mixed breed dog ($n = 6$), Collie ($n = 2$), Labrador Retriever ($n = 2$), and Rottweiler ($n = 1$), Springer Spaniel ($n = 1$), Australian Cattle Dog ($n = 1$), Shetland Sheepdog ($n = 1$), Siberian Husky ($n = 1$), Golden Retriever ($n = 1$), German Shepherd Dog ($n = 1$), and Irish Wolfhound ($n = 1$). The mean age was 7.6 ± 3.8 years (range, 0.3–13.0 y) and the mean weight was 30.6 ± 16.2 kg (range, 12.0–86.4 kg). The underlying disease process was recorded for each dog, including: sepsis ($n = 7$), hemoabdomen ($n = 5$), sterile peritonitis (gastric perforations without bacterial growth on culture) ($n = 2$), traumatic injury ($n = 2$), intestinal foreign body obstruction ($n = 1$), and 1 postarrest patient ($n = 1$).

Thirteen dogs survived to discharge, 4 were euthanized and 1 died. Euthanasia was the result of development of complications in all cases. Two dogs were euthanized during the study period, both for postoperative development of peritonitis and septic shock. Two dogs were euthanized due to complications (acute renal failure, pancreatitis with underlying GI lymphoma) that began well after the study period had ended (3 and 4 days, respectively). One dog died after the study period of ventricular fibrillation associated with norepinephrine administration. Eleven dogs survived for 28 days after admission. The 2 additional dogs that died both had hemoabdomen and died of their disease process within 28 days of admission.

A total of 81 CO measurements were taken (18 dogs over 5 time periods). Readings could not be obtained at all time points in some dogs due to death or euthanasia, or technical problems. Most technical problems were related to the arterial catheter, such as occlusion of or slow flow rates through the catheter. These problems prevented obtaining a LiDCO measurement and required catheter replacement. Arterial catheters were replaced only if the primary clinician had requested continued direct arterial blood pressure monitoring, not solely for LiDCO measurement. Minor technical problems included patient movement during a measurement or inability of the machine to contact the lithium sensor. Minor problems required either replacement of the sensor or repeating the measurement, but after correction, resulted in LiDCO readings.

Control group

Eight dogs were enrolled as controls. All were mixed breed dogs. Four were spayed females, and 4 were castrated males. The mean age was 6.1 ± 2.3 years (range, 2.0–9.3 years) and the mean weight was 24.4 ± 7.1 kg (range, 17.1–39.4 kg). Mean hemoglobin concentration was 146 ± 8 g/L (14.6 ± 0.8 g/dL), mean S_aO_2 was $94.4 \pm 0.7\%$, and mean P_aO_2 was 84.8 ± 3.4 mmHg. These values were similar to normal values established for dogs at an average barometric pressure of 640 mmHg.[43] Mean CI was 4.18 ± 0.22 L/min/m^2 and mean DO_2I was 785.24 ± 45.99 mL O_2/min/m^2. CI and DO_2I for the control group were similar to previously established normals for healthy dogs.[44]

CI and DO_2I in SIRS patients compared with controls

The effect of time on CI and DO_2I measurements was analyzed using a repeated measures analysis of variance. There was no significant difference in CI ($P = 0.43$) or DO_2I ($P = 0.75$) between different time periods for the study group. CI and DO_2I for each study dog were averaged over the 5 time measurements for this comparison as there was no significant effect of time. The mean CI for study dogs over all time periods ($n = 18$) was 3.32 ± 0.95 L/min/m^2 and was significantly lower than control dogs at 4.18 ± 0.22 L/min/m^2 ($P < 0.001$). The mean DO_2I for study dogs over all time periods ($n = 18$) was 412.91 ± 156.67 mL O_2/min/m^2 and was significantly lower than control dogs at 785.24 ± 45.99 mL O_2/min/m^2 ($P < 0.001$).

Study dogs ($n = 18$) averaged over all time periods had significantly lower hemoglobin concentration than control dogs (93 ± 25 g/L [9.3 ± 2.5 g/dL] *versus* 146 ± 8 g/L [14.6 ± 0.8 g/dL], $P < 0.001$), as well as significantly lower calculated oxygen content (12.0 ± 3.1 *versus* 18.7 ± 0.4 mL O_2/dL blood, $P < 0.001$). While S_aO_2 was significantly lower in study dogs compared with control dogs (92.3 ± 0.9 *versus* $94.4 \pm 0.7\%$, $P = 0.008$), P_aO_2 was significantly higher (107.3 ± 8.9 *versus* 84.8 ± 1.2 mmHg, $P = 0.01$). The range of P_aO_2 in the study group was 59.4 to 416 mmHg. The pH of study dogs was significantly lower than control dogs (7.38 ± 0.02 *versus* 7.42 ± 0.01, $P = 0.01$). Heart rate was not significantly different in study dogs *versus* control dogs (117.9 ± 7.5 *versus* 112.8 ± 4.9/min, $P = 0.41$, power = 0.2).

Correlations of CI and DO_2I with physical exam and laboratory data

Spearman's correlation coefficients were computed for all physical exam parameters, blood gas data, and hemoximetry data with each measured CI and DO_2I ($n = 81$). Variables analyzed included: rectal temperature, heart rate, respiratory rate, capillary refill time, systolic blood pressure, diastolic blood pressure, mean blood pressure, urine output, pH, P_aO_2, P_aCO_2, bicarbonate concentration, base excess, sodium concentration, potassium concentration, chloride concentration, ionized calcium concentration, serum lactate concentration, blood glucose concentration, calculated oxygen content, packed cell volume (PCV), total solids, and hemoglobin concentration. CI was significantly correlated with pH ($r = 0.39$, $P = 0.003$, $n = 81$). Figure 1 shows the scatterplot of pH and CI. The *r*-value is low despite being the only significant correlation for CI. Oxygen delivery index was significantly correlated with heart rate ($r = 0.30$, $P = 0.005$, $n = 81$), calculated oxygen content ($r = 0.66$, $P < 0.001$, $n = 81$), PCV ($r = 0.65$, $P < 0.001$, $n = 81$) and hemoglobin concentration ($r = 0.66$, $P < 0.001$, $n = 81$). Power was not achieved for those values not having significant relationships with CI and DO_2I.

Serum lactate concentration did not appear to be correlated with either CI ($r = -0.14$, $P = 0.2$, $n = 81$) or DO_2I ($r = -0.05$, $P = 0.68$, $n = 81$). To determine if a high serum lactate concentration was related with either CI or DO_2I, we divided the readings into normal and high lactate groups based on the reference interval established by the manufacturer for the blood gas analyzer.[b] A normal serum lactate concentration was defined as ≤ 1.6 mmol/L, and a high serum lactate concentration was defined as > 1.6 mmol/L. The initial time period was chosen as this was felt to be most reflective of the SIRS state, and lactates improved over time based on main effects repeated measures ANOVA. There were a total of 11 readings in the normal serum lactate concentration group with a mean of 1.00 ± 0.01 mmol/L, and 7 readings in the high serum lactate concentration group with a mean of 2.9 ± 0.8 mmol/L (Figure 2). A high serum lactate concentration was not significantly correlated with either CI ($r = -0.47$, $P = 0.14$, power = 0.23), or DO_2I ($r = -0.12$, $P = 0.39$, power = 0.12).

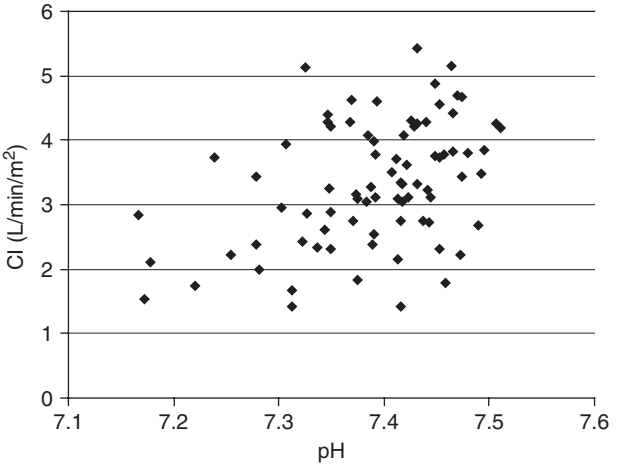

Figure 1: Scatterplot of pH *versus* cardiac index (CI) (L/min/m^2). pH was significantly correlated with CI ($r = 0.39$, $P = 0.003$, $n = 81$); however, the low *r*-value makes biological significance questionable.

Medications and CI and DO_2I

To determine if the use of various medications was associated with significantly changed CI and DO_2I, a main effects repeated measures analysis of variance was performed ($n = 81$). Use of colloid infusions, colloid boluses (5.26 ± 1.1 mL/kg), acepromazine, inotropes, pressors,

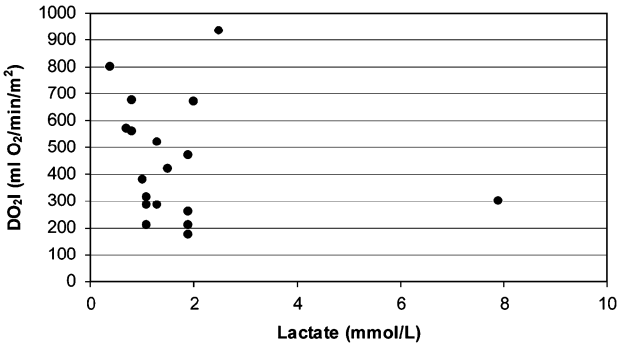

Figure 2: Scatterplot of oxygen delivery index (DO_2I) *versus* serum lactate concentrations at initial time period. There was no significant correlation between DO_2I and serum lactate concentrations ($r = -0.15$, $P = 0.33$, $n = 18$).

Table 1: Association of therapeutic interventions, CI and DO_2I

Treatment	No. of patients receiving treatment		Cardiac index		Oxygen delivery index	
			LS mean ± SE	*P*	LS mean ± SE	*P*
Colloids	Y	42	4.17 ± 0.58	0.59	545.91 ± 76.46	0.37
	N	39	4.23 ± 0.60		581.44 ± 80.96	
Colloid boluses	Y	6	3.91 ± 0.83	0.64	567.21 ± 179.01	0.41
	N	75	4.21 ± 0.48		611.79 ± 87.26	
Acepromazine	Y	5	4.45 ± 0.70	0.20	618.36 ± 95.21	0.07
	N	76	3.79 ± 0.49		509.01 ± 66.89	
Opioids	Y	75	4.19 ± 0.39	0.68	551.46 ± 112.43	0.31
	N	6	3.99 ± 0.65		499.10 ± 91.13	
Inotropes	Y	10	4.86 ± 0.78	0.04	638.79 ± 106.36	0.05
	N	71	3.39 ± 0.46		488.57 ± 62.13	
Pressors	Y	4	4.31 ± 0.80	0.62	581.56 ± 107.28	0.52
	N	77	3.93 ± 0.46		545.80 ± 62.75	
Transfusions	Y	17	4.08 ± 0.56	0.67	556.04 ± 75.65	0.53
	N	64	4.16 ± 0.61		571.32 ± 82.48	
Antiarrhythmics	Y	39	4.39 ± 0.55	0.23	574.87 ± 74.46	0.87
	N	42	3.85 ± 0.63		552.49 ± 85.86	
Magnesium	Y	11	4.01 ± 0.67	0.77	570.63 ± 90.96	0.81
Supplementation	N	70	4.23 ± 0.53		556.73 ± 71.29	

CI, cardiac index; D_2OI, oxygen delivery index; LS, least squares; N, not receiving treatment; SE, standard error; Y, receiving treatment. Significance = $P < 0.01$.

blood transfusions (5.9 ± 3.4 mL/kg), antiarrhythmics, and magnesium supplementation did not appear to be related to changes in CI and DO_2I, although power was not achieved. The least squares means and SE of CI and DO_2I *versus* each therapeutic intervention are presented in Table 1.

Survival to discharge

There was no significant difference in CI or DO_2I between dogs that survived to discharge ($n = 13$) *versus* those that did not ($n = 5$). The mean CI of survivors was 3.34 ± 0.12 L/min/m^2 while the mean CI of non-survivors was 3.58 ± 0.25 L/min/m^2 ($P = 0.49$, power = 0.17). The mean DO_2I of dogs that survived to discharge was 416.88 ± 41.34 mL O_2/min/m^2 while the mean DO_2I of non-survivors was 479.10 ± 62.56 mL O_2/min/m^2 ($P = 0.51$, power = 0.15). Time did not significantly affect CI and DO_2I in either the survivors or the non-survivors. Non-survivors did not appear to worsen or improve over time (Figures 3 and 4).

The mean serum lactate concentration of survivors to discharge averaged over all time periods was significantly lower than non-survivors (1.0 ± 0.3 *versus* 2.0 ± 0.8 mmol/L, $P = 0.04$, $n = 18$). The mean blood glucose concentration of survivors averaged over all time periods was also significantly lower than non-survivors (5.7 ± 0.6 mmol/L [102.7 ± 10.9 mg/dL] *versus* 7.1 ± 1.1 mmol/L [127.7 ± 19.4 mg/dL], $P = 0.03$, $n = 18$). There was no significant difference in base excess averaged over all time periods between survivors and non-survivors (-4.3 ± 0.7 *versus* -2.0 ± 1.3 mEq/L, $P = 0.17$, $n = 18$).

Twenty-eight-day survival

Mean CI and DO_2I were calculated for dogs surviving to 28 days after admission. The mean CI and DO_2I for dogs that survived to 28 days ($n = 11$) were 3.41 ± 0.70 L/min/m^2 and 453.64 ± 39.43 mL O_2/min/m^2, respectively. The mean CI and DO_2I for dogs that did not survive to 28 days ($n = 7$) were 3.40 ± 0.64 L/min/m^2

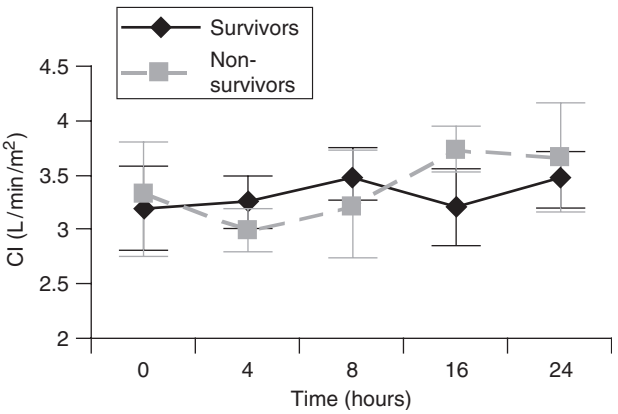

Figure 3: Effect of time on cardiac index (CI) of survivors ($n = 13$) *versus* non-survivors ($n = 5$) to discharge. Over all time periods, there was no significant difference between CI of survivors and non-survivors to discharge ($P = 0.49$). There was no significant effect of time on CI of survivors *versus* non-survivors ($P = 0.74$).

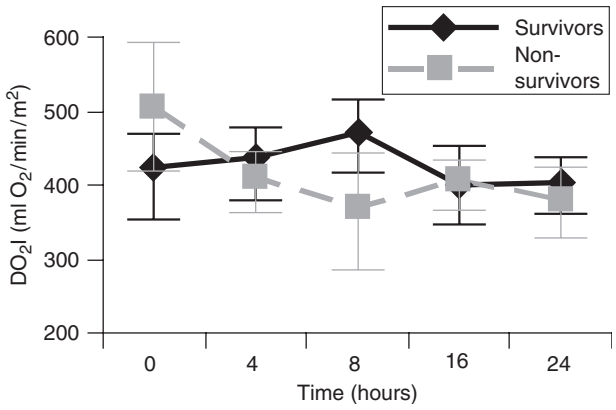

Figure 4: Effect of time on oxygen delivery index (DO_2I) of survivors ($n = 13$) *versus* non-survivors ($n = 5$) to discharge. Over all time periods, there was no significant difference between DO_2I of survivors and non-survivors ($P = 0.51$) to discharge. There was no significant effect of time on DO_2I of survivors *versus* non-survivors ($P = 0.71$).

and 399.34 ± 67.39 mL O_2/min/m^2. There was no significant difference in mean CI and DO_2I between survivors and non-survivors for 28-day survival ($P = 0.97$ and $P = 0.50$, respectively). Time did not significantly affect CI and DO_2I in either the survivors or the non-survivors. Serum lactate concentrations were significantly lower in 28-day survivors *versus* non-survivors (0.9 ± 0.1 *versus* 1.72 ± 0.46 mmol/L, $P = 0.002$). Blood glucose concentrations were significantly lower in 28-day survivors than non-survivors (5.7 ± 0.2 mmol/L [103.4 ± 3.9 mg/dL] *versus* 6.6 ± 0.6 mmol/L [119.5 ± 11.1 mg/dL], $P = 0.007$).

Hospitalization time

Hospitalization times for survivors ranged from 1 to 12 days, with an average of 5.6 ± 1.0 days. Hospitalization time of non-survivors was not entered into statistical analysis. There was no significant correlation between CI and hospitalization time for both survival to discharge ($r = -0.12$, $P = 0.32$, $n = 13$) and 28-day-survival ($r = -0.35$, $P = 0.14$, $n = 11$). However, a higher DO_2I was significantly correlated with increased hospitalization time for dogs that survived to discharge ($r = 0.34$, $P = 0.005$). Dogs with longer than average hospital stays ($n = 7$) had significantly higher PCV ($33.4 \pm 3.3\%$) than dogs with shorter than average hospital stays ($n = 6$) ($27.6 \pm 4.3\%$, $P = 0.001$). For 28-day survival, there was no significant correlation between DO_2I and hospitalization time ($r = 0.12$, $P = 0.36$, $n = 11$).

Discussion

This study provides evidence that CO and DO_2 are significantly lower in dogs that meet criteria of the systemic inflammatory response syndrome *versus* normal controls. If DO_2 is described by the equation:

$$DO_2 = CO \times C_aO_2,$$

then the difference in DO_2 between the control and SIRS patients could be explained by decreases in either CO or arterial oxygen content.

CI is the product of heart rate and stroke volume indexed to body surface area. In this study, heart rate was not significantly different between SIRS patients and the control group. Because tachycardia is one of the SIRS criteria, one may wonder why there was no difference in heart rate between these groups. SIRS was diagnosed based on presenting physical exam, but LiDCO measurements were not obtained until after the patient had been stabilized and instrumented, and client consent obtained. This delay may be responsible for normal heart rates in the SIRS population. In addition, dogs only needed to meet 3 of 4 SIRS criteria for enrollment; therefore, not all dogs had tachycardia as part of their manifestation of SIRS. Heart rates were measured during LiDCO measurements, and are an accurate reflection of the patient at that time. Because there is no difference in heart rate between the control and SIRS group, then the main cause of decreased CO in the SIRS patients must be decreased stroke volume.

Stroke volume is dependent on preload, afterload, and cardiac contractility. Decreased preload could be a result of hypovolemia from blood loss, decreased intravascular volume, maldistribution of blood flow, or decreased venous return. Decreased intravascular volume may be due to dehydration or increased vascular permeability resulting in inability to maintain intravascular volume. Central venous pressure was not measured in most of the patients, so preload was not determined in this study.

Decreased CI from increased afterload is generally caused by arteriolar constriction. This may be secondary to systemic catecholamine release from stress, pain, or the underlying disease process. Systemic vascular resistance was not routinely measured in this patient population and therefore was not examined in this study.

A third possible cause of reduced CI in our study population is poor cardiac contractility. The systemic inflammatory response syndrome is characterized by a generalized pro-inflammatory state. A variety of endogenous inflammatory mediators, including interleukins 1 and 6, and tumor necrosis factor-alpha are released in the SIRS patient. All of these cytokines have been implicated in producing myocardial depression in either *in vivo* or *ex vivo* studies.[45,46] There may also be a synergistic effect between various factors, producing far greater myocardial depression when combined than

any agent alone.[47] Because all of the study patients met criteria of SIRS, it is possible that reduced CI could be explained by reduced cardiac contractility secondary to inflammatory cytokines. Myocardial depression caused by cytokines cannot be proven without measurement of cytokines in addition to clinical assessment of contractility.

The other component of the oxygen delivery equation is arterial oxygen content. Arterial oxygen content was significantly lower in the SIRS group than the control group. Arterial oxygen content is defined by the following formula:

$$C_aO_2(\text{mL O}_2/\text{dL blood}) = (1.34(\text{mL}O_2/\text{gHb}) \times SaO_2(\%) \times \text{Hb(g/dL)}) + (0.003(\text{mL}O_2/\text{dL/mmHg}) \times PaO_2(\text{mmHg}))$$

In this study, dogs with SIRS had significantly lower hemoglobin concentrations than control dogs. The low hemoglobin levels may reflect blood loss (e.g., external hemorrhage from trauma, hemorrhagic cavitary effusions, gastrointestinal bleeding), red blood cell lysis, hemodilution from IV fluid administration, or decreased production of red blood cells. Mean P_aO_2 was significantly higher in the study group than in the control group, while mean S_aO_2 was significantly lower. This may represent right shifting of the oxyhemoglobin-dissociation curve from a significantly lower pH in the SIRS group. In addition, many dogs in the SIRS group were breathing supplemental oxygen from 40% to 100%. Based on the slope of the oxyhemoglobin dissociation curve, P_aO_2 continues to increase with increasing inspired fraction of oxygen but S_aO_2 cannot be increased above 100%. Values of $P_aO_2 > 200$ mmHg are likely to significantly skew the mean for this variable. However, increasing P_aO_2 contributes very little to an increase in C_aO_2, and the significant increase is not likely to change overall C_aO_2. Low C_aO_2 in dogs with SIRS is a combination of low hemoglobin concentrations and impaired gas exchange from primary or secondary pulmonary disease. The significant decreases in C_aO_2 and CO together contribute to a much lower DO_2 in SIRS patients compared with controls.

Much of the human literature on CO in SIRS focuses on hemodynamic alterations during sepsis. In recent reviews, sepsis is thought to consist of an early, hyperdynamic state with increased CO, followed by a hypodynamic phase characterized by low CO.[48,49] The hyperdynamic phase is characterized by increased CO, decreased systemic vascular resistance and myocardial depression.[45,50] Increased CO in the face of myocardial depression is achieved through reversible biventricular dilation that increases stroke volume despite decreased contractility.[45] Human patients with SIRS after cardiopulmonary bypass or gastrointestinal surgery have also demonstrated high CO states.[51,52]

In this study, we found canine SIRS patients to be in a significantly lower CO state than normal controls. While this may reflect a true difference between human and canine patients, the length of time dogs had SIRS was not known, and an early, hyperdynamic phase may have been missed. Preload was not routinely assessed in these patients, so the absence of adequate volume loading may have artificially decreased CO. Another complicating factor is that the veterinary community lacks a consensus statement on the definition of SIRS, so SIRS may have been over- or under-diagnosed in our patients. Only 18 dogs were included in the study, and the length of time they met SIRS criteria is unknown. However, illness in this population was composed of a variety of disease states and likely represents an accurate clinical picture of patients presented to a tertiary care facility. We also did not investigate systemic vascular resistance, left ventricular end-diastolic volume, or other indices that have been used to fully evaluate cardiovascular function in human studies. This is a potential area for future veterinary research.

Few correlations were found between physical exam and laboratory data and measured CI. In the clinical setting, treatment decisions are traditionally based on estimated CO using parameters such as blood pressure, urine output, serum lactate concentration, mucous membrane color, and heart rate. The results of the study reported here indicate that none of these commonly measured parameters correlated well with the measured CI. However, power was not achieved due to the small sample size, so a larger study may find significant correlations. Obviously, clinicians do not estimate CO based on a single variable, and statistical analyses of multiple parameters at once in association with CI and DO_2I were not performed.

Only pH was found to have a significant correlation with CI, with acidemia correlating with a lower CI. It is known that severe acidosis can decrease CO by impairing cardiac contractility.[53] In this study, the *r*-value was low indicating only a weak correlation. While statistical significance was achieved, the true biological significance is questionable given the low *r*-value. These correlations do not indicate a cause and effect relationship between CI and pH.

Poor correlations were also found between physical exam and laboratory data and measured DO_2I. However, power was not achieved due to the small sample size. Only heart rate, hemoglobin concentration, oxygen content and packed cell volume were significantly correlated with DO_2I. As these are all variables in the oxygen delivery equation, it is not surprising to have found statistically significant results.

This study found no significant correlations between CI, DO_2I, and serum lactate concentrations. In 1 early study, serum lactate concentrations were found to have a negative, nonlinear correlation with CO and DO_2.[54] However, other studies have failed to demonstrate this connection.[55,56] Serum lactate concentrations are a balance of lactate production and clearance, and can represent global oxygen debt. While tissue hypoperfusion is one cause of hyperlactemia, non-hypoxic increases in serum lactate concentrations can occur secondary to reduced clearance in liver failure, pyruvate dehydrogenase dysfunction in sepsis, or amino acid conversion to pyruvate during muscular protein degradation.[57] Increases in glycolysis (whether from an inflammatory state or increased catecholamine levels) in excess of mitochondrial oxidative capacity lead to hyperlactemia even in the presence of normal tissue perfusion.[58]

In this study, 11 of 18 dogs had normal initial serum lactate concentrations despite low DO_2I. Normal lactate concentrations imply adequacy of perfusion, and therefore indicate sufficient DO_2 to remain in the delivery independent portion of the oxygen consumption curve. Increases in oxygen extraction would be a method of remaining in the delivery independent portion of the oxygen consumption curve despite reductions in DO_2. Additionally, the patients in this study were all resting in a cage, which should be associated with a lower DO_2 requirement than would be the case in an active animal. Our findings support the idea that CI and DO_2I are only 2 of many factors that determine serum lactate concentrations.

In this study, no changes in therapy were made in response to or because of CO measurements. The primary clinician treated each patient with any interventions he or she felt necessary, including one or more of the following: fentanyl,[d] morphine,[l] hydromorphone,[m] acepromazine,[j] lidocaine,[n] or procainamide.[o] The dogs were also variably treated with plasma, blood or human albumin transfusions,[p] fluid boluses, or magnesium chloride[q] supplementation. Many were receiving supplemental oxygen. Some patients were also being treated with positive inotropes or vasopressors, including constant rate infusions of dobutamine,[r] dopamine,[s] vasopressin,[t] norepinephrine[u] or epinephrine.[v] While it would have been ideal to perform CO measurements without any interventions, this was not clinically or ethically feasible. We feel that our study accurately reflects the clinical picture because a combination of these interventions is used in many critically ill patients. None of the therapeutic interventions investigated were associated with alterations in CI and DO_2I, but power was not achieved due to the small sample size.

The use of inotropes was not found to be significantly associated with increased CI and oxygen delivery index when significance was set at $P < 0.01$. Both dobutamine and dopamine were considered inotropes for purposes of this analysis. In human studies, these drugs have been used to achieve supranormal levels of CO.[10–12] Possible reasons for lack of correlation include the low number of patients receiving these drugs, or extremely low CO states that were marginally improved with inotropic support.

Of all the physical exam and laboratory data collected during this study, only serum lactate concentration and blood glucose concentration were found to be significantly associated with outcome. Non-survivors had significantly higher blood glucose concentrations than survivors. This may reflect increased physiologic stress associated with more severe illness. Recent meta-analysis of glycemic control in critically ill human patients has shown 15% lower short-term mortality[59] in those patients where euglycemia was maintained. Current guidelines in the Surviving Sepsis Campaign recommend use of insulin or dextrose to maintain euglycemia.[60] In veterinary medicine, a rabbit model of critical illness showed improved immune system function with glycemic control,[61] and insulin therapy to maintain euglycemia improved 4-day-survival in a rat model of sepsis.[62] There are no published prospective clinical studies on glycemic control in veterinary patients.

Serum lactate concentration was found to be significantly higher in non-survivors than in survivors. This has been demonstrated in human studies, where serum lactate concentrations have been shown to be a nondependent predictor of mortality in sepsis,[63] acute renal failure,[64] and vascular injury from trauma.[65] Serial elevations in serum lactate concentrations have been shown to correlate with mortality in both human[66,67] and veterinary medicine.[68,69] Both serum lactate concentrations and base excess have been investigated as predictors of occult tissue hypoperfusion and mortality.[65,70–72] Base excess, like serum lactate concentration, was not associated with DO_2 in this study.

There may be several explanations for the absence of a significant relationship between CO, DO_2, and mortality in our study. First, this study involved a small number of patients, and power was not achieved. A larger study might reveal a more distinct trend or significant difference. Another possibility for the lack of association between DO_2 and survival is that oxygen extraction was sufficient to maintain tissue health. Mammals possess significant physiologic reserves, so that large decreases in DO_2 must occur before oxygen consumption becomes supply dependent.[73,74] The patients with the lowest DO_2I were above the critical DO_2 (approximately 5 mL/kg/min),[75] implying that DO_2

was sufficient such that CI and DO_2I were not associated with mortality.

The question becomes: when is DO_2 'enough'? Evaluation of oxygen transport variables such as CO and DO_2 may not be sufficient to detect occult tissue hypoxia. Parameters such as base excess, serum lactate concentrations, pH, and mixed venous oxygen saturations should provide valuable insight to adequacy of oxygenation at the cellular level. While we did not assess oxygen extraction in this study, evaluating oxygen extraction and consumption in relation to DO_2 and CO would be the next logical step for future studies.

Another explanation for a poor relationship between CO, DO_2, and survival is the length of the study period, which extended for only 24 hours after admission. The data obtained from the non-survivors group may not accurately reflect the overall level of CI and DO_2I throughout the disease process. Although not a problem in this study, the difficulty of designating animals as survivors or non-survivors is an inherent limitation in designing veterinary studies, especially with the option of euthanasia due to poor long-term prognosis or financial constraints.

CI was not found to be correlated with hospitalization time. DO_2I was found to be significantly positively correlated with hospitalization time in animals that survived to discharge, such that increasing DO_2I increased numbers of days in hospital. This correlation was weak, and is possibly related to more blood transfusions and oxygen supplementation for sicker dogs that stayed in hospital longer. In support of this, dogs with longer than average hospital stays had significantly higher PCVs than dogs with shorter hospitalization times. As previously discussed, hemoglobin concentration is an important component of the oxygen content equation, and is significantly correlated with DO_2I. It follows that because animals with longer hospital stays had higher PCVs, that higher DO_2I would be correlated with longer hospitalization.

In conclusion, this study has shown that CI and DO_2I are significantly lower in canine SIRS patients compared with controls. While CI and DO_2I are lower in canine SIRS patients, most physical exam parameters and laboratory data are not correlated with measured CI and DO_2I. Only a low pH was significantly associated with lowered CI, although the low *r*-value makes biological significance questionable. DO_2I is correlated only with the variables that make up its equation. CI and DO_2I are not significantly associated with outcome for either survival to discharge or 28-day-survival. The only parameters significantly associated with survival are lower serum lactate concentrations and lower blood glucose concentrations.

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Footnotes

[a] LiDCO Plus Hemodynamic Monitor, LiDCO Plus Plc., London, UK.
[b] ABL 800 Flex Blood Gas Analyzer, Radiometer Inc., Copenhagen, Denmark.
[c] OSM-3 Hemoximeter, Radiometer Inc.
[d] Fentanyl Citrate Injection, Hospira Inc., Lake Forest, IL.
[e] Midazolam HCl Injection, Bedford Laboratories, Bedford, OH.
[f] PropoFlo, Abbott Laboratories, Chicago, IL.
[g] Naloxone HydroChloride, Hospira Inc.
[h] Flumazenil, Apotex Inc., Toronto, ON.
[i] SPSS for Windows Statistical Package, SPSS Inc., Chicago, IL.
[j] Acepromazine Maleate, Vedco Inc., St. Joseph, MO.
[k] 6% Hetastarch in 0.9% Sodium Chloride, Hospira Inc.
[l] Morphine Sulfate Injection, Baxter HealthCare Corp., Deerfield, IL.
[m] Hydromorphone HCl, Hospira Inc.
[n] Lidocaine HCl, Hospira Inc.
[o] Procainamide Hydrochloride Extended Release, TEVA Pharmaceuticals, Sellersville, PA.
[p] 25% Human Albumin, Buminate 25%, Baxter HealthCare Corp.
[q] Magnesium Chloride Injection, American Regent Inc., Shirley, NY.
[r] Dobutamine injection, Bedford Laboratories, Bedford, OH.
[s] Dopamine HCl, Hospira Inc.
[t] Vasopressin Injection, American Regent Inc., Shirley, NY.
[u] Levophed, Hospira Inc.
[v] Epinephrine Injection, IMS Limited, So. El Monte, CA.

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