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# Serum procalcitonin concentrations in dogs with induced endotoxemia

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## Abstract

**Background:** Procalcitonin (PCT) is an important biomarker for sepsis in human medicine, but there is little information regarding PCT as a biomarker for sepsis in dogs. There are no controlled studies evaluating serial concentrations of PCT in dogs.

**Hypothesis/Objective:** That PCT would be rapidly detectable in serum after injection of LPS and would remain increased for at least 24 hours. Objective was to evaluate serial serum PCT concentrations in dogs after a single IV injection of LPS compared to placebo.

**Animals:** Six healthy mixed breed dogs.

**Methods:** A nonrandomized, placebo-controlled, crossover study was performed. Dogs were initially injected with placebo (0.9% NaCl; 1 mL, IV) and then experimental endotoxemia was induced by injecting lipopolysaccharide (LPS; 2 μg/kg, IV, once) after a 5-day washout period. Serial blood samples were collected for measurement of serum PCT after each injection. Difference in median PCT concentration between serial time points was assessed using a mixed effects model.

**Results:** After LPS administration, blood pressure decreased and body temperature increased along with the development of lethargy, vomiting, and diarrhea. Procalcitonin was significantly increased compared to baseline by 2 hours after injection of LPS (median = 67.9 versus 172.8, range = 46.0-74.1 versus 99.5-295.9, $P$ = .0002) and remained significantly increased for 12 hours (median = 205.9, range = 119.9-297.4) with return to baseline by 48 hours. Procalcitonin was significantly higher than placebo 2, 4, 6, 8, 10, 12, and 24 hours after injection. There were no significant differences in PCT between time 0 and any of the subsequent time points in the saline group.

**Conclusions and Clinical Importance:** Procalcitonin expression is likely to be a clinically useful biomarker for sepsis in dogs and might have an additional role in prognostication and therapeutic decision-making.

KEYWORDS

animal model, biomarker, lipopolysaccharide, sepsis

**Abbreviations:** CALC-I, calcitonin I; GDV, gastric dilatation volvulus; LPS, lipopolysaccharide; MAP, mean arterial pressure; PCT, procalcitonin; RI, reference interval.

## 1 | INTRODUCTION

Sepsis is an important cause of morbidity and mortality in humans and animals with rates in dogs as high as 70% and 47%, respectively.[1,2] Studies in humans and dogs suggest that early and aggressive treatment of sepsis might improve survival and it is well documented in humans that early intervention with appropriate antimicrobials decreases morbidity and case fatality rate.[3,4] However, it remains challenging to promptly and accurately diagnose sepsis, as other inflammatory disease states appear similar and can share clinical and laboratory findings, and standard microbiological testing takes days to perform. Biomarkers have been shown to assist in the rapid diagnosis of sepsis in humans.[5]

Procalcitonin (PCT), the precursor of calcitonin, is one of the most widely evaluated and valuable biomarkers of sepsis in human medicine.[6] In healthy humans, PCT concentrations are low to undetectable in serum or plasma.[7] Procalcitonin is primarily produced in the C cells of the thyroid gland after upregulation of the calcitonin I (CALC-I) gene in response to increased plasma calcium concentrations.[8] It is then cleaved into 3 products (katacalcin, calcitonin, and an N terminal fragment) in the thyroid gland[9,10] and calcitonin is released into the bloodstream. However, in response to infection, there is an increase in CALC-I gene expression and subsequent PCT production by extra-thyroidal tissues including the liver, kidneys, pancreas, spleen, and adipocytes.[10,11] Calcitonin I gene expression and PCT production is activated specifically in response to pathogen associated molecular patterns such as lipopolysaccharides (LPS) making it an ideal biomarker for sepsis.[10,11] For humans, PCT is used as a biomarker to assist with the diagnosis of sepsis, severe sepsis, and septic shock and has also proven to be useful in guiding antibiotic treatment.[12]

To date, there is little information regarding PCT in dogs. This is in part caused by a previous lack of valid assays for the detection of canine PCT.[13] However, recently developed assays validated for the detection of canine PCT allow for further investigation of this potential biomarker in canine sepsis.[14] Dogs with a clinical suspicion of sepsis have significantly higher serum PCT concentrations than do healthy controls.[14] Furthermore, higher PCT concentrations are associated with the development of multiple organ dysfunction syndrome and septic shock in dogs.[15] Additionally, reduction in PCT concentration in the first 24 hours is associated with survival and recovery from sepsis.[15]

However, there is no data on serial concentrations of PCT in dogs in response to LPS administration in a controlled setting. The aim of the present study was to evaluate the response of serum PCT concentration after a single sublethal injection of LPS to healthy dogs. We hypothesized that PCT is increased within 2 hours compared to baseline and remains increased for 24 hours after a single injection of LPS.

## 2 | MATERIALS AND METHODS

### 2.1 | Animals

Six mixed-breed, male intact, purpose bred dogs aged 6 to 12 months that weighed between 18.7 and 22.4 kg were used in this study. All dogs were considered to be healthy before the study on the basis of physical examination and screening laboratory tests (CBC, serum biochemistry, and urinalysis). Dogs were housed in animal facilities accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. Care was provided in accordance with the principles outlined by the National Institutes of Health and the study was reviewed and approved by the Animal Care and Use Committee at North Carolina State University (#09-170-O).

### 2.2 | Study design

A nonrandomized, placebo-controlled, crossover study was performed. All dogs were initially treated with a placebo (saline solution; 0.9% NaCl; 1 mL, IV) and then undiluted lipopolysaccharide (*Escherichia coli* serotype 0127:B8, Sigma-Aldrich, St. Louis, Missouri; LPS; 2 lg/kg, IV) after a 5-day washout period. The injection and monitoring of this population were previously described.[16] Briefly, each of the 6 dogs received a single IV injection of saline (0.9% NaCl; 1 mL) and then 5 days later, a single IV injection of LPS (*E. coli* serotype 0127:B8, Sigma-Aldrich; 2 μg/kg). Vital signs (rectal temperature, heart rate, respiratory rate, and blood pressure) were recorded at time 0 (time of injection) and every 30 minutes thereafter for 6 hours and then at 8, 10, 12, 24, 48, and 72 hours after both injections. Venous blood samples were collected from a jugular catheter 0, 2, 4, 6, 8, 10, 12, 24, 48, and 72 hours after injection. Serum was separated within 1 hour of collection and stored at −80°C.

### 2.3 | Test methods

Serum PCT concentrations were measured in duplicate and the mean value for each time point was used for analysis. Procalcitonin was measured using the canine PCT ELISA kit (Biovendor, Asheville, North Carolina) per the manufacturer's instructions with minor modifications. The modification was the use of a 1:1 dilution of serum with the supplied dilution buffer, rather than a 1:5 dilution. Previous investigators determined that the recommended dilution of 1:5 resulted in absorbance values below the assay's limit of detection for some samples.[14]

### 2.4 | Statistical analyses

All statistical analyses were performed in R 3.4.1 (R Core Team [2017]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/).The median and range of PCT at each time point was calculated. The data collected included multiple repeated measurement of each dog's PCT, to assess PCT response over the time period of the study. Because repeated measurements from a particular dog are likely to be more similar to each other than measurements from different dogs, this correlation was considered in the analysis.[17,18] A linear mixed effects model was used to explicitly account for the correlation between repeated measurements of PCT on each dog. The model was constructed using the lme4 package (Douglas Bates, Martin Maechler, Ben Bolker, Steve Walker. Fitting linear

mixed-effects models using lme4. *J Stat Softw*. 2015; 67(1), 1-48) with dog as a random effect (Bates, DG. "lme4: Mixed-Effects Modeling with R". Springer, June 2010. http://webcom.upmf-grenoble.fr/LIP/Perso/DMuller/M2R/R_et_Mixed/documents/Bates-book.pdf). Mean PCT (the average of 2 replicates at each time point) was the outcome variable and time point was considered as a categorical fixed effect. The model was fitted using the REML method. The PCT at each time point was compared post hoc using a Tukey adjustment for multiple comparisons with the emmeans package (Russell Lenth [2019]. emmeans: estimated marginal means, aka least-squares means. R package version 1.3.2. https://CRAN.R-project.org/package=emmeans), with the assumption that the sample dog PCT come from a normal distribution of PCT in the dog population at each time point. The model fit was assessed by examining the q-q plot and testing for normal distribution of the residuals using the Shapiro-Wilk Normality test. To assess the difference between the control group and LPS group, treatment group was also considered as a fixed categorical explanatory variable using an interaction term for treatment and time. To assess the correlation between iCa and PCT, spearman correlation coefficients were calculated. Statistical significance was defined as $P < .05$.

## 3 | RESULTS

### 3.1 | Placebo group (saline injection)

Dogs did not develop lethargy or abnormal clinical signs after saline injection. There was no significant decrease in mean arterial pressure (MAP) or increase in body temperature after saline injection. No clinical or laboratory abnormalities were detected in any of the dogs.[16]

Compared to their own baseline, PCT was not significantly increased after placebo in any dog at any time point.

### 3.2 | LPS group (endotoxin injection)

All dogs developed lethargy and abnormal clinical signs within 30 minutes of LPS administration: all dogs vomited 2-6 times (median 3.5 times) and 5 of 6 dogs developed diarrhea (Figure S1). Within 1 hour of LPS administration, all dogs had a decrease in MAP and within 2 hours of LPS administration all dogs developed a fever. Five of 6 dogs became hemodynamically unstable (SAP <90 mm Hg, MAP <70 mm Hg, or HR > 180 bpm) after LPS injection, and were administered lactated Ringer's solution (Lactated Ringers, Baxter Healthcare Corporation/Hospira, Lake Forest, Illinois; 10 mL/kg, IV, bolus), which was repeated as necessary to maintain hemodynamic stability. Lethargy was improved and vital signs returned to normal in all dogs by 6 hours after LPS administration. By 24 hours after LPS administration, activity level was normal and clinical and laboratory abnormalities were resolved.

Median and ranges for PCT at each time point after injection of LPS are shown in Figure 1B. Serum PCT concentration increased compared to their own baseline in all dogs after LPS administration (Figure 1). All dogs had serum PCT concentrations above their own baseline by 2 hours after LPS administration ($P = .0002$) with an

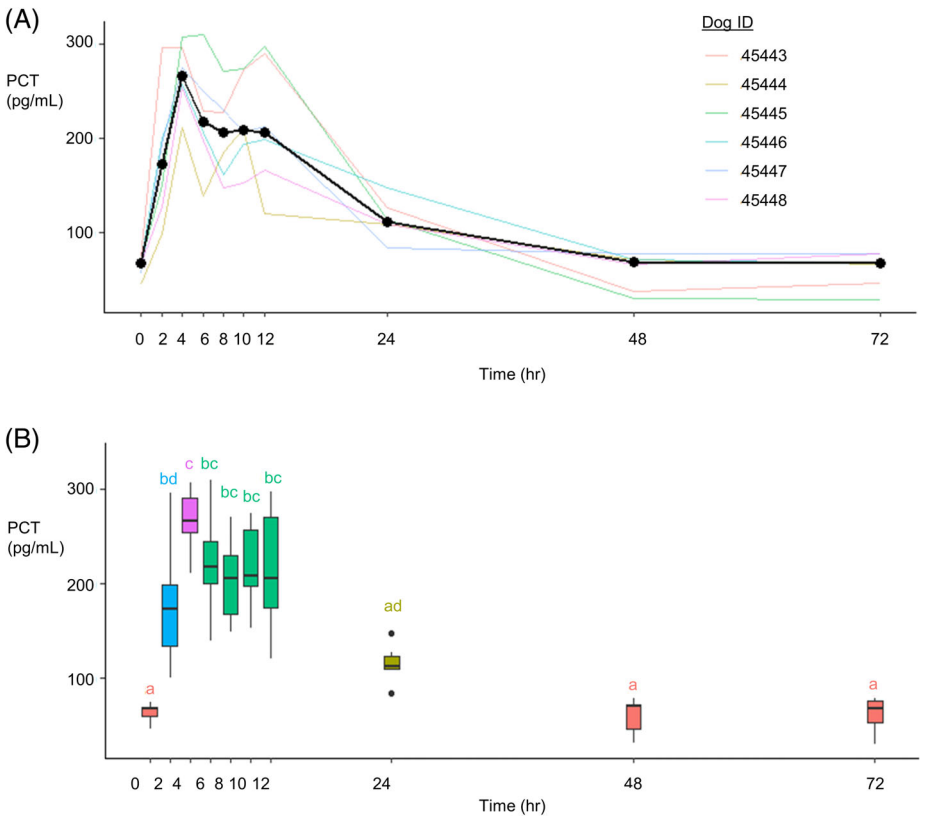


**FIGURE 1** A, Concentrations of serum procalcitonin (PCT, pg/mL) in healthy dogs before and after injection of lipopolysaccharide (LPS). Colors represent serum PCT concentration for each dog (the average of 2 replicates); the black line shows the median PCT concentration). B, Boxplot of serum PCT (pg/mL). For each time point, median PCT is shown by the short black line within the box, IQR is shown by the box itself, and the range is shown by the thin black lines (or black dots if the point was considered an outlier). Time points with different letters are significantly different from each other based on Tukey's honestly significant difference test

apparent peak at 4 hours. Serum PCT concentrations remained significantly increased through 12 hours after LPS administration. Procalcitonin concentrations were not significantly different from their own baseline at 24, 48, or 72 hours.

Compared to placebo, PCT concentrations after injection of LPS were significantly increased at 2, 4, 6, 8, 10, 12, and 24 hours after injection. The model including the time and treatment interaction was the best model based on ANOVA comparison with time as the only fixed effect (AIC 1199.3 compared to 1357.2, $P < .0001$). As an indicator of appropriate model specification, this model had normally distributed residuals ($P = .49$ for Shapiro-Wilk test of normality).

### 3.3 | Procalcitonin and iCa

The overall correlation between iCa and PCT was −0.660 ($R^2 = 0.435$). However, the correlation between iCa and PCT varied when compared between time points and treatment groups. Median PCT (pg/mL) and mean iCa (mmol/L) after injection of saline and LPS at each time point are provided (Figure S2).

## 4 | DISCUSSION

In the present study, administration of a single sublethal IV injection of LPS to healthy dogs resulted in a systemic inflammatory response similar to sepsis including fever, hypotension, tachycardia, and tachypnea along with vomiting and diarrhea. Additionally, LPS administration resulted in repeatable and reliable responses in the form of measurable increases in serum PCT. This response occurred rapidly after administration of LPS with concentrations above baseline at 2 hours after injection. Procalcitonin remained above baseline for at least 12 hours with return to baseline by 48 hours after administration of endotoxin, whereas PCT was not significantly increased at any time point after saline injection. The rapid and repeatable responses of PCT after endotoxin injection identified in this study further support its use as a biomarker for sepsis in dogs.

Although previous studies have documented increased PCT in dogs with clinical evidence of naturally occurring sepsis,[14,15] this study evaluated serial concentrations of PCT in dogs with experimentally induced endotoxemia. The temporal course of induction and subsequent decline of PCT after a single dose of LPS documented in the current study are similar to those described in humans and horses. In humans, PCT becomes markedly increased 2 to 4 hours after endotoxin administration in healthy subjects and remains detectable for 24 hours, with the level persisting until recovery.[7,19] Increased plasma PCT concentrations occur within 1 hour after sublethal LPS infusion in healthy horses, with concentrations remaining above baseline for 24 hours.[20] Because the expression of PCT in dogs appears to be similar to that of humans, we believe that it will perform similarly as a diagnostic and therapeutic biomarker in dogs. A reference range for procalcitonin has been established in a group of healthy control dogs.[14] The reference interval (RI) was calculated to be 5.8-91.1 pg/mL, however the 90% confidence interval for the upper bound was greater than 0.2 times the width of the RI suggesting uncertainty with the upper limit of the RI.[14,21] Compared to the published RI, PCT concentrations were within the RI at all time points after saline injection in 2 out of 6 dogs in the current study. One dog had a single PCT measurement above the published RI at a single time point, 1 dog had PCT measurements above the published RI at 2 time points, and 2 dogs had PCT measurements above the published RI at 8 time points after saline injection. A consideration for these differences includes uncertainty with the upper limit of the RI. Additionally, the RI was calculated using healthy dogs that were not catheterized (central and peripheral venous and urinary). It is probable that despite the use of aseptic technique, there was an increased level of exposure to bacteria or bacterial products and some toll-like receptor stimulation that could have stimulated PCT expression. This might be relevant as many dogs that are likely to be suspected of sepsis and screened will have similar indwelling catheters for similar periods of time.

As mentioned, the samples in the current study were obtained from dogs in a published study investigating hypocalcemia in dogs with induced endotoxemia.[16] In that study, ionized hypocalcemia occurred as early as 2 hours after LPS administration. Hypocalcemia is widely recognized in septic animals though the pathophysiology remains poorly understood.[22,23] Several mechanisms of hypocalcemia have been suggested, including the influence of calcitonin precursors, such as PCT.[16,22] Furthermore, studies in human medicine have identified correlations between ionized hypocalcemia and increased PCT in sepsis, particularly in those with positive blood cultures.[24] In hamster models of sepsis, increased PCT was an early systemic biomarker which correlated closely with mortality and had an inverse correlation with serum calcium levels.[25] Although not the primary aim of this study, ionized hypocalcemia was negatively associated with PCT overall. However when compared between time points and treatment groups the associations between iCa and PCT varied. In order to further assess the relationship between PCT and hypocalcemia, measurements of these analytes would need to be obtained between 0 and 2 hours after LPS administration. Alternatively, the response of calcium to the infusion of recombinant PCT could be assessed. The potential role of PCT as not only a biomarker, but possibly a mediator of sepsis in animals warrants further investigation.

An important limitation for our study was that a single IV injection of LPS from a single *E. coli* serotype 0127:B8 was used as a model for sepsis. Although endotoxemia in dogs secondary to LPS administration continues to be a common experimental model to simulate sepsis, the sources, concentrations and kinetics of LPS in dogs, and subsequent expression of PCT with naturally occurring sepsis are likely to be highly variable. In 2 previous studies evaluating PCT in dogs with naturally occurring sepsis, PCT was significantly elevated compared to healthy controls, however there was considerable variability in the PCT concentrations within these subjects.[15,16] Interestingly, serial PCT concentrations were assessed in 1 of these groups, with survivors having significantly improved PCT concentrations by 48 hours compared to nonsurvivors.[16]

The specificity of PCT for use as a biomarker in dogs with sepsis also remains poorly defined as PCT increases in some noninfectious

inflammatory states in humans, specifically in people after liver transplantation, severe and prolonged cariogenic shock, in patients with heat shock, severe pancreatitis, certain autoimmune disorders, and rhabdomyolysis.[9,26] The consideration that PCT is also increased after similar noninfectious inflammatory disease states in dogs should also be considered, although only limited investigations have been performed. In 1 previous study, there was no significant difference in PCT concentration between a group of healthy dogs and dogs with gastric dilatation volvulus syndrome (GDV).[14] Interestingly, no significant difference in PCT concentration between dogs with GDV syndrome and septic dogs was identified.[14] One consideration for the lack of significant difference in the latter includes some level of endotoxemia secondary to ischemic mucosal damage and resultant disruption of the intestinal mucosal barrier.[27]

Additional limitations of our study include that the first measured time point in our study was 2 hours after LPS, so the early behavior of PCT after LPS administration remains unknown. Further limitations to consider include our relatively small sample size as well as the potential effect of duration of storage time on the samples. Long-term storage of human samples at −80°C causes a slight decrease in the PCT concentration of approximately 12% after 6 years of storage. There are no studies evaluating similar effects on samples from dogs.[28]

The results of the current study suggest that PCT was expressed in response to experimentally induced endotoxemia and PCT expression is likely to be a clinically useful biomarker for sepsis in dogs. Importantly, as changes in serial measurements appear to correspond with clinical improvement, PCT might have an additional role in prognostication and therapeutic decision-making. Further investigations to assess the expression of PCT in nonseptic inflammatory states as well as the behavior of PCT in naturally occurring sepsis to assess its value as a prognostic and therapeutic biomarker in dogs are warranted.

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## CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

## OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

## INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

This study was reviewed and approved by the IACUC at North Carolina State University.

## HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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