

Low central venous oxygen saturation is associated with increased mortality in critically ill dogs

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OBJECTIVES: To investigate relationships between central venous oxygen saturation (ScvO₂) and survival to hospital discharge in dogs. Central venous oxygen saturation is an accessible measure of the balance between systemic oxygen delivery and consumption.

METHODS: Prospective observational cohort study, enrolling 126 client-owned dogs with central venous catheters. Central venous oxygen saturation was measured over the 24 hours following intensive care unit admission. Poor outcome was defined as death or euthanasia performed for moribund status. Regression analysis identified independent predictors of non-survival and physiologic parameters associated with central venous oxygen saturation. Area under the receiver operator curve analysis identified a cut-off point of central venous oxygen saturation, below which central venous oxygen saturation decrease was associated with increased mortality risk.

RESULTS: Mortality risk was 30.9%. Low central venous oxygen saturation was associated with poor outcome (P<0.05). Area under the receiver operator curve analysis selected a central venous oxygen saturation of 68% as the point below which a fall in central venous oxygen saturation was associated with increased mortality risk. For each 10% drop in central venous oxygen saturation below 68%, odds of non-survival increased by 2.66 times (P=0.0002, 95% confidence interval of odds ratio=1.45 to 4.85). Central venous oxygen saturation was equivalent to lactate in predicting non-survival. Predictors of central venous oxygen saturation (packed cell volume, mean arterial blood pressure, fever, % arterial haemoglobin saturation as measured by pulse oximeter) were consistent with hypothesised physiologic mechanisms.

CLINICAL SIGNIFICANCE: Central venous oxygen saturation was a strong mortality predictor. Further work is needed to determine if therapy targeting central venous oxygen saturation can reduce mortality in canine intensive care unit patients.

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INTRODUCTION

Central venous oxygen saturation is the percentage oxygen saturation of haemoglobin measured in the right atrium, cranial or caudal vena cava (Shepherd and Pearse 2009). "Normal" saturation values differ by sampling location, and the term ScvO₂ will be used hereafter to refer to central venous oxygen saturation measured in the cranial vena cava. ScvO₂ can be measured using co-oximetry on blood samples obtained by intermittent sampling from a central venous catheter (CVC), or alternatively by spectrophotometric catheter (Marx and Reinhart 2006). Decreased ScvO₂ suggests a mismatch between oxygen supply (DO₂) and tissue oxygen consumption (VO₂) in the tissues upstream from the point of measurement (Ander and others 1998, Vallet and others 2005, Dellinger and others 2008). The pathophysiology behind the reduction in ScvO₂ is partially summarised in Fig 1. ScvO₂ falls either when tissue oxygen delivery falls below a critical level, or tissue oxygen consumption increases without a comparable and concurrent increase in oxygen delivery. The relative venous desaturation that ensues reflects the switch in tissue oxygen consumption to a state limited by supply. Oxygen delivery is determined by cardiac output, blood haemoglobin content, haemoglobin integrity and pulmonary function. In turn, haemoglobin content is typically a function of red blood cell mass, while normal haemoglobin integrity requires an absence of carbon monoxide or other ligands that can compromise haemoglobin function with respect to oxygen uptake and release. Oxygen consumption is a function of tissue activity and metabolic rate. Thus, a low ScvO₂ can reflect a wide range of underlying pathologies, including relative or absolute hypovolemia, cardiac dysfunction, anaemia, lung disease, fever and seizures. A high ScvO₂ can occur with relative tissue inactivity, hypothermia and mitochondrial dysfunction.

Human studies have identified associations between an ScvO₂ below 65% and increased illness severity, organ failure, mortality and other adverse outcomes in the context of trauma (Scalea and others 1990), sepsis (Rady and others 1992), myocardial infarction (Hutter and Moss 1970), cardiac failure (Ander and others 1998), brain injury (Di Filippo and others 2009) and post-operative care (Pearse and others 2005, Nogueira and others 2010).

ScvO₂ above 70% has been recommended as a therapeutic end-point in the management of sepsis (Dellinger and others 2008), and goal-directed therapy protocols which target this end-point have been shown to reduce mortality in both adults and children (Rivers and others 2001, Donati and others 2007, de Oliveira and others 2008). These protocols require titration of fluids, pressors, inotropes, and in some cases red cell transfusions to normalise ScvO₂. Fair correlation between ScvO₂ and tissue oxygenation has been demonstrated in human critical care patients (Napoli and others 2010), with similar trending performance. Therapy targeted to ScvO₂ ≥ 70% has been shown to be equivalent in improving mortality outcomes to therapy targeted to lactate clearance (Jones and others 2010).

ScvO₂ decreases with incremental blood loss in experimental dogs, showing a linear association with the severity of the shock state (Scalea and others 1988). Investigation of ScvO₂ monitoring has been suggested for veterinary critical care patients in a recent review of perfusion assessment techniques (Boag and Hughes 2005).

The purposes of this study were to determine: (1) if an association exists between ScvO₂ and outcome in a cohort of canine intensive care unit (ICU) patients; (2) if a cut-off value for ScvO₂ predictive of non-survival could be determined and (3) if reductions in ScvO₂ in this patient population were consistent with the hypothesised human physiologic mechanisms discussed above. In accordance with previous work investigating associations between ScvO₂ and outcome (Scalea and others 1990, Pearse and others 2005, Zimmerman and others 2006, Di Filippo and others 2009, Nogueira and others 2010), the lowest ScvO₂ observed within 24 hours of admission was selected as likely to be an informative summary measure of ScvO₂ status.

MATERIALS AND METHODS

Study population

This single-centre prospective observational cohort study was conducted in a veterinary teaching hospital ICU. Client-owned dogs were consecutively enrolled with inclusion criteria consisting of a clinical indication for a CVC (Mila International Inc., Erlanger, KY) with entry via the jugular vein placed within

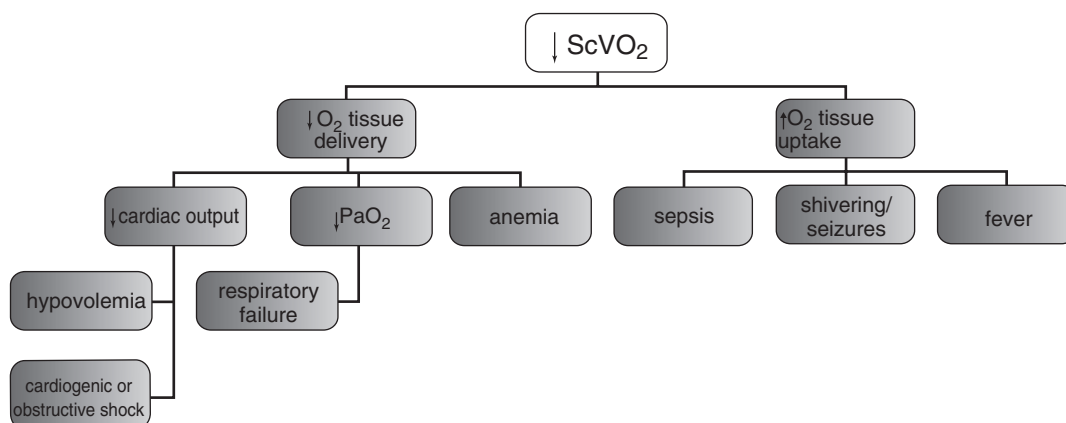


FIG 1. Physiologic and pathologic factors that influence venous oxygen saturation (ScvO and SmvO₂) (reproduced with permission from Shepherd SJ, Pearse RM *Anesthesiology* 2009;111:649-656)

2 hours of admission. Dogs were subsequently excluded if euthanased because of financial constraints. Dogs were enrolled over a 6-month period.

Criteria for ICU admission were a requirement for intravenous (IV) access for continuous fluid or medication administration, and/or close observation. For canine ICU admissions over the study period, 89% were on an emergency basis following an unscheduled appointment, while 11% of admissions followed scheduled appointments. Seventy-one per cent of admissions were secondary or tertiary referral. The hospital was structured as an integrated emergency department and ICU – all emergency stabilisation of hospital admissions took place within the ICU, and for emergent patients hospital admission implied ICU admission. Informed owner consent was waived by the hospital ethics committee, given the non-interventional nature of the study design.

CVC placement

The decision to place a CVC was made by the primary clinician in consultation with the ICU clinicians. Indications included patients for whom frequent blood sampling and/or monitoring of central venous pressure (CVP) was required (n=121), patients receiving IV hyperosmolar solutions (n=3) and patients for whom obtaining or maintaining peripheral venous access was difficult or impractical (n=2). CVC placement was considered absolutely or relatively contraindicated in patients with severe coagulopathy, or open wounds/local neoplasia limiting jugular access. Placement of the CVC was performed by trained technicians or clinicians following application of a topical local anaesthetic (EMLA cream, lidocaine and prilocaine 2.5%, APP pharmaceuticals, IL) and administration of systemic opioid analgesia, if systemic analgesic therapy was not already provided. Following CVC placement, hospital protocol required radiographic evaluation of catheter position. The catheter was adjusted as needed to achieve placement of the catheter tip within the intra-thoracic cranial vena cava.

Measurement of ScvO₂ and other variables

ScvO₂ was measured by co-oximetry (128 wavelength co-oximeter, ABL 800 Flex, Radiometer Medical Aps, Bronshoj, Denmark), as part of a standard laboratory panel including measurement of concentrations of electrolytes, blood lactate and blood gas parameters. Laboratory equipment was automatically calibrated every hour, and weekly quality control checks were performed according to the manufacturer's instructions. The ScvO₂ was determined every 6 to 12 hours for each patient by intermittent sampling. For the purposes of the study, the lowest ScvO₂ value observed within 24 hours of admission for each patient was recorded as a summary measure. Additional summary measures recorded included the highest blood lactate concentration, lowest packed cell volume (PCV), lowest blood pH, lowest mean arterial blood pressure (MAP), highest respiratory and heart rates, lowest % arterial haemoglobin saturation as measured by pulse oximeter (SpO₂), and rectal temperature showing the greatest departure from 38.3°C. Elevated body temperature was defined as a rectal temperature over 39.7°C. The PCV was determined

from heparinised blood centrifuged at 200,000 g units for 3 minutes. SpO₂ was measured using a handheld pulse oximeter (Nonin, 8500 digital).

The severity prediction index (SPI2) (King 2009) was calculated for each patient. This is a numerical score validated for use on canine ICU patients that provides an estimation of canine mortality risk, where a value of 1.0 estimates 0% mortality and a value of 0.5 estimates 50% mortality.

Within the ICU, before and during this study the co-oximeter information provided with each blood gas result was regarded as uninformative if the blood sample was not arterial. Although the primary clinician was not blinded to the ScvO₂ data, ScvO₂ was not monitored for clinical purposes, therapeutically targeted, or reported to the owner.

The primary disease process for each dog was recorded and managed in consultation with the owners according to the standard of care for the ICU. Dogs were diagnosed with sepsis if they fulfilled $\geq 2/4$ systemic inflammatory response syndrome criteria (Otto 2007) and had an infectious focus documented by cytology or microbiology.

Measured outcomes

Recorded outcomes included vital status at hospital discharge and length of hospital stay. Dogs were excluded from the study group if humane euthanasia was performed for any reason other than the patient being assessed by the primary clinician as moribund and near death in the face of severe disease. The circumstances of euthanasia were determined contemporaneously and cross-checked with the written medical record. If clarification was required, the circumstances were reviewed with the primary clinician. Dogs euthanased as described above were considered equivalent to those that died for the purpose of analysis. Poor outcome was defined as euthanasia performed in association with moribund disease status or death.

STATISTICAL METHODS

Data are presented as means \pm standard deviation (sd) where normally distributed, as medians [interquartile range (IQR)] where not normally distributed, or for categorical variables as a percentage of the group from which they were derived. When multiple values for a parameter were available, a single summary measure was selected as described in the section *Materials and Methods*. Normality was tested with the Shapiro-Wilk test. Associations between categorical data were tested with the Fisher's exact test. Associations between continuous data were tested with the student's *t* test where data were normally distributed and the Mann-Whitney test where not normally distributed. The association between individual parameters and mortality were assessed by univariate logistic regression analysis, with discriminant ability assessed by evaluation of the area under the receiver operator curve (AUROC) characteristics for each parameter. Associations between continuous variables and binary outcome were assessed graphically using locally weighted scatterplot smoothing (LOWESS) plots as previously described (Cleveland and Devlin 1988). AUROC curves were constructed

to identify optimal cut-off values for association with outcome, as previously described (Pearse and others 2005, Shepherd and Pearse 2009). The optimum cut-off was defined as the value associated with the highest sum of sensitivity and specificity. A multiple logistic regression model was used to identify independent risk factors for mortality. Linear univariate and multivariate regression analyses were performed to test associations between putative predictor variables and ScvO₂. Homoskedasticity for the linear regression models, defined as a constant outcome variance for all values of predictor variable, was tested with the Cook-Weisburg test. Analyses were performed in Stata version 10.1 (StataCorp LP, College Station, TX), and significance was set at P<0.05.

RESULTS

Study population characteristics

One hundred and twenty-eight dogs met the criteria for inclusion in the study. Two dogs were subsequently excluded (treatment discontinued because of financial restrictions). Of the 126 dogs remaining, 38 were euthanased, while 1 died, with a total non-survival incidence of 30.9%. ICU mortality for dogs without CVCs over the same period was significantly lower (P<0.001) at 13.5%. The median SPI2 score (IQR) for study dogs was 0.70 (0.59 to 0.83). The median SPI2 score for dogs without CVCs over the same period was significantly higher (P<0.001) at 0.80 (0.69 to 0.87). The mean hospital stay for non-surviving dogs in the study group was significantly shorter than survivors (2.8 *versus* 4.7 days, P=0.006). For the dogs euthanased, euthanasia was performed only in association with moribund status and one of the following conditions: organ failure (n=27); septic shock refractory to treatment (n=3); devastating surgical findings (n=4); or immune-mediated disease with persistent transfusion dependency together with respiratory or neurologic complications (n=4). Dogs with organ failure suffered respiratory failure (n=10), renal failure (n=9), hepatic failure (n=3), cardiac failure (n=3) and neurologic failure (n=2).

Approximately half (57%) of the study dogs were male. The median age (IQR) was 7 (2 to 9) years. Of the dogs in the study group, 20% (n=25) had a primary diagnosis associated with pancreatic or gastrointestinal disease, including gastric dilation/

volvulus (n=7), severe pancreatitis (n=6), intestinal resection/anastomosis (n=5), haematemesis or haemorrhagic gastroenteritis (n=4), perforating oesophageal foreign body (n=1), mesenteric torsion (n=1) and protein losing enteropathy (n=1). Septic dogs accounted for 15% of the study group (n=19), typically with septic peritonitis or pneumonia. A primary diagnosis of heart failure accounted for 8% of the study group (n=10), trauma 9% (n=11), immune-mediated disease 10% (n=12), and Addisonian crisis, diabetic ketoacidosis or hyperglycaemic hyperosmolar syndrome 11% (n=14). The remaining dogs were hospitalised for a range of primary diagnoses, including acute hepatic (n=8) and renal failure (n=9), chemotherapy complications (n=9), intracranial disease (n=4), spinal or peripheral neuropathy (n=3), uterine rupture (n=1) and acetaminophen toxicity (n=1). Mechanical ventilation was used to support 9% of the dogs (n=12) at some point in their hospital stay, and therapy with pressors was instituted in 17% (n=22) of dogs during their hospital stay.

The SPI2 score was significantly higher (P<0.001) in the dogs in the study group that survived [median (IQR) SPI2=0.77 (0.64 to 0.84)] compared with those that died [median (IQR) SPI2=0.65 (0.55 to 0.70)].

Association between measured variables including ScvO₂ and outcome

Measured physiological, biochemical and demographic variables and their associations with outcome for the 126 study dogs are presented in Table 1.

Lactate concentration, heart rate and respiratory rate were significantly lower in dogs that survived to hospital discharge compared with the non-survivors, while ScvO₂, SpO₂, PCV and pH were significantly higher.

ScvO₂ was associated with survival outcome in logistic regression analysis (P<0.001). A graphical plot of the association between ScvO₂ and non-survival using a running mean smooth is shown in Fig 2. There was a steadily increasing mortality risk as ScvO₂ fell below 68% (see Fig 2), with no association found between ScvO₂ and mortality risk above an ScvO₂ of 68%, where the graph tends to the horizontal. The point at which decline in ScvO₂ first became associated with increased mortality risk was confirmed by AUROC analysis, where maximal sensitivity and specificity (61 and 64%) for the association between ScvO₂ and

Table 1. Patient sample characteristics, biochemical and physiologic data for survivors and non-survivors in ScvO₂ group

Parameter	Survivors Median (IQR), mean±sd	Non-survivors Median (IQR), mean±sd	P value
Number in group	89	39	
Age (years)	8 (2 to 5)	11 (6 to 9)	0.001
ScvO ₂ (%)	69.4 (59.3 to 84.7)	60.2 (44.7 to 82.3)	0.015
MAP (mmHg)	115 (89 to 129)	99 (66 to 130)	0.203
Heart rate (bpm)	133±42	155±39	0.005
Respiratory rate (rpm)	36 (24 to 48)	48 (40 to 72)	0.001
SpO ₂ (%)	97 (95 to 98)	92 (85 to 98)	0.011
PCV (%)	39±10.5	34±12.9	0.034
Lactate (mmol/L)	2.1 (1.4 to 3.4)	3.3 (2.5 to 5.6)	<0.001
pH	7.34 (7.30 to 7.40)	7.29 (7.21 to 7.39)	0.038
Base excess	-3.25 (-5.6 to 1.05)	-3.9 (-9.9 to 1.2)	0.231
SPI2 score	0.77 (0.64 to 0.84)	0.65 (0.55 to 0.70)	<0.001

IQR Interquartile range, ScvO₂ Central venous oxygen saturation, MAP Mean arterial blood pressure, PCV Packed cell volume, SPI2 Severity prediction index

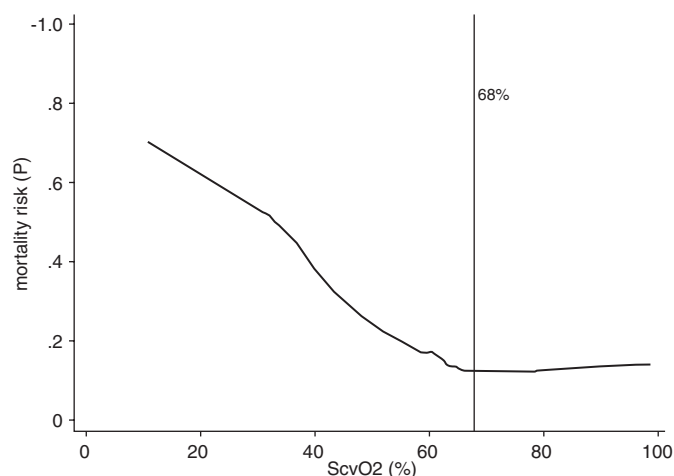


FIG 2. Locally weighted scatterplot smoothing (LOWESS) plot of the association between non-survival risk and ScvO₂

mortality were obtained at $P=0.304$, equivalent to $ScvO_2=68\%$. For each fall in $ScvO_2$ of 10% below 68%, the odds of non-survival increased by 2.66 times ($P=0.0002$, OR 95%CI=1.45 to 4.85). When patients with an $ScvO_2$ below 68% ($n=64$) were assessed as a separate group, the optimal discriminant cut-point of $ScvO_2$ to distinguish survivors from non-survivors occurred at an $ScvO_2$ of 48% (sensitivity=74%, specificity=92%). Increases in $ScvO_2$ above 68% were not associated with improved survival odds.

The discriminant capacity of $ScvO_2$ to predict non-survival compared with other clinical parameters was evaluated. The AUROC characteristic is a reflection of the capacity of a parameter to accurately determine outcome, in this case non-survival, with a value of 1.0 implying perfect accuracy. $ScvO_2$ less than 68% was associated with non-survival with an AUROC equiva-

lent to or better than other commonly measured clinical parameters such as lactate concentration, as shown in Table 2. The association between $ScvO_2$ and non-survival risk was retained in multivariate analysis, suggesting that similar to lactate and SpO_2 , $ScvO_2$ has a strong independent association with non-survival.

Evaluation of predictors of ScvO₂

Low SpO_2 , PCV and MAP and the presence of an elevated body temperature identified within 24 hours of admission were significantly associated with lower $ScvO_2$ over the same period in dogs (see Table 3, $P<0.05$). The SpO_2 , PCV and MAP carried a positive association with $ScvO_2$, while an elevated body temperature carried a negative association with $ScvO_2$. The presence of seizures ($n=12$) over the 24-hour admission period was not found to be associated with $ScvO_2$ ($P=0.23$).

DISCUSSION

The objective of this study was to perform a pilot analysis of $ScvO_2$ associations in clinical canine patients. We investigated the association between lowest $ScvO_2$ identified within the first 24 hours of admission, and patient survival to hospital discharge. We evaluated the prognostic capacity of $ScvO_2$ in comparison with a number of other commonly monitored clinical parameters. Finally, we investigated the associations between $ScvO_2$ and body temperature, PCV, MAP and SpO_2 .

We found that a fall in $ScvO_2$ below 68% in the initial 24-hour period was associated with a greater risk of a poor outcome. For each fall in $ScvO_2$ of 10% below 68%, the odds of non-survival increased by 2.66 times [$P=0.0002$, odds ratio (OR) 95% confidence interval (CI)=1.45 to 4.85]. $ScvO_2$ had the highest predictive capacity for ultimate outcome of all the parameters assessed

Table 2. Association between measured parameters and mortality in 128 canine ICU patients

Parameter	OR	P value (likelihood ratio test)	95% CI for the OR	AUROC	95% CI for AUROC
$ScvO_2<68\%^*$	0.92	<0.001	0.87 to 0.97	0.76	0.62 to 0.88
Lactate*	1.30	<0.001	1.12 to 1.61	0.71	0.61 to 0.80
SpO_2^*	0.82	<0.001	0.73 to 0.95	0.69	0.54 to 0.83
Respiratory rate	1.03	0.002	1.01 to 1.04	0.69	0.59 to 0.78
Heart rate	1.01	0.005	1.01 to 1.03	0.69	0.58 to 0.79
pH	0.02	0.037	0.001 to 0.86	0.62	0.50 to 0.73
PCV	0.96	0.035	0.92 to 0.99	0.61	0.49 to 0.72

OR, Odds ratio, CI Confidence interval, AUROC Area under the receiver operator curve, $ScvO_2$ Central venous oxygen saturation, SpO_2 % arterial haemoglobin saturation as measured by pulse oximeter, PCV Packed cell volume

*variables retaining significance ($P<0.05$) in a multivariate model

Table 3. Associations between ScvO₂ and SpO₂, PCV, MAP and hyperthermia in univariate analysis

Variable	P value	β coefficient	95% CI
SpO_2 (%)	0.020	0.710	0.112 to 1.308
PCV (%)	0.004	0.419	0.140 to 0.698
MAP (mmHg)	0.001	0.191	0.086 to 0.297
$T>39.7^\circ C$	0.045	-10.400	-20.575 to 0.220

CI Confidence interval, $ScvO_2$ Central venous oxygen saturation, SpO_2 % arterial haemoglobin saturation as measured by pulse oximeter, PCV Packed cell volume, MAP Mean arterial blood pressure

(AUROC=0.76, 95% CI=0.62 to 0.88). Patients with low $ScvO_2$ were more likely to have lower PCV, lower SpO_2 , lower MAP and high body temperature compared with other patients. Additional increases in $ScvO_2$ above 68% were not associated with improved survival odds.

This study was conducted on a subset of ICU patients for whom central lines were placed as requested by the primary clinician, with a wide range of primary diagnoses. These patients were more severely ill when compared to the canine ICU population as a whole, and this is reflected in the higher

mortality rates and lower SPI2 scores. Conducting this study on this group of patients reflects a focus on a patient subset to whom sensitive haemodynamic monitoring techniques are most likely to be clinically applied, and thus may improve the transferability and clinical relevance of the findings.

We elected to use the lowest ScvO₂ recorded within 24 hours of admission as a summary measure of our main variable of interest for a number of reasons. Firstly, other studies both examining the prognostic associations of clinical parameters and establishing cut-points for ScvO₂ to predict poor outcome have set a precedent of using an ScvO₂ summary measure in this manner (Scalea and others 1990, Pearse and others 2005, Zimmerman and others 2006, Di Filippo and others 2009, Nogueira and others 2010). One study evaluating associations between low ScvO₂ and multiple organ failure (MOF) in the post-operative period failed to identify an association between admission ScvO₂ and MOF, but found a strong association between the lowest ScvO₂ identified in the post-operative period and MOF, suggesting that this is a more sensitive measure (Pearse and others 2005). Second, the initial stabilisation period is often the period of greatest physiologic instability, and current paradigms suggest that inadequate stabilisation or further deterioration occurring over this period may result in increased incidence of MOF and morbidity later in the hospital stay (Rivers and others 2001, Dellinger and others 2008). Third, it was anticipated that 24-hour data would be available for all patients enrolled in the study, while this might not be true for all other time-points; non-survivors typically have a shorter hospital stay than survivors, raising concerns regarding the possibility of an information bias if the entire hospital stay period had been used. The use of ScvO₂ data limited to the initial 24-hour period of hospitalisation should be taken into consideration before extrapolating the results of this study to the clinical floor; no statement can be made about the prognostic information provided by a low ScvO₂ identified later in the hospital stay.

ScvO₂ reflects the balance between oxygen delivery and oxygen consumption, and is decreased by factors that increase oxygen consumption such as increased body temperature, as well as factors that reduce oxygen delivery such as poor cardiac output or decreased arterial oxygen content (Shepherd and Pearse 2009). A key concept in critical care is the maintenance of sufficient oxygen delivery to tissues to allow unimpeded aerobic metabolism. When cellular partial pressure of oxygen declines below a critical level, cell oxygen consumption and ATP production become supply limited, with transition to anaerobic metabolism and ultimately cell death. Resuscitation of this form of shock requires restoration of a state of tissue oxygen consumption that is not supply limited. Identification of low ScvO₂ suggests an imbalance in tissue oxygen supply/utilisation. The responsiveness of ScvO₂ to accruing tissue insult may explain the associations identified between low ScvO₂, organ failure and poor outcome.

A number of studies investigating ScvO₂ in human ICU patients have identified associations between low ScvO₂ and MOF and mortality outcomes (Nogueira and others 2010, Pope and others 2010). To our knowledge this is the first study investigating associations between ScvO₂ and outcome in canine patients. The cut-off for non-survival association of 68% iden-

tified by our data agrees closely with the 65 to 70% used as a therapeutic target in human shock resuscitation protocols (Rivers and others 2001, de Oliveira and others 2008).

While associations between low ScvO₂ and increased mortality risk have been reported in a number of studies of human patients, a recent study also reported an association between increased mortality risk and high ScvO₂ (ScvO₂>90%; OR=2.2; 95% CI=1.3 to 3.7) in a cohort of septic patients (Pope and others 2010). This was hypothesised to be because of a combination of sepsis-associated microcirculatory alterations resulting in functional shunting of oxygen at the capillary level, together with mitochondrial dysfunction and failure of cellular respiration and oxygen uptake. We did not find evidence of an association between high ScvO₂ and increased mortality risk; however, septic dogs made up a relatively small proportion of our study group.

The associations identified between ScvO₂ and SpO₂, PCV, hyperthermia and MAP in a heterogeneous group of clinical canine patients agree with postulated mechanisms of ScvO₂ fluctuation in human beings and lend weight to the consideration of ScvO₂ as a surrogate marker for DO₂ adequacy relative to VO₂ in dogs.

The affinity of haemoglobin for oxygen varies with the number of oxygen molecules bound. This phenomenon explains the sigmoid nature of the oxygen-haemoglobin equilibrium curve. The relationship between haemoglobin % saturation and the local partial pressure of oxygen (PO₂) is further modified by the presence of acidemia, hypercarbia, increased temperature and increased 2,3-diphosphoglycerate concentration, which cause a shift of the haemoglobin dissociation curve to the right. The presence of these conditions results in a lower haemoglobin saturation for any given PO₂ and increased release of oxygen from haemoglobin into the tissue beds. Due to the interdependency of % haemoglobin saturation and pH, it is difficult to separate the clinical effects of acidemia from those of decreased ScvO₂ in this study. However, the fact that ScvO₂ remained an independent predictor of outcome in a multivariate model whereas pH did not may suggest that ScvO₂ has a stronger association with outcome than pH, and may be the primary determinant in this relationship. Further studies specifically assessing the influence of pH on the ScvO₂/outcome relationship are indicated. A number of studies in human beings have failed to show alkalinisation therapy to have a positive influence on outcome (Dellinger and others 2008). Current standard-of-care guidelines for the management of sepsis in human beings make a strong recommendation for therapy targeted to an ScvO₂ greater than 70%, and recommend against the use of bicarbonate therapy when pH is greater than 7.15; below this pH, no recommendation is made (Dellinger and others 2008).

ScvO₂ is closely related to mixed venous oxygen saturation (SmvO₂) in physiologic terms. The key advantage of ScvO₂ over SmvO₂ is that a pulmonary artery catheter is not required to obtain samples, increasing clinician accessibility and reducing expense. At our institution, the unit cost of CVC placement is considerably lower than for a PAC, and PACs are not in routine clinical use for monitoring purposes. There has been a trend away from the use of PACs in human critical care patients,

with several studies documenting increased morbidity associated with PAC use and no or negative impact on mortality outcome despite the increased information on cardiac output parameters they provide to the clinician (Ivanov and others 2000, Binany and others 2005, Harvey and others 2006, Saunders and others 2007). Direct comparisons with human patients randomised to PACs or CVC have identified no difference in clinical outcomes with twice as many catheter-associated complications in the PAC group (Wheeler and others 2006). CVCs are in routine use in dogs, are quickly and easily placed and have a low reported patient complication rate, although there have been no direct comparisons with PACs performed to date (Abrams-Ogg and others 1992, Blaiset and others 1995, Adamantos and others 2010). The incorporation of a spectrophotometer in the CVC catheter tip offers interesting possibilities for continuous monitoring of ScvO₂ in the context of shock resuscitation. The use of this monitoring technique has been assessed in human paediatric critical care patients and been shown to result in improved outcomes compared with CVC alone (de Oliveira and others 2008). Although co-oximetry was used in the current study to directly measure ScvO₂, the calculated SO₂ value obtained by extrapolation of dissolved oxygen content via the oxyhaemoglobin equilibrium curve may also prove to be of value, and may be more routinely available.

The key limitation of this study was the high incidence of euthanasia as the main mortality outcome. Euthanasia is an information-based decision; if a low ScvO₂ triggers clinicians to recommend euthanasia, then a spurious mortality association may be created where none exists in the absence of the euthanasia bias. We are reasonably confident that this bias was not a major factor in our study, for several reasons. First, within our institution ScvO₂ has not been a monitored or therapeutically targeted parameter because of lack of information regarding the biology or prognostic capacity of this parameter in dogs. Second, the study authors were not the primary clinicians for the majority of the cases (>90%) concerned. Third, the ScvO₂ was recorded over the 24 hours following admission, while the euthanasia took place on average after 2.8 days (range 1 to 9 days) – it seems unlikely that the decision to euthanase would be influenced by an unmonitored experimental parameter measured over a day prior. Fourth, the objective disease severity measure, the SPI2 score, was significantly lower in the non-survivors than the survivors, suggesting that they were truly “sicker”. Finally, it should be recognised that while the purest form of survival outcome study would be performed on a population limited to those experiencing natural death only, this population does not exist in clinical veterinary medicine. Mortality cannot always usefully be replaced with surrogate outcome measures, particularly across populations with a broad case mix. As such, while the possibility of bias should always be considered, mortality studies in which euthanasia is performed can still provide a valuable source of information in the veterinary literature, and we argue that this is the case here.

Additional limitations included the potential for ascertainment bias if a low ScvO₂ was not identified because of intermittent sampling techniques, and the potential for both institutional variation and the effect of individual variations in therapy affect-

ing associations with outcome. External validation of these initial findings is required, and the authors recommend particular caution in over-interpreting the sensitivity and specificity values reported for the various cut-points of ScvO₂ until this occurs. These measures typically lack robustness in small patient groups and are sensitive to minor data variations. Finally, the co-oximetry equipment used to measure ScvO₂ utilised human haemoglobin absorption coefficients, and to our knowledge has not been validated in dogs. While this is likely to have been associated with only minimal inaccuracies (Scott and others 2005), and the association between low ScvO₂ and poor outcome is likely to still hold, the cut-point of 68% identified in this study may not be transferable to alternate measurement methodologies adjusted to canine haemoglobin. In recognition of the study limitations, we recommend that euthanasia decisions in particular should not be made on the basis of low ScvO₂ results.

There are a number of potential future research directions. These include evaluation of the impact on patient-relevant outcomes of therapeutically targeting ScvO₂ in dogs, and evaluation of the use of ScvO₂ less than 68% as a possible transfusion trigger in dogs already optimised to volume status. A low ScvO₂ that persists or arises after the initial 2 to 3 hours of resuscitation, and in the face of normovolemia, may be a more specific marker of poor outcome than a low ScvO₂ identified at any time-point. Finally, investigation of the relationship between ScvO₂ and SO₂ on a sample obtained by jugular venepuncture might widen the accessibility of this parameter further, as jugular sampling is routine in veterinary practice.

In conclusion, drop in ScvO₂ below 68% was a risk factor for poor outcome in a cohort of canine ICU patients with a broad spectrum of primary diagnoses. Continued decline of ScvO₂ below 68% was associated with a steady increase in mortality risk. Monitoring of the ScvO₂ parameter should be considered, particularly in high-risk patients. A low ScvO₂ may appropriately serve as an alert for additional diagnostics and increased clinical supervision, with consideration of the physiologic mechanisms outlined in Fig 1. Clinical use of the sensitivity and specificity results to prognosticate individual patients is not recommended, and euthanasia decisions should not be made based on ScvO₂ results. Further work is needed to determine if therapeutic intervention directed at normalising ScvO₂ can reduce mortality and morbidity in canine ICU patients.

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Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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