

# Lactate in Veterinary Critical Care: Pathophysiology and Management

The measurement of blood lactate in people has proven to be a useful tool in the diagnosis, monitoring, and prognosis of a wide range of clinical syndromes. Its use in small animals is increasing, and several studies have been completed that demonstrate its potential role in critical care. This article summarizes the current state of knowledge regarding the physiology and pathophysiology of lactate production and lactic acidosis; current indications and the utility of measurement in a critical care setting are described; novel applications in the evaluation of cavitory effusions are highlighted; and a guide to the therapy of lactic acidosis is presented. *J Am Anim Hosp Assoc* 2007;43:270-279.

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## Introduction

Hyperlactatemia and lactic acidosis occur commonly in veterinary critically ill patients having clinical disorders such as shock, low cardiac output states, acute liver failure, severe sepsis, neoplasia, seizure, poisoning, and drug therapy.<sup>1-5</sup> With the advent of hand-held lactate analyzers that are inexpensive and readily available, lactate is rapidly becoming a valuable test in the armamentarium of clinicians in the assessment of lactate kinetics and response to therapy. In addition to reflecting the systemic repercussions of various disease states, increased attention is being focused on the use of lactate as a diagnostic tool and prognostic indicator in cavitory effusions.<sup>2,6-22</sup> The purposes of this article are to summarize the physiology and pathophysiology of lactate production and lactic acidosis, to describe current indications for measurement, to highlight novel applications in the evaluation of cavitory effusions, and to present a guide to therapy of lactic acidosis.

## Definitions

The following definitions are based on human definitions. Hyperlactatemia is usually a mild to moderate (2 to 5 mmol/L<sup>-1</sup>) increase in lactate concentration without concurrent metabolic acidosis. Lactic acidosis is a persistently elevated (often >5 mmol/L<sup>-1</sup>) lactate concentration in association with metabolic acidosis (pH<7.35).

Studies in dogs and cats have investigated normal lactate levels and identified the presence of hyperlactatemia, although a precise definition of lactic acidosis in dogs and cats has not yet been determined. The following section summarizes studies of normal lactate levels in dogs and cats published to date.

## Normal Plasma Lactate Levels

It is important to realize that lactate is produced under normal conditions of aerobic metabolism in low concentrations. This equates to lactate production of approximately 0.8 mmol/L<sup>-1</sup> per kg<sup>-1</sup> per hour<sup>-1</sup> in people,

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resulting in a resting value of  $<1$  mmol/L.<sup>23-25</sup> Similarly, several studies have investigated resting lactate values in dogs and cats, the findings of which are summarized below. These provide guidelines as to the normal range of values for plasma lactate.

An earlier study aiming to establish baseline values for plasma lactate in healthy beagles, ranging in age from 5 to 9 months, reported a mean (range) of plasma lactate concentrations of 1.11 (0.42 to 3.58) mmol/L.<sup>26</sup> Samples were analyzed using an enzymatic technique, and samples were collected from a jugular vein.

A study by McMichael *et al.*, aimed to generate a reference range for plasma lactate values in young (4- to 80-day-old) and adult, healthy, mixed-breed dogs. Thirty to 52 dogs were sampled at each age level.<sup>27</sup> Adult dogs were found to have a mean ( $\pm$  standard deviation [SD]) plasma lactate concentration of  $1.80 \pm 0.84$  mmol/L.<sup>27</sup> Dogs aged 70 or 80 days at the time of sampling did not have a statistically significant difference in lactate levels when compared with adult dogs. In contrast, resting lactate levels were higher in dogs  $<70$  days of age, with the highest values found in the youngest sampling group (4-day-old dogs;  $3.83 \pm 1.38$  mmol/L). Lactate levels decreased from age 4 days to 70 days, reaching adult values at 70 days of age. Samples were analyzed using enzymatic amperometry (see below), and all samples were taken from a jugular vein.

A study investigating the effect of sampling site on plasma lactate measurements reported that samples from the jugular vein of 60 healthy, adult dogs revealed a mean  $\pm$  SD of  $1.25 \pm 0.49$  mmol/L.<sup>28</sup> Furthermore, although there was a significant difference between samples obtained from different sites, this difference was small, and it was suggested that normal plasma lactate values in dogs are  $<2.5$  mmol/L regardless of sampling site.<sup>28</sup>

From the above studies, it can be concluded that in healthy, adult dogs at rest, lactate concentrations are  $<2.0$  mmol/L, although the normal range may extend up to approximately 3.5 mmol/L.

In cats, two studies have reported plasma lactate concentrations that were sampled from the jugular vein in healthy, adult animals. One study investigating differences between 12 healthy and diseased cats reported lactate levels of  $1.6 \pm 1.0$  mmol/L in the healthy population.<sup>29</sup>

A second study, with the aim of recording the effect of a standardized stressor (bathing) on various biochemical values, including lactate, reported mean (range) resting lactate levels of 0.77 (0.30 to 1.69) mmol/L.<sup>30</sup> This study also demonstrated a 10-fold increase in lactate levels in response to the stress of bathing. This increase was transient.

In summary, plasma lactate concentrations in healthy, adult cats at rest are  $<2$  mmol/L. However, this concentration is derived from the small number of animals studied, and acute stress/struggling may have a marked impact on lactate concentration.<sup>30</sup>

Ideally, reference ranges should be developed by individual hospitals for their patient population, and they should be specific to the lactate analyzer in use. Most

blood-gas analyzers (bench-top and hand-held) use enzymatic amperometry specific to the measurement of L-lactate. Hand-held point-of-care analyzers are now easily available, inexpensive, and they compare favorably to bench-top analyzers.<sup>31,32</sup>

Enzymatic amperometry involves the indirect measurement of a substance of interest (in this case, lactate) by the enzyme-driven generation of an electroactive analyte. A commonly employed technique uses the enzyme lactate oxidase. Lactate oxidase, immobilized in the lactate biosensor, selectively converts lactate to pyruvate and hydrogen peroxide ( $H_2O_2$ ). The liberated hydrogen peroxide (the electroactive analyte) is oxidized at a platinum electrode to produce a current that is proportional to the sample lactate concentration. Another electroactive analyte in common use is potassium ferrocyanide—this time generated by the enzymatic activity of lactate oxidase upon lactate and potassium ferricyanide.

Blood chemistry analyzers often use a spectrophotometric method, whereby the oxidation of L-lactate by oxidized nicotinamide adenine dinucleotide (NAD<sup>+</sup>) is catalyzed by lactate dehydrogenase, producing reduced nicotinamide adenine dinucleotide (NADH). The NADH is then detected using spectrophotometry at a wavelength of 340 nanometer. The levels of NADH are in linear proportion to the level of L-lactate in the sample.

### Sampling Techniques

Clinicians should be aware of several potential pitfalls regarding sampling techniques. The sampling site can have a minor effect on the measurement of lactate levels, particularly as peripheral venous samples will tend to reflect regional lactate kinetics. A study of 60 healthy dogs identified the following variations in lactate levels: cephalic vein ( $1.57 \pm 0.47$  mmol/L), femoral artery ( $1.43 \pm 0.52$  mmol/L), and jugular vein ( $1.25 \pm 0.49$  mmol/L).<sup>28</sup> Although it is clear that sampling sites do affect lactate measurement, these differences do not appear to be clinically significant. Theoretically, arterial samples would better reflect systemic lactate concentrations, as they are less influenced by regional differences in lactate kinetics.<sup>28,33</sup> It is also possible to have a mild increase in lactate levels with prolonged occlusion of a vein when drawing the blood sample for lactate analysis.<sup>34</sup> When venous samples are taken, blood stasis should be avoided by collecting the sample using a free-flow technique. Stress and struggling (induced by bathing) was demonstrated to result in a tenfold increase in plasma lactate concentrations in cats.<sup>30</sup> This should be taken into account when interpreting lactate levels in light of clinical history.

As red blood cells do not contain mitochondria, they are lactate producers. Lactate production by red blood cells continues following blood sampling.<sup>29</sup> Lactate concentrations may increase by as much as 20% during each hour of storage at 25°C in serum clot tubes.<sup>29</sup> This may be clinically significant given the relatively narrow normal range for lactate. Therefore, it is essential that blood samples are analyzed rapidly ( $<5$  minutes) following sampling.

Alternatively, samples may be temporarily stored on ice, although this does not arrest lactate production.

Blood samples submitted for laboratory analysis should be collected in tubes containing sodium fluoride (NaF). Sodium fluoride inhibits several glycolytic enzymes, limiting significant increases in lactate levels (and cellular consumption of glucose).<sup>29</sup> The reported means for NaF and serum clot samples in this study were  $1.6 \pm 1.0$  mmol/L and  $2.0 \pm 1.1$  mmol/L, respectively. Again, it is debatable if such a difference would affect clinical decision making.

A human study demonstrated that intravenous fluid solutions containing lactate, which are inadequately cleared from intravenous catheters, can falsely increase the lactate concentrations measured in blood samples collected from that catheter.<sup>35</sup> The reverse is also true, in that solutions that do not contain lactate, which are inadequately cleared from intravenous catheters, can falsely decrease blood lactate concentrations through a dilutional effect.<sup>35</sup> This emphasizes the importance of proper blood collection technique if samples are to be drawn through indwelling intravenous catheters. In addition, solutions containing 5% dextrose, in either normal saline or Ringer's lactate, have been shown to result in significant increases in blood lactate concentration over time.<sup>36</sup>

### Lactate Physiology and Pathophysiology

Several in-depth reviews of lactate physiology and pathophysiology exist, and what follows is an overview of lactate metabolism.<sup>33,34,37</sup>

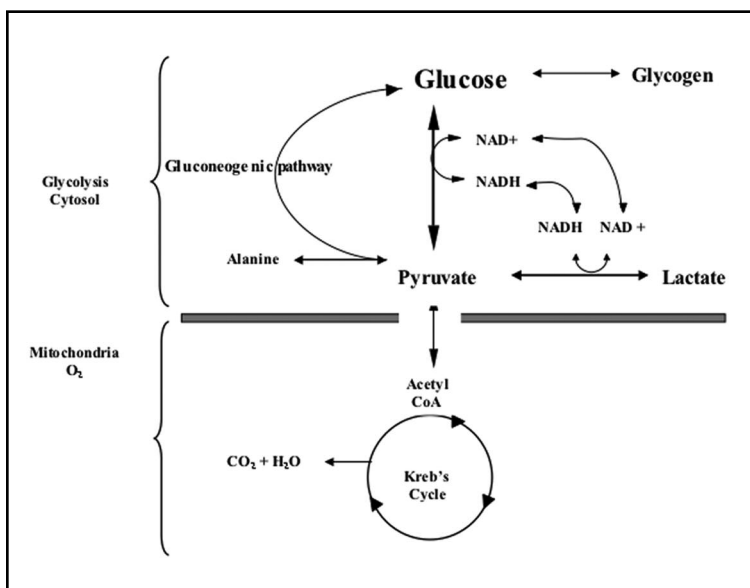
It should be noted that lactate exists as a pair of stereoisomers (more specifically, enantiomers). The following discussion pertains to the L (+) stereoisomer of lactate, as this is the stereoisomer produced by mammalian cells and has greater clinical significance. Accumulation of the D (-) stereoisomer and subsequent lactic acidosis have been reported in people and ruminants.<sup>38,39</sup> D-lactate is produced following metabolism of glucose and carbohydrates by

bacteria in the gastrointestinal tract. In man, this has been associated with short-bowel syndrome following significant small intestinal resection. In ruminants, D-lactic acidosis has been associated with grain overload, as well as diarrhea in calves.<sup>39,40</sup>

Lactate may be produced by all body tissues as a byproduct of glycolysis. However, skeletal muscle, brain, erythrocytes, and renal medulla are responsible for the majority of normal production.<sup>25</sup>

Under normal conditions, all lactate is derived from pyruvate, which is generated as a normal step in glycolysis [see Figure].<sup>41</sup> This reaction is catalyzed by lactate dehydrogenase. Under aerobic conditions, the majority of pyruvate enters mitochondria and undergoes oxidative decarboxylation, resulting in the production of carbon dioxide and water and the generation of 30 to 36 moles of adenosine triphosphate (ATP) per molecule of glucose metabolized.<sup>42</sup> Under anaerobic conditions, including states of hypoperfusion, pyruvate can no longer undergo oxidative decarboxylation, and energy production becomes predominantly dependent on the process of glycolysis. The generation of ATP in anaerobic states is greatly reduced (2 moles of ATP for every mole of glucose metabolized to lactate) compared with aerobic metabolism.<sup>42</sup> Despite being an inefficient means of energy production, anaerobic metabolism does allow for the continued production of energy. The metabolism of pyruvate results in the production of lactate and water [see Figure]; thus, lactate formation is a necessary and critical step in the process of anaerobic metabolism and continued ATP production.

The relatively small quantity of lactate produced under normal conditions is consumed primarily by the liver and kidneys.<sup>34,37</sup> Within these organs, lactate is converted back to pyruvate, the reaction catalyzed by lactate dehydrogenase. The majority of the produced pyruvate then enters into oxidative metabolism (Kreb's cycle) or gluconeogenesis (Cori cycle [see Figure]).



**Figure**—The majority of the metabolically derived pyruvate originates from glucose (or glycogen) via glycolysis. Pyruvate can have several metabolic fates: oxidation via the Kreb's cycle for energy production, conversion to lactate with recycling of oxidized nicotinamide adenine dinucleotide (NAD<sup>+</sup>), or transformation into glucose via gluconeogenic pathways (via the Cori cycle). Lactate that is produced will ultimately be reconverted to pyruvate.

The liver accounts for the majority (60% to 70%) of lactate consumption, and experimental hepatectomy in dogs resulted in significant increases in plasma lactate levels.<sup>34,37,43</sup> Lactate is also metabolized (20% to 30%) by the kidneys, where it is freely filtered by the glomerulus (before near complete reabsorption in the proximal convoluted tubule), resulting in <2% excretion in urine.<sup>34,37,45</sup> Provided there is adequate oxygen delivery, both hepatic and renal consumption of lactate may substantially increase during hyperlactatemia to accommodate the increased lactate load.<sup>45</sup> It should be noted, however, that lactate consumption by these organs is a saturable process and that hyperlactatemia rapidly ensues when lactate production exceeds consumption.<sup>37</sup> In addition, skeletal muscle may act as an important site of lactate consumption (via oxidation) during hyperlactatemia.<sup>37</sup>

The key role of the liver in lactate homeostasis is reflected by the severe abnormalities that result from liver dysfunction. In shock states, the role of the liver as a consumer of lactate may switch to being that of a lactate producer.<sup>28,34</sup> In cases of experimental hepatic insufficiency in dogs, metabolism of lactate continued until total hepatic blood flow fell to 70% of control levels, or until hepatic venous partial pressure of oxygen (PO<sub>2</sub>) was <24 mm Hg, at which point plasma lactate concentrations rapidly increased.<sup>46</sup> The role of the liver as the primary consumer of lactate, accounting for 60% to 70% of lactate consumption, highlights the importance of reinstating adequate hepatic perfusion and oxygen delivery during therapy for states of hypoperfusion, such as shock (see following section on **Therapy**). Similarly, severe renal hypoperfusion (i.e., a 90% decrease in renal blood flow) results in a switch from renal consumption of lactate to production.<sup>47</sup>

Hyperlactatemia may exist without a concurrent state of acidosis or acidemia. The hydrogen ions necessary for lactic acid formation are not produced as a direct result of lactate production. Instead, hydrogen ions are generated from the hydrolysis of ATP to adenosine diphosphate (ADP) and inorganic phosphate in the cytosol. Ordinarily, the hydrogen ions produced may be titrated by bicarbonate and nonbicarbonate buffers or consumed by oxidative phosphorylation, provided the oxygen supply is adequate. Lactic acid formation is favored when these processes are impaired, resulting in lactic acidosis. Therefore, hyperlactatemia may be present without concurrent acidosis or acidemia when buffering systems are able to titrate a decrease in pH and organ perfusion is adequate.<sup>48</sup>

During recovery from a state of lactic acidosis or hyperlactatemia, the availability of oxygen results in conversion of lactate back into pyruvate (catalyzed by lactate dehydrogenase) and subsequent entry into the Krebs cycle as aerobic metabolism continues, or gluconeogenesis by entry of pyruvate into the Cori cycle [see Figure].

In summary, hyperlactatemia and lactic acidosis result when lactate production exceeds consumption and/or pathways for lactate consumption are defective. Hyperlactatemia may occur without lactic acidosis, provided tissue perfusion,

oxygenation, and buffering systems are intact. In such cases, continued overproduction or decreased uptake and clearance of lactate will eventually lead to lactic acidosis as homeostatic mechanisms are exceeded.

### Classification of Lactic Acidosis

Following initial work by Huckabee in recognizing the presence of lactic acidosis, with and without adequate oxygen delivery, Cohen and Woods developed a classification of lactic acidosis.<sup>23,24,34</sup> The broad divisions of the original classification have remained, with some refinement and new examples added over time. Originally, type A lactic acidosis encompassed all causes of hypotension with resultant hypoperfusion and arterial oxygen desaturation. Type B lactic acidosis originally described any cases that did not fall into the type A classification; that is, lactic acidosis cases without clinical/measurable evidence of poor tissue perfusion or oxygenation. Subsequently, the original classification has been repeatedly adapted in human and veterinary medicine.

Currently, type A lactic acidosis may be subclassified as that resulting from inadequate oxygen delivery or increased oxygen demand—both of which cause tissue hypoperfusion [Table 1].<sup>25</sup> Shock is a classic example of decreased oxygen delivery, and seizures are an example of increased oxygen demand with a rapid increase in metabolic rate outstripping lactate consumption and glucose metabolism exceeding the oxidative capacity of mitochondria.<sup>49,50</sup>

In contrast, type B lactic acidosis occurs in the presence of normal blood oxygen content and systemic arterial blood pressure, the causes of which may be subclassified into inadequate utilization of oxygen, congenital errors of metabolism, drugs/toxins, and other causes [Table 2].

Type A lactic acidosis is more frequently encountered in clinical practice, although critically ill patients frequently have features of both types A and B lactic acidosis.<sup>4,51</sup>

**Table 1**

#### Causes of Type A Lactic Acidosis

Decreased Oxygen Delivery	Increased Oxygen Demand
Volume depletion <sup>1</sup>	Exercise <sup>85</sup>
Blood loss	Seizures <sup>4</sup>
Cardiogenic shock <sup>4</sup>	Shivering
Septic shock	
Severe anemia	
Severe hypoxemia <sup>46</sup>	
Carbon monoxide poisoning	

**Table 2****Causes of Type B Lactic Acidosis****Inadequate Oxygen Utilization**Systemic inflammatory response syndrome<sup>4</sup>Sepsis<sup>7</sup>

Renal failure

Diabetes mellitus

Neoplasia<sup>3,4</sup>

Total parenteral nutrition

Thiamine deficiency

**Congenital Errors of Metabolism\*****Drugs/Toxins\*****Other**

D-lactic acidosis

\* See Table 3

Note: In cases where pH was not measured, hyperlactatemia was diagnosed with a clinical suspicion of lactic acidosis.

**Table 3****Causes of Type B Lactic Acidosis Associated With Drugs/Toxins and Errors of Metabolism****Drugs/Toxins**Ethylene/propylene glycol<sup>4</sup>

Catecholamines

Cyanide

Carbon monoxide

Strychnine

Salicylates<sup>4</sup>

Nitroprusside

Bicarbonate

Halothane

Acetaminophen

Terbutaline

Activated charcoal<sup>5</sup>**Errors of Metabolism**

MELAS\*

Enzyme deficiencies†

\* MELAS=mitochondrial encephalomyopathy with lactic acidosis and stroke syndrome

† Enzyme deficiencies not believed to be of importance in dogs or cats<sup>34</sup>

Sepsis is an example that often has features involving types A and B presentations, including tissue hypoperfusion, reduced lactate clearance and entry of pyruvate into Krebs' cycle, and abnormal mitochondrial function.<sup>52</sup>

Note: Many of the examples in Tables 1 through 3 have been associated with hyperlactatemia in veterinary patients. However, it is not always clear whether a definitive diagnosis of lactic acidosis has been achieved, as blood-gas analysis has not been routinely performed or reported.<sup>1,4,7,46</sup>

**Lactic Acidosis During Shock and Sepsis**

The most common cause of lactic acidosis in dogs and cats is tissue hypoperfusion.<sup>4</sup> Therefore, hyperlactatemia and certainly lactic acidosis should prompt a search for tissue hypoperfusion. Shock is simply defined as a failure of oxygen delivery (DO<sub>2</sub>) to meet oxygen demand (VO<sub>2</sub>). Shock states stemming from various origins (e.g., hypovolemic, distributive, cardiogenic) result in a decrease in DO<sub>2</sub> and tissue hypoperfusion, generating type A lactic acidosis.

Studies in humans have consistently demonstrated the occurrence of hyperlactatemia and lactic acidosis in cases of shock.<sup>53-56</sup> Work in veterinary species associating lactic acidosis in patient subpopulations is minimal.<sup>3,5</sup> One study in critically ill dogs, including animals in shock, did identify the occurrence of hyperlactatemia.<sup>4</sup>

Sepsis is defined as a systemic inflammatory response to the presence of infection (e.g., bacterial, viral, protozoal, or fungal). Sepsis may or may not be associated with a decrease in DO<sub>2</sub>, depending on the severity and nature of the infection. Although lactic acidosis is a common finding in critically ill human patients with sepsis and a powerful predictor of mortality, the pathogenesis of this hyperlactatemia in septic patients is complex and incompletely understood.<sup>57</sup> Evidence is strong that large amounts of lactate can be produced and released under both anaerobic and aerobic conditions. It has been suggested that hyperlactatemia in sepsis results from inadequate tissue perfusion, leading to increased levels of anaerobic metabolism and reduced lactate clearance stemming from severe hypoperfusion.<sup>52</sup> Aerobic production of lactate in patients with sepsis is believed to result from accelerated glycolytic fluxes,

inhibition of the enzyme pyruvate dehydrogenase, and changes in intermediary metabolism.<sup>57</sup> The role of lactate in veterinary patients with sepsis requires further investigation, although one study in dogs with severe *Babesia* infection did document the presence of hyperlactatemia and lactic acidosis.<sup>58</sup> An extensive discussion of the pathophysiology of shock and sepsis is beyond the scope of this article and has been reviewed in depth elsewhere.<sup>59-61</sup>

### Prognostic Value of Lactate

In people, numerous studies in different critically ill patient populations have demonstrated the prognostic value of lactate levels.<sup>62-66</sup> In some cases, a single measurement of lactate levels was associated with a prognosis of survival.<sup>54,62,66</sup> However, other studies have found no significant differences in lactate levels between survivors and nonsurvivors at initial presentation, and decreased lactate levels (hours to days after presentation) in response to therapy provided a better prediction of outcome.<sup>56,63-65,67</sup> The patient populations studied included critically ill surgical patients and those with septic shock. Furthermore, hemodynamic parameters should not be disregarded, as the use of lactate levels in conjunction with assessment of systemic arterial blood pressure and/or evaluation of acid-base status have been shown in some studies to more accurately predict outcome than lactate levels alone.<sup>56,63,65,66</sup>

From the available evidence, it appears that human patients with hypotension and elevated lactate levels (>5 mmol/L) have a high mortality rate (>80%), as do patients who fail to clear lactate within 24 to 48 hours.<sup>25</sup> At present, it is unclear if these or similar conclusions apply to veterinary patients. Furthermore, it is important to note that lactate levels reflect the global, systemic situation. Individual organs or regions may be hypoxic and produce increased levels of lactate without a detectable effect systemically.

A few studies have investigated the relationship between hyperlactatemia and outcome in dogs. An early study evaluated lactate levels in dogs that were presented to an intensive care unit (ICU) with various underlying disease conditions; this study showed that dogs with the highest blood lactate levels at admission were more likely to die.<sup>4</sup> In a study investigating 102 dogs with gastric dilatation and volvulus (GDV), those with plasma lactate levels >6 mmol/L had a 58% survival rate, whereas those with values <6 mmol/L had a survival rate of 99%.<sup>1</sup> This study also found that preoperative measurement of plasma lactate levels might be useful in determining the risk of gastric necrosis in dogs with GDV.<sup>1</sup> In a more recent study evaluating lactate measurements in dogs with GDV, only one of nine dogs with a lactate level >6 mmol/L died.<sup>68</sup> Although drawing definite conclusions from the small study population (n=28) is difficult, the increased survival rate in this study emphasizes the concern of determining prognosis based on a single lactate measurement. In addition, the magnitude of a single lactate value may be misleading if taken out of context of the disease.<sup>56,63,65</sup> An early study in human patients presenting with various types of shock demonstrated that

the prognosis of lactic acidosis tends to vary with the underlying cause of hypoperfusion.<sup>55</sup> It was demonstrated in this study that patients with hemorrhagic shock tolerate higher lactate levels than patients with cardiogenic shock. In animals, prognosis also appears to vary with the underlying disease, and some animals with very high lactate values (>10 mmol/L) may still respond to resuscitative efforts and survive.<sup>4</sup> Studies in people have also demonstrated that serial lactate measurements and the change in lactate levels in response to therapy are more reliable at determining outcome than a single-admission lactate measurement (see above). These findings are further supported in a study of dogs suffering from severe or complicated canine babesiosis.<sup>58</sup> In this study, although the presence of hyperlactatemia prior to therapy was suggestive of a poor prognosis, serial lactate measurements and response to therapy were much stronger predictors of survival. Dogs with lactate levels >4.4 mmol/L after 24 hours, despite therapeutic efforts, had a very poor prognosis. To the authors' knowledge, no studies have examined the prognostic significance of blood lactate levels in cats, although clinical experience would suggest a similar relationship exists.

### Lactate Measurement in Cavitory Effusions

The value of measuring lactate concentration in body fluids other than blood has been investigated. Body fluid lactate concentrations may increase from diverse processes, including reduced blood flow, hypoxia, and the increased production of lactate by granulocytic or bacterial metabolism when these cells are present in the body fluids.<sup>22</sup>

#### Abdominal Fluid

A study by Levin *et al.* found increased (>2.5 mmol/L) lactate concentrations in abdominal fluid from dogs with septic bacterial effusions when compared to nonseptic effusions.<sup>7</sup> A similar study by Swan *et al.* concluded that lactate levels >5.5 mmol/L in abdominal effusions were strongly suggestive of bacterial peritonitis.<sup>20</sup> Nestor *et al.* found lactate concentrations were also increased (mean 3.81±1.6 mmol/L) in abdominal fluid from dogs with neoplastic effusions when compared to dogs with nonneoplastic effusions.<sup>6</sup> Lactate concentrations are believed to be elevated in septic effusions due to bacterial metabolites and neutrophilic glycolysis.<sup>22</sup> One might also expect to see elevated lactate levels secondary to neutrophilic glycolysis in nonseptic, highly suppurative effusions. Neoplastic cells have been shown to use anaerobic glycolysis for energy, thereby producing lactate, which may explain the increased lactate levels in the abdominal fluid of dogs with neoplastic effusions.<sup>6</sup> In an effort to increase the accuracy of detecting bacterial abdominal effusions, Levin *et al.* examined the abdominal fluid to peripheral blood lactate gradient and found that a difference of >2 mmol/L was 63% sensitive and 100% specific for the detection of septic effusions in dogs, while an abdominal fluid to peripheral blood lactate gradient >0.5 mmol/L was 78% sensitive and 78% specific at detecting septic abdominal effusions in cats.<sup>7</sup> Unfortunately, the number of cases in this

study was small (19 dogs and 18 cats), and future studies using a larger number of cases with more diverse disease processes should be performed to further evaluate the diagnostic significance of lactate concentrations in abdominal effusions.

It is clear that conclusions regarding the value of lactate concentrations in abdominal fluid of small animals are conflicting, and, in light of the current veterinary literature, high abdominal fluid lactate levels ( $>2.5$  mmol/L) should prompt consideration of septic or neoplastic processes. Conclusions should also be interpreted in conjunction with patient history, physical examination, and other clinical findings. Abdominal fluid to peripheral blood lactate differences  $>2$  mmol/L in dogs or cats warrant a search for underlying bacterial infection.<sup>7</sup>

### *Synovial Fluid*

The value of lactate concentrations in synovial fluid has been investigated in humans. Data suggest that low synovial fluid lactate levels can be valuable in rapidly excluding a diagnosis of septic arthritis with a negative predictive value of 98%.<sup>10</sup> When differentiating septic arthritis from other forms of inflammatory arthritis (rheumatoid), the value of synovial fluid lactate concentrations is less clearly defined, as both septic and nonseptic forms of arthritis have been shown to result in increased lactate levels.<sup>15</sup>

### *Pericardial Fluid*

Pericardial fluid lactate concentrations were investigated in dogs as a potential diagnostic aid in differentiating pericardial effusions associated with neoplasia from those effusions believed to be nonneoplastic in origin.<sup>2</sup> The pericardial effusion was considered neoplastic in origin if echocardiography identified a mass associated with the heart or pericardium, or if histopathology of a surgical biopsy, cytology of the effusion, or postmortem examination supported the diagnosis of neoplasia. The pericardial effusion was considered nonneoplastic on the basis of surgical biopsy, postmortem examination, or failure to identify a mass with echocardiography and survival at 1 year of age. Although a statistically significant difference in median (range) values was found between suspected neoplastic pericardial effusions (9.1 mmol/L [1.9 to 12.5 mmol/L]) and pericardial effusions believed to be benign (3.7 mmol/L [1.3 to 12.7 mmol/L]), the authors concluded that too great an overlap existed between the two groups to make lactate a useful diagnostic aid in differentiating neoplastic from nonneoplastic causes of pericardial effusions.<sup>2</sup>

### *Pleural Fluid*

Lactate levels have also been measured in pleural fluid accumulations in people, and, similar to results in abdominal fluid, the finding of a low lactate level makes a septic process unlikely. A high level is most often associated with sepsis, although other nonseptic processes (e.g., tuberculosis and some forms of neoplasia) may also cause raised pleural lactate concentrations.<sup>9,13,18</sup>

### *Cerebrospinal Fluid (CSF)*

Lactate levels have also been evaluated in the CSF of people. Plasma lactate is in an ionized form within the normal physiological range of pH, and, as such, its transfer across the blood-brain barrier is limited. This makes analysis of CSF lactate largely independent of plasma lactate concentrations.<sup>21,69</sup> Levels of CSF lactate may serve as predictors of morbidity and mortality when associated with status epilepticus.<sup>8</sup> In addition, CSF lactic acidosis, which implies brain tissue acidosis, may play a role in the clinical course of severe head injury.<sup>11,12,70</sup> Over a 4-day post-trauma period, patients with a post-traumatic brain injury and poor outcome had a higher ventricular CSF lactate level than patients with moderate disabilities or a good outcome.<sup>11</sup> Serial measurements of cerebral-arterial lactate difference (the difference between jugular bulb and arterial lactate concentrations) have also been found to correlate with the severity of brain injury and outcome in patients with traumatic brain injury.<sup>16</sup> Finally, CSF lactate levels have been shown to correlate with the presence of bacterial meningitis, although elevated lactate levels have also been reported in people with viral infections.<sup>14,17</sup> As D-lactate is not produced by mammalian cells and is only produced by bacterial metabolism, its presence in CSF fluid was found to be highly sensitive (92%) and specific (99%) for the presence of bacterial meningitis.<sup>19</sup> To the authors' knowledge, no clinical veterinary studies have looked at CSF lactate levels in dogs or cats in association with brain or spinal cord disorders.

### **Therapy**

Type A lactic acidosis unto itself is not a disease, but rather a consequence of decreased  $DO_2$  to the tissues or increased  $VO_2$  [Table 1], which may reflect an underlying disease process or transient imbalance in homeostasis. Therefore, the therapy for type A lactic acidosis must be directed toward identifying and treating the underlying cause while simultaneously improving  $DO_2$  to the tissues. Appropriate resuscitative efforts include restoration of the effective circulating volume, improving or increasing cardiac function, resection of ischemic or necrotic tissue, and correction of septic conditions.<sup>61,71</sup> In the absence of cardiac disease, which may preclude fluid therapy, this will usually involve aggressive fluid resuscitation using crystalloids, colloids, blood products, or a combination thereof.<sup>61</sup> As hemoglobin content is an important component in determining  $DO_2$ , animals with concurrent acute anemia may benefit from a blood transfusion to maintain the hematocrit  $>18\%$  to  $21\%$ .<sup>72</sup> Acute hemodilution to a hematocrit  $<10\%$  is associated with hyperlactatemia.<sup>72</sup> In people, it has been suggested that persistent hyperlactatemia in the face of appropriate resuscitative efforts warrants a poor prognosis, and a search for an undiagnosed underlying cause (such as an unidentified focus of infection) should be undertaken.<sup>73</sup> Although not investigated, one can infer that similar results will be found in dogs and cats. If a septic focus is identified, the source should be removed as soon as the animal is

stabilized. This may require surgical intervention. When assessing lactate in regard to the patient's response to therapy, it is important to remember that lactate dynamics vary with the cause of hyperlactatemia, and, therefore, the expected decline following resuscitative efforts will also vary. For example, the half-life of lactate (i.e., the time for plasma lactate concentrations to decrease by 50%) during seizures in people is approximately 60 minutes with little, if any, impairment of lactate metabolism.<sup>74</sup> In contrast, the half-life of lactate in human patients with shock may be as long as 18 hours.<sup>73</sup> This difference in lactate half-life may be the result of a decrease in clearance of lactate, a persistent increase in its production, or a combination of the two in hypovolemic or septic patients.<sup>75,76</sup> To the authors' knowledge, the half-life of lactate in healthy dogs and cats and in patients with various underlying states of hypoperfusion has not been investigated. In people with circulatory shock, it has been suggested that if after 1 hour of aggressive therapy a decrease in lactate of >10% is not achieved, a change in therapy should be considered.<sup>74</sup> In the authors' experience, the decrease in lactate concentration following successful aggressive therapy for circulatory shock is often significantly >10% within 1 hour, although it does tend to vary with the underlying cause of shock.

A common concern that is frequently encountered in treating patients with lactated Ringer's solution (LRS) is whether the lactate contained within this fluid will influence blood lactate values. Lactated Ringer's solution contains 28 mmol/L of sodium lactate in the form of a racemic mixture (containing both D- and L-isomers of lactate in varying concentrations, depending on the product used).<sup>77</sup> Interestingly, it has been demonstrated in human and canine studies that LRS administered as a 15 to 20 mL/kg bolus does not result in a significant change in plasma L-lactate concentrations in normal subjects and those with hemorrhagic shock.<sup>36,78,79</sup> This is likely explained by analyzers measuring only the L-isomer and not the D-isomer of lactate contained in LRS.<sup>33</sup> The dilution and metabolism of L-lactate following its administration may also minimize any increases in lactate that might otherwise have occurred.<sup>36</sup> In contrast, when measured using specific enzyme analyzers, D-lactate levels in swine have been shown to increase up to 20-fold following large boluses of LRS.<sup>80</sup> The clinical significance of an increase in D-lactate following the administration of LRS remains to be determined. However, as most analyzers do not detect it, any increase in the D-isomer concentration should not affect interpretation of lactate measurements. To the authors' knowledge, no studies in dogs or cats have evaluated the effect of large boluses (60 to 90 mL/kg) of LRS on plasma lactate concentrations. The administration of LRS at a rate of 4.125 mL/kg per hour for 6 hours to dogs with lymphoma resulted in a transient increase in the L-isomer concentration.<sup>3</sup> It was concluded that dogs with lymphoma have a transient inability to handle an increased lactate load and that lactate-containing fluids should be used cautiously in dogs with lymphoma.<sup>3</sup> It is possible that patients with impaired liver and/or renal function may also

have increased levels of lactate following administration of lactate-containing solutions, which could make the interpretation of hyperlactatemia difficult in these patients.

The administration of sodium bicarbonate to patients with lactic acidosis has received a lot of attention, and the current general consensus is that sodium bicarbonate is not of benefit in the therapy of most cases of lactic acidosis.<sup>25,45,71,81</sup> Following successful resuscitative efforts with improved DO<sub>2</sub> to the tissues, pH will often improve as the metabolism of lactate is accompanied by a concurrent increase in bicarbonate production by the liver.<sup>73</sup> This may result in an overshoot alkalosis in cases that previously received sodium bicarbonate. Further detrimental effects associated with the administration of sodium bicarbonate include a transient fall in mean arterial pressure and an increase in intracranial pressure following rapid intravenous administration, decreased ionized calcium concentration (which may affect left ventricular contractility), decreased DO<sub>2</sub> through decreased unloading of oxygen from hemoglobin at the tissue level (Bohr effect), and paradoxical central nervous system acidosis (especially in patients that are hypercarbic due to hypoventilation).<sup>81-84</sup>

Although hypoperfusion is the most common cause of lactic acidosis, it is important to consider other causes (type B) and look for supporting evidence of impaired DO<sub>2</sub> in patients presenting with hyperlactatemia. Supporting evidence of impaired DO<sub>2</sub> may include tachycardia, pale mucous membranes, weak pulses, prolonged capillary refill time, decreased mentation, and hypotension. For example, it would be inappropriate to institute shock therapy for treatment of hyperlactatemia in the lymphoma patient that is hemodynamically stable with normal tissue perfusion. As type B lactic acidosis, by definition, is not associated with tissue hypoxia, its therapy does not usually require the same emergency interventions associated with type A lactic acidosis.<sup>71</sup> In addition, very little information is available regarding nonacidotic hyperlactatemia or type B lactic acidosis in dogs and cats, and further studies are required before recommendations regarding outcomes or therapy can be made in these patients. However, the presence of hyperlactatemia in symptomatic and asymptomatic cancer patients, or in those receiving medications such as activated charcoal, may confound the assessment of lactate levels in animals presented with life-threatening conditions. As is the case for type A lactic acidosis, type B lactic acidosis is the result of an underlying disease process, and therapy is generally directed at identifying and correcting the underlying disease.

## Conclusion

Lactate measurement is a very useful diagnostic test, which may be performed at the bedside. It aids in the detection of hypoperfusion (the most common cause of lactic acidosis in veterinary species), and it has prognostic implications for type A lactic acidosis and its treatment. Lactate measurement may also prove useful in helping to detect or rule out the presence of a septic effusion in various cavity effusions,



and it may have prognostic implications when measured in fluids such as CSF following trauma. Published studies in veterinary medicine are few at this time, and future studies will likely further define the role of lactate in the diagnosis and management of dogs and cats presenting to the ICU.

## References

- de Papp E, Drobatz KJ, Hughes D. Plasma lactate concentration as a predictor of gastric necrosis and survival among dogs with gastric dilatation-volvulus: 102 cases (1995-1998). *J Am Vet Med Assoc* 1999;215:49-52.
- de Laforcade AM, Freeman LM, Rozanski EA, *et al.* Biochemical analysis of pericardial fluid and whole blood in dogs with pericardial effusion. *J Vet Intern Med* 2005;19:833-836.
- Vail DM, Ogilvie GK, Fettman MJ, *et al.* Exacerbation of hyperlactatemia by infusion of lactated Ringer's solution in dogs with lymphoma. *J Vet Intern Med* 1990;4:228-232.
- Lagutchik MS, Ogilvie GK, Hackett TB, *et al.* Increased lactate concentrations in ill and injured dogs. *J Vet Emerg Crit Care* 1998;8:117-127.
- Burkitt JM, Haskins SC, Aldrich J, *et al.* Effects of oral administration of a commercial activated charcoal suspension on serum osmolality and lactate concentration in the dog. *J Vet Intern Med* 2005;19:683-686.
- Nestor DD, McCullough SM, Schaeffer DJ. Biochemical analysis of neoplastic versus nonneoplastic abdominal effusions in dogs. *J Am Anim Hosp Assoc* 2004;40:372-375.
- Levin GM, Bonczynski JJ, Ludwig LL, *et al.* Lactate as a diagnostic test for septic peritoneal effusions in dogs and cats. *J Am Anim Hosp Assoc* 2004;40:364-371.
- Calabrese VP, Gruemer HD, James K, *et al.* Cerebrospinal fluid lactate levels and prognosis in status epilepticus. *Epilepsia* 1991;32:816-821.
- Chavalittamrong B, Angsusingha K, Tuchinda M, *et al.* Diagnostic significance of pH, lactic acid dehydrogenase, lactate and glucose in pleural fluid. *Respiration* 1979;38:112-120.
- Curtis GD, Newman RJ, Slack MP. Synovial fluid lactate and diagnosis of septic arthritis. *J Infect* 1983;6:239-246.
- DeSalles AA, Kontos HA, Becker DP, *et al.* Prognostic significance of ventricular CSF lactic acidosis in severe head injury. *J Neurosurg* 1986;65:615-624.
- Enevoldsen EM, Jensen FT. Cerebrospinal fluid lactate and pH in patients with acute severe head injury. *Clin Neurol Neurosurg* 1977;80:213-225.
- Gastrin B, Lovestad A. Diagnostic significance of pleural fluid lactate concentration in pleural and pulmonary diseases. *Scand J Infect Dis* 1988;20:85-90.
- Genton B, Berger JP. Cerebrospinal fluid lactate in 78 cases of adult meningitis. *Intensive Care Med* 1990;16:196-200.
- Gobelet C, Gerster JC. Synovial fluid lactate levels in septic and non-septic arthritides. *Ann Rheum Dis* 1984;43:742-745.
- Murr R, Stummer W, Schurer L, *et al.* Cerebral lactate production in relation to intracranial pressure, cranial computed tomography findings, and outcome in patients with severe head injury. *Acta Neurochir (Wien)* 1996;138:928-937.
- Nelson N, Eeg-Olofsson O, Larsson L, *et al.* The diagnostic and predictive value of cerebrospinal fluid lactate in children with meningitis. Its relation to current diagnostic methods. *Acta Paediatr Scand* 1986;75:52-57.
- Pettersson T, Ojala K, Weber TH. Diagnostic significance of pleural fluid lactate concentrations. *Infection* 1985;13:257-259.
- Smith SM, Eng RH, Campos JM, *et al.* D-lactic acid measurements in the diagnosis of bacterial infections. *J Clin Microbiol* 1989;27:385-388.
- Swann H, Hughes D. Use of abdominal fluid pH, pO<sub>2</sub>, [glucose], and [lactate] to differentiate bacterial peritonitis from non-bacterial causes of abdominal effusion in dogs and cats. Proceed International Veterinary Emergency and Critical Care Society meeting, San Antonio, TX 1996:884.
- Venkatesh B, Scott P, Ziegenfuss M. Cerebrospinal fluid in critical illness. *Crit Care Resusc* 2000;2:42-54.
- Watson MA, Scott MG. Clinical utility of biochemical analysis of cerebrospinal fluid. *Clin Chem* 1995;41:343-360.
- Huckabee WE. Abnormal resting blood lactate. I. The significance of hyperlactatemia in hospitalized patients. *Am J Med* 1961;30:833-839.
- Huckabee WE. Abnormal resting blood lactate. II. Lactic acidosis. *Am J Med* 1961;30:840-848.
- Fall PJ, Szerlip HM. Lactic acidosis: from sour milk to septic shock. *J Intensive Care Med* 2005;20:255-271.
- Evans GO. Plasma lactate measurements in healthy beagle dogs. *Am J Vet Res* 1987;48:131-132.
- McMichael MA, Lees GE, Hennessey J, *et al.* Serial plasma lactate concentrations in 68 puppies aged 4 to 80 days. *J Vet Emerg Crit Care* 2005;15:17-21.
- Hughes D, Rozanski ER, Shofer FS, *et al.* Effect of sampling site, repeated sampling, pH, and PCO<sub>2</sub> on plasma lactate concentrations in healthy dogs. *Am J Vet Res* 1999;60:521-524.
- Christopher MM, O'Neill S. Effect of specimen collection and storage on blood glucose and lactate concentrations in healthy, hyperthyroid and diabetic cats. *Vet Clin Pathol* 2000;29:22-28.
- Rand JS, Kinnaird E, Baglioni A, *et al.* Acute stress hyperglycemia in cats is associated with struggling and increased concentrations of lactate and norepinephrine. *J Vet Intern Med* 2002;16:123-132.
- Thorneloe C, Bedard C, Boysen S. Evaluation of a hand held lactate analyzer in dogs. *Can Vet J* 2007;48:283-287.
- Karagiannis M, Mann F, Wagner-Mann C, *et al.* Comparison of a dry chemistry lactate meter (Accutrend) and a wet chemistry lactate analyzer (I-STAT) for the determination of blood lactate in dogs. *J Vet Emerg Crit Care* 2006;16:S11.
- Lagutchik MS, Ogilvie GK, Wingfield WE, *et al.* Lactate kinetics in veterinary critical care: a review. *J Vet Emerg Crit Care* 1996;6:81-95.
- Cohen RD, Woods HF. Clinical and biochemical aspects of lactic acidosis. 1st ed. Osney Meade, Oxford, UK: Blackwell Scientific, 1976.
- Jackson EV Jr, Wiese J, Sigal BS, *et al.* Effects of crystalloid solutions on circulating lactate concentrations: Part I. Implications for the proper handling of blood specimens obtained from critically ill patients. *Crit Care Med* 1997;25:1840-1846.
- Didwania A, Miller J, Kassel D, *et al.* Effect of intravenous lactated Ringer's solution infusion on the circulating lactate concentration: part 3. Results of a prospective, randomized, double-blind, placebo-controlled trial. *Crit Care Med* 1997;25:1851-1854.
- Madias NE. Lactic acidosis. *Kidney Int* 1986;29:752-774.
- Oh MS, Phelps KR, Traube M, *et al.* D-lactic acidosis in a man with short-bowel syndrome. *N Engl J Med* 1979;301:249-252.
- Dunlop DH, Hammond PB. D-lactic acidosis of ruminants. *Annals of the New York Academy of Sciences* 1965;119:1061-1065.
- Grude T, Lorenz I, Rademacher G, *et al.* Levels of D- and L-lactate in rumen liquid, blood, and urine in calves with and without evidence of ruminal drinking. In: Proceed 32nd Annual Conference of the American Association of Bovine Practitioners, Nashville, TN 1999:213-214.
- Gauthier PM, Szerlip HM. Metabolic acidosis in the intensive care unit. *Crit Care Clin* 2002;18:1-20.
- Stryer L. Oxidative Phosphorylation. In: Stryer L, ed. *Biochemistry*. 4th ed. New York, NY: WH Freeman and Company, 1995:529-558.
- Arieff AI, Park R, Leach WJ, *et al.* Pathophysiology of experimental lactic acidosis in dogs. *Am J Physiol* 1980;239:F135-F142.
- De Backer D. Lactic acidosis. *Intensive Care Med* 2003;29:699-702.
- Bellomo R. Bench-to-bedside review: lactate and the kidney. *Crit Care* 2002;6:322-326.

46. Tashkin DP, Goldstein PJ, Simmons DH. Hepatic lactate uptake during decreased liver perfusion and hypoxemia. *Am J Physiol* 1972;223:968-974.
47. Nellimarkka O, Halkola L, Ninikoski J. Renal hypoxia and metabolism in hemorrhagic shock in dogs. *Crit Care Med* 1984;12:656-660.
48. Divatia JV, Kulkarni AP. Lactic acidosis in the intensive care unit: pathophysiology and management. *Indian Journal of Critical Care Medicine* 2001;2:94-101.
49. Levy B, Bollaert BE, Charpentier C, *et al.* Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. *Intensive Care Med* 1997;23:282-287.
50. Orringer CE, Eustace JC, Wunsch WD, *et al.* Natural history of lactic acidosis after grand-mal seizures. *N Engl J Med* 1977;297:796-799.
51. Stacpoole PW, Wright EC, Baumgartner TG, *et al.* Natural history and course of acquired lactic acidosis in adults. *Am J Med* 1994;97:47-54.
52. Cariou A, Vinsonneau C, Dhainaut J-F. Adjunctive therapies in sepsis: an evidence-based review. *Crit Care Med* 2004;32:S562-S570.
53. Weil MH, Afifi AA. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). *Circulation* 1970;41:989-1001.
54. Weil MH, Ruiz CE, Michaels S, *et al.* Acid-base determinants of survival after cardiopulmonary resuscitation. *Crit Care Med* 1985;13:888-892.
55. Vitek V, Cowle RA. Blood lactate in the prognosis of various forms of shock. *Annals of Surgery* 1971;173:308-313.
56. Bakker J, Gris P, Coffernils M, *et al.* Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg* 1996;171:221-226.
57. Bellomo R, Ronco C. The pathogenesis of lactic acidosis in sepsis. *Curr Opin Crit Care* 1999;5:452-457.
58. Nel M, Lobetti RG, Keller N, *et al.* Prognostic value of blood lactate, blood glucose, and hematocrit in canine babesiosis. *J Vet Intern Med* 2004;18:471-476.
59. Brady CO, Otto CM. Systemic inflammatory response syndrome, sepsis, and multiple organ dysfunction. *Vet Clin N Am* 2001;31:1147-1162.
60. Reinhart K, Bloos F. The value of venous oximetry. *Curr Opin Crit Care* 2005;11:259-263.
61. Kline JA. Shock. In: Marx JA, ed. *Rosen's Emergency Medicine: Concepts and Clinical Practice*. 5th ed. St. Louis, MO: Mosby, 2002:33-48.
62. Cheifetz IM, Schulman SR, Greely WJ, *et al.* Serum lactates correlate with mortality after operations for complex congenital heart disease. *Ann Thorac Surg* 1997;64:735-738.
63. Bernardin G, Pradier C, Tiger F, *et al.* Blood pressure and arterial lactate level are early indicators of short-term survival in human septic shock. *Intensive Care Med* 1996;22:17-25.
64. Cerovic O, Golubovic V, Spec-Marn A, *et al.* Relationship between injury severity and lactate levels in severely injured patients. *Intensive Care Med* 2003;29:1300-1305.
65. Meregalli A, Olivieri RP, Friedman G. Occult hypoperfusion is associated with increased mortality in hemodynamically stable, high-risk, surgical patients. *Crit Care Med* 2004;8:R60-R65.
66. Kaplan LJ, Kellum JA. Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular surgery. *Crit Care Med* 2004;32:1120-1124.
67. Hussain FA, Martin MJ, Mullenix PS, *et al.* Serum lactate and base deficit as predictors of mortality and morbidity. *Am J Surg* 2003;185:485-491.
68. Burgener IA, Kovacevic A, Mauldin GN, *et al.* Cardiac troponins as indicators of acute myocardial damage in dogs. *J Vet Intern Med* 2006;20:277-283.
69. Posner JB, Plum F. Independence of blood and cerebrospinal fluid lactate. *Arch Neurol* 1967;16:492-496.
70. Sood SC, Gulati SC, Kumar M, *et al.* Cerebral metabolism following brain injury. II. Lactic acid changes. *Acta Neurochir (Wien)* 1980;53:47-51.
71. Luft FC. Lactic acidosis update for critical care clinicians. *J Am Soc Nephrol* 2001;12:S15-S19.
72. Jutkowitz LA. Blood transfusion in the perioperative period. *Clin Tech Small Anim Pract* 2004;19:75-82.
73. Mizock BA, Falk JA. Lactic acidosis in critical illness. *Crit Care Med* 1992;20:80-93.
74. Vincent JL, Dufaye P, Berre J, *et al.* Serial lactate determinations during circulatory shock. *Crit Care Med* 1983;11:449-451.
75. Levraut J, Ciebiera JB, Chave S, *et al.* Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. *Am J Respir Crit Care Med* 1998;157:1021-1026.
76. Revelly JP, Tappy L, Martinez A, *et al.* Lactate and glucose metabolism in severe sepsis and cardiogenic shock. *Crit Care Med* 2005;33:2235-2240.
77. Pascoe PJ. Perioperative management of fluid therapy. In: DiBartola SP, ed. *Fluid, electrolyte, and acid-base disorders in small animal practice*. 3rd ed. St. Louis, MO: Elsevier, 2006:391-419.
78. James PM Jr, Bredenberg CE, Collins JA, *et al.* Tolerance to long and short term lactate infusions in men with battle casualties subjected to hemorrhagic shock. *Surg Forum* 1969;20:543-545.
79. Us MH, Ozcan S, Oral L, *et al.* Comparison of the effects of hypertonic saline and crystalloid infusions on haemodynamic parameters during haemorrhagic shock in dogs. *J Int Med Res* 2001;29:508-515.
80. Wang X, Mertz M, Aziz M, *et al.* Resuscitation of combined traumatic brain injury and hemorrhagic shock with racemic vs. L-lactated Ringer's. *Acad Emerg Med* 2004;11:439-440.
81. Forsythe SM, Schmidt G. Sodium bicarbonate for the treatment of lactic acidosis. *Chest* 2000;118:882-884.
82. Cooper DJ, Walley KR, Wiggs BR, *et al.* Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis: a prospective, controlled clinical study. *Ann Intern Med* 1990;112:492-498.
83. Heseby JS, Gumprecht DG. Hemodynamic effects of rapid bolus hypertonic sodium bicarbonate. *Chest* 1981;79:552-554.
84. Lang RM, Fellner SK, Neumann A, *et al.* Left ventricular contractility varies directly with blood ionized calcium. *Ann Intern Med* 1988;108:524-529.
85. Toll PW, Gaehtgens P, Neuhaus D, *et al.* Fluid, electrolyte, and packed cell volume shifts in racing greyhounds. *Am J Vet Res* 1995;56:227-232.