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Biological Variability of C-Reactive Protein and Specific Canine Pancreatic Lipase Immunoreactivity in Apparently Healthy Dogs

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Background: C-reactive protein (CRP) and specific canine pancreatic lipase immunoreactivity (Spec cPL) are biomarkers of generalized or nonspecific inflammation and pancreatic inflammation in dogs, respectively. The extent of inter- and intraindividual variation over time of these analytes is not well defined in dogs. The minimal critical difference for sequential determinations of these markers (ie, the smallest change necessary to represent physiological change rather than biological variation), has not been defined.

Objectives: To determine the inter- and intraindividual variability (CV_G and CV_I) and minimal critical difference for sequential determinations of serum CRP and Spec cPL concentrations in apparently healthy dogs.

Animals: Eleven apparently healthy dogs owned by staff or students at a veterinary teaching hospital.

Methods: Blood was collected repeatedly at varying intervals over 12 weeks. CRP and Spec cPL concentrations were determined with commercially available assays. Indices of inter-, intraindividual, and assay variability and 1-sided minimal critical differences for sequential concentrations were calculated.

Results: For CRP, CV_G was 90.8%, CV_I was 115.5%, and the analytical variability (CV_A) was 6.3%; the index of individuality was 0.78, and 1-sided critical difference was 269.9%. For Spec cPL, CV_G = 49.48%, CV_I = 193.8%, CV_A = 8.4%, index of individuality = 0.26, and 1-sided critical difference was 452.6%. [Correction statement added after online publication 12 May 2011: Index of indivdiuality values corrected.]

Conclusions and Clinical Importance: A population-based reference range is appropriate for Spec cPL, but questionable for CRP in dogs. Large changes in serial measurements of Spec cPL are necessary to infer clinical importance, more modest changes in CRP are likely to be meaningful.

Key words: Biological variation; Critical change value; Diagnostic testing; Inflammatory markers.

C-reactive protein (CRP) and specific canine pancreatic lipase immunoreactivity (Spec cPL) concentrations are used in dogs as biomarkers of generalized or nonspecific inflammation and pancreatic inflammation, respectively. When measuring these proteins, the concentration for the individual is evaluated by comparison with a reference range established from a population of apparently healthy animals. Whereas some clinical chemistry analytes are constrained within a narrow range that tends to be consistent among individuals, other analytes may vary over a broad range of normal values both when measured within the same individual sequentially (intraindividual variability [CV_I]) and among individuals when measured simultaneously (interindividual variability [CV_G]). CV_I and CV_G, together with the variability inherent to a given biochemical assay (CV_A), comprise the total variability (CV_T) for an analyte in a population (ie, $CV_T = CV_I + CV_G + CV_A$).[1,2]

The clinical utility of a reference range depends largely upon the magnitude of these components of variability. An overly broad reference range might obscure clinically meaningful changes for a given individual if the results still fall within the reference range. Conversely, variation in an apparently normal animal may lead to results that fall outside of the reference range.[1] Thus, reference ranges for clinical chemistry variables displaying high degrees of CV_I or CV_G may not provide clinically useful information when applied to an individual. In these instances, application of the minimal critical difference for sequential values ($P < .05$) may be of greater utility. The minimal critical difference for sequential values ($P < .05$) represents the smallest change of a variable being monitored in an individual over time that is statistically more likely to be because of a change in the individual's biological state rather than because of biological or analytical variation,[1–3] with a P-value $< .05$ (indicating a $< 1:20$ chance of a false positive determination of meaningful change).

CRP, an acute phase reactant, was first identified in humans with pneumonia, and a canine correlate subsequently has been described.[4] CRP is routinely utilized in human medicine as an indicator of inflammatory states, to evaluate therapy, and to monitor disease progression.[5] In dogs, serum CRP concentration has been demonstrated to increase significantly in a variety of experimentally induced and spontaneous conditions.[6–9]

Abbreviations:

CRP	C-reactive protein
CV_A	analytical variability
CV_G	interindividual variability
CV_I	intraindividual variability
CV_T	total variability
Spec cPL	specific canine pancreatic lipase immunoreactivity
TPR	temperature, pulse, and respirations

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The canine specific lipase (Spec cPL) assay measures serum concentrations of canine pancreatic lipase.[10] This immunoassay has been shown to have higher sensitivity than previously available diagnostic tests, and has shown promise as a sensitive and specific biomarker of pancreatic inflammation.[10,11] Currently recommended cut-off values for making the diagnosis of pancreatitis by Spec cPL feature a large "gray zone" between the established reference range and results considered consistent with pancreatitis, raising the possibility that meaningful change for an individual may be lost within the broad reference range. Serial measurement of Spec cPL has been used anecdotally to monitor response to therapy,[12] but no published data indicate the magnitude of change in serial measurements that is likely to be clinically relevant.

The objectives of the study described here were to measure serial serum concentrations of CRP and Spec cPL daily, weekly, and monthly to determine biological variability, the validity of applying reference ranges for both analytes, and the critical difference for sequential results in healthy dogs.

Materials and Methods

The study was performed as a prospective cohort design, using an initial enrollment of 12 dogs owned by veterinary students and staff at the College of Veterinary Medicine, Oregon State University. The institutional animal care and use committee approved this study. All dogs were considered healthy, based on owner-reported observations and the absence of signs of systemic disease on routine physical examination at the onset of the study. At the time of enrollment, none of the dogs had histories of previous clinically relevant illness. None of the enrolled dogs had histories suggestive of chronic pancreatitis. The dogs were maintained in their home environment for the duration of the study.

To minimize preanalytical variability, blood was collected by a limited number of operators (P.C.C., C.G.R.) from each dog by jugular venipuncture. Blood samples were collected with the dogs in a sitting position, with 20 G needles and 6 mL syringes.[a] After collection, blood was transferred into sterile glass collection tubes.[a] Samples were obtained daily for 7 days, weekly for 6 weeks, and a final sample was collected at 3 months. Sampling took place after an overnight fast, and at approximately the same time each day to minimize diurnal variation. Samples were allowed to clot for 10 minutes at room temperature, were centrifuged at $1,500 \times g$ for 10 minutes, and serum then was decanted and stored in 2 identical sealed aliquots at $-80^{\circ}C$ until analysis. At each collection, owners were questioned about the health of the dog over the time period between the current and previous sampling, and the dog underwent brief physical examination by the operators. Temperature, pulse, and respiration (TPR) were recorded for each dog at each time point.

At the end of the study period, serum CRP and Spec cPL concentrations were measured for each sample with commercially available, previously validated assays.[b,c] Both assays were performed according to the manufacturers' recommendations. The lower and upper limits of quantification of the 2 assays are 0.75–200 mg/L for the CRP assay and 29–954 μg/L for Spec cPL,[10] respectively. Interassay variation of the CRP assay ranges from 10 to 7% for low- and high-concentration samples, respectively.

Serum CRP was quantified at Oregon State University using the 1st aliquot, whereas the 2nd aliquot was shipped overnight on dry ice for Spec cPL determination at the Gastrointestinal Laboratory at College of Veterinary Medicine, Texas A&M University. All samples were evaluated in duplicate and were run in large batches to minimize interanalytical variability.

Routine biochemical panels were performed on all dogs using serum from the 1st sampling day. No abnormalities were noted in any dogs.

Statistical analyses were performed in the statistical programming environment "R."[13] Three levels of analysis for outliers (individual sample outlier analytical variability [CV_A], outlier values within individuals, and individuals with outlying variability relative to the group as a whole) were carried out by the Cochran test at $P < .05$.[14] Samples with outlying interassay analytical variability (ie, samples with substantial disagreement between duplicate well determinations in the single assay) were reassayed if the individual sample coefficient of variation of duplicate determinations was >15%, following our respective laboratories protocols for allowable intra-assay variability in these assays. Samples were stored at $-80^{\circ}C$ between assay runs. Previous work in our laboratories with both CRP and Spec cPL has shown that the samples are stable after repeated freeze-thaw cycles (data not shown). Single time point results identified as potential outliers for a given individual (ie, outlier values when compared with the total data set for the animal) were excluded if the TPR or owner-provided history indicated the possible presence of recent disease. Samples were excluded from analysis if owner history or physical examination findings suggested the dog had changed in some way or became ill at the time of sampling. One sample from 1 dog and the entire data set from another dog were excluded on this basis. Samples with the greatest apparent discordance with the individual data sets for Spec cPL (3 samples each from dogs 5 and 11) and CRP (7 samples total from dogs 1, 4, 8, 10, and 11) were measured again to confirm that the results were not because of laboratory error, all repeated results were < 10% different from the original results, and thus the original results obtained were used for further analysis.

Data from the entire data set (all included samples, all dogs) were consistent with a Gaussian distribution for both Spec cPL and CRP by the D'Agostino-Pearson Omnibus test for normality.

The sums of squares of the components of biologic variability were calculated by a nested analysis of variance.[1] The index of individuality was calculated as $CV_G/(CV_I{}^2 + CV_A{}^2)^{1/2}$. Correlations of subsequent sample measurements with the 1st sample concentrations of CRP and Spec cPL were assessed by Spearman's test. Correlation of the concentrations of CRP and Spec cPL for the entire data set also was assessed by Spearman's test. [Correction statement added after online publication 12 May 2011: Index of individuality calculation corrected.]

Results

Participant Demographics

The median age of the 11 dogs from which data were analyzed was 5 years (range, 1–9 years). Seven dogs were spayed females, 3 were neutered males, and 1 was an intact male. Four dogs were either Labrador Retrievers or Labrador crosses, 2 dogs were Beagle Hound crosses, with 1 each of American Eskimo, Dogo Argentino, German Short-Haired Pointer, Boston Terrier, and Pomeranian cross. None were from breeds considered at risk for either acute or chronic pancreatitis.

Outlier Values

One sample from a single dog was excluded prospectively, and all samples from 1 dog were excluded from analysis retrospectively because of statistical evidence of their outlier state or the presence of clinically relevant change in history and physical examination findings. The

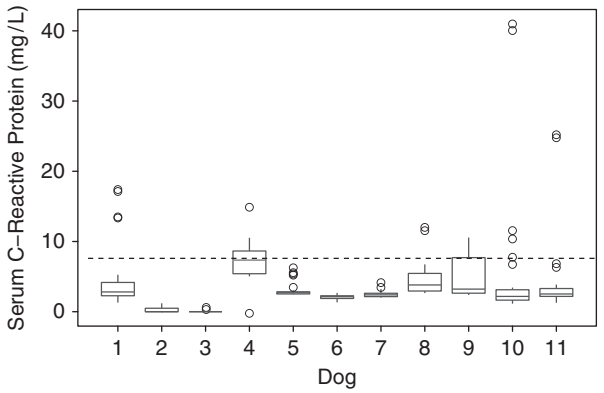

Fig 1. Box and whisker plot of serum C-reactive protein concentrations (plotted as individual well values, reported results are the average of 2 wells) in 11 apparently healthy dogs sampled 14 times at varying intervals. The broken line represents the upper limit of the reference range for canine C-reactive protein concentration determined at the Gastrointestinal Laboratory from 51 apparently healthy dogs (7.6 mg/L).[d]

single sample from 1 dog was excluded because of a history of vomiting after ingestion of a foreign object on the morning of sample collection, the other dog was excluded because of diagnosis of chronic inflammatory skin disease, clinical signs of which were manifested within 14 days of the sample collection period. Two samples from 2 separate dogs were excluded from the Spec cPL but not from the CRP data sets because of repeated excessive intra-assay variance (>15% disagreement between replicate wells after 2 separate assay runs).

CRP

Mean serum CRP concentration for all samples was 3.5 mg/L (range, 0–40.5 mg/L; Fig 1). CV_G was 90.8%, CV_I was 115.5%, and CV_A was 6.3%, yielding an index of individuality of 0.78 and a 1-sided critical difference for sequential values ($P < .05$) of 269.9%. CRP results showed significant but gradually decreasing autocorrelation in the short term (ie, over the course of the 1st week) but not on longer time scales (Table 1). [Correction statement added after online publication 12 May 2011: Index of individuality corrected.]

Spec cPL

The mean serum concentration for all samples was 62.3 μg/L (range, 29.0–516.2 μg/L; Fig 2). CV_G was 49.5%, CV_I was 193.8%, and CV_A was 8.4%, yielding an index of individuality of 0.26 and a 1-sided critical difference for sequential values ($P < .05$) of 452.6%. Subsequent measurements showed no autocorrelation (Table 1). [Correction statement added after online publication 12 May 2011: Index of individuality corrected.]

Correlations of Spec cPL and CRP

Using all nonexcluded samples from all dogs, there was no correlation detected between serum Spec cPL and CRP concentrations (Spearman $r = -0.14$, $P = .072$; Fig 3).

Discussion

For any assay, an index of individuality of <0.7 supports use of a population-based reference range, whereas a value >1.7 indicates negligible utility of a population-based reference range.[1] Using these criteria, the use of a reference range for Spec cPL is considered appropriate, whereas the use of a population-based reference range for CRP in dogs requires more critical assessment. Both CRP and Spec cPL have relatively large critical differences for sequential results, meaning that a more than 2-fold (CRP) or approximately 5-fold (Spec cPL) change must be demonstrated before any observed difference in sequential results in an apparently healthy dog is statistically likely to reflect a change in the animal rather than biological variation. For both analytes, these large critical differences are a consequence of large CV_I, indicating that apparently healthy dogs can have marked temporal fluctuations in both CRP and Spec cPL. The sources of these changes in our study group are not apparent. The random occurrence of high Spec cPL results in our study group was not related to the high CRP concentrations (see Fig 3), suggesting that substantial systemic inflammation was not present during the periods when Spec cPL was high.

A "two hit" hypothesis has been suggested for development of acute pancreatitis in human beings.[15] This hypothesis suggests that an additional insult beyond direct alterations in pancreatic physiology is necessary for the development of more severe disease. If this is the case, changes in pancreatic cellular permeability may occur in some dogs without development of clinically relevant disease, and these changes in permeability could result in increased serum Spec cPL concentrations. What process may cause such a change in permeability is speculative, but in a previous study of dogs presented for necropsy 47/73 (64%) canine pancreata examined microscopically

Table 1. Correlation between serum C-reactive protein (CRP) and classical pancreatic lipase (Spec cPL) concentrations at varying time points in 11 apparently healthy dogs.

	Time from Baseline:	1 Day	2 Days	3 Days	4 Days	5 Days	6 Days	7 Days	2 Weeks	3 Weeks	4 Weeks	5 Weeks	6 Weeks	12 Weeks
CRP	Spearman *r*	0.954	0.936	0.753	0.879	0.653	0.733	0.217	0.516	0.733	0.442	0.473	0.318	0.634
	Significance	<0.001	<0.001	<0.001	<0.01	<0.05	<0.05	NS	NS	<0.05	NS	NS	NS	<0.05
Spec cPL	Spearman *r*	0.377	0.312	−0.048	0.421	0.414	0.150	0.315	−0.192	0.30	0.544	0.386	0.344	0.044
	Significance	No significant correlations												

NS, not statistically significant ($P > .05$); Spec cPL, specific canine pancreatic lipase immunoreactivity.

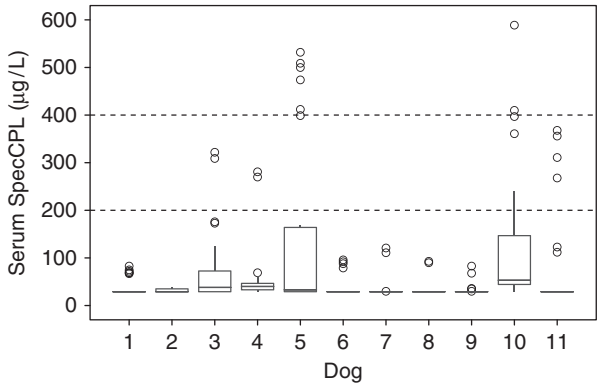

Fig 2. Box and whisker plot of serum specific canine pancreatic lipase immunoreactivity (Spec cPL) concentrations (plotted as individual well values, reported results are the average of 2 wells) in 11 apparently healthy dogs sampled 14 times at varying intervals. The broken lines represent the upper limit of the current reference range for Spec cPL (200 µg/L) and the current diagnostic threshold considered compatible with pancreatitis in a dog with clinical signs (400 µg/L).

at necropsy showed evidence of pancreatitis, with no gross lesions noted and no clinical suspicion that the dogs had pancreatitis.[16] This previous report suggests that subclinical pancreatitis may be common in dogs, and it is possible that some dogs in our study could have microscopic lesions if pancreatic biopsy specimens had been examined. Obvious ethical issues prevented such an approach in this study. The 2 dogs with the greatest increases in Spec cPL in this study (dogs 5 and 11) still had the majority of their samples below the upper limit of normal for this assay (200 µg/L; Fig 2), suggesting that any subclinical pancreatitis in these dogs is either sporadic and transient or does not result in sufficient enzyme leakage to cause persistently increased Spec cPL concentrations.

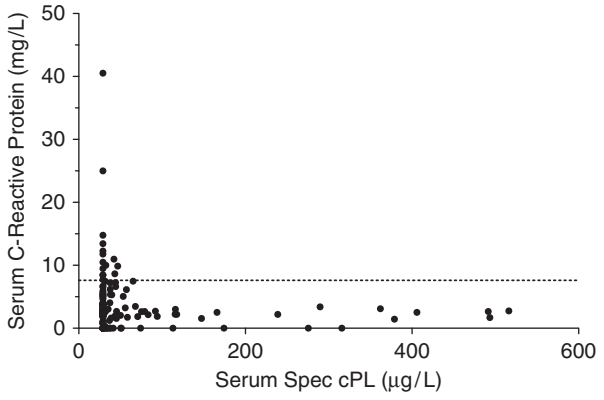

Fig 3. Scatter plot of serum specific canine pancreatic lipase immunoreactivity (Spec cPL) concentrations against serum C-reactive protein concentrations using all nonexcluded samples from 11 apparently healthy dogs sampled 14 times at varying intervals. The broken line represents the upper limit of the reference range for canine C-reactive protein concentration determined at the Gastrointestinal Laboratory from 51 apparently healthy dogs (7.6 mg/L).[d] No correlation was detected between serum concentrations of Spec cPL and C-reactive protein in this data set.

Interestingly, applying the minimal critical difference for Spec cPL to the mean serum concentration of 62.3 µg/L yields a value of 283 µg/L, which is slightly higher than the current upper end of the reference range for Spec cPL.[10]

The cut-off value for Spec cPL considered suggestive of pancreatitis has been shown to have a sensitivity of 63.6% in dogs with well characterized, grossly evident pancreatic pathology.[11] The clinical relevance of results within the "gray zone" (between 200 and 400 µg/L) remains uncertain, particularly in dogs without physical examination findings or histories suggestive of pancreatitis. The data presented here demonstrate that results within this range can be documented in apparently healthy dogs, but the presence of subclinical pancreatitis in these dogs cannot be ruled out without evaluation of pancreatic biopsy samples. This approach cannot be justified in a study of this kind or in the management of asymptomatic animals. Within the context of the complete data set, however, samples with Spec cPL concentration >200 µg/L represent only 9/152 samples analyzed (5.9% of all samples). Because the upper limit of the reference range for Spec cPL is the 97.5th percentile of a group of apparently healthy dogs,[10] it is statistically likely that 2.5% of samples from apparently healthy dogs will be higher than this concentration, leaving 5/152 (3.2%) samples that can be considered diagnostically discordant.

The study reported here utilized dogs with no evidence of current pancreatic or other inflammatory disease. CRP and Spec cPL results may vary less in individuals with chronic disease. For example, NT-Pro BNP shows lower interindividual variation in human patients with stable chronic heart failure than in healthy controls.[17] If biological variation in Spec cPL is lower in dogs with chronic pancreatic disease, critical change results would be better derived from a well-characterized population of dogs with stable chronic disease rather than apparently healthy dogs as described here. Thus, additional studies of temporal variation in Spec cPL in dogs with clinical signs consistent with chronic pancreatitis are warranted, but such studies are likely to be challenging because of a lack of consensus on diagnostic criteria for this disease.

In contrast to Spec cPL, CRP demonstrates pronounced between-subject variability (CV_G), which results in a higher index of individuality and hence difficulty in applying a reference range. Analytes with high CV_G typically lead to a relatively broad reference range, meaning some individuals may have pathologic changes in the concentration of the analyte that still fall within the reference interval or normal physiologic changes that exceed the upper end of the reference interval, thus generating potentially substantial overlap between healthy and diseased subpopulations, as observed in several previously published studies in dogs.[18–21] Laboratory Beagles have been shown to have significant differences in serum CRP concentration among subjects.[22] CRP therefore may be best used to monitor

individuals with an inflammatory condition based on deviations from previous measurements within the same subject. A number of studies in the veterinary literature demonstrate the prognostic utility of changes in CRP over time, whereas absolute concentrations of CRP have little prognostic value. Serum CRP concentration does not correlate with outcome in dogs with primary immune-mediated hemolytic anemia, but survivors are more likely to show significant decreases after initiating treatment.[23] Similarly, although CRP concentration at diagnosis has no prognostic value in bitches with pyometra, postoperative changes (or lack of a decrease) are a good indicator of postoperative complications.[24,25] Changes in CRP after admission predict recovery in dogs with sepsis, but the concentration at presentation has no prognostic significance.[26] In severely ill animals, CRP has been shown to be significantly higher than in healthy controls, but there was no difference between survivors and nonsurvivors.[27] In dogs treated for steroid-responsive meningitis-arteritis, patients with complete clinical and cytological remission demonstrated significant decreases in serum CRP concentration but generally do not have CRP concentrations within the reference range.[28] Use of the reference range rather than changes from baseline might therefore erroneously misclassify remission status in these patients, although the persistent increase suggests continued subclinical inflammation.[28,29]

The relative contributions of CV_G and CV_I to total biological variability of CRP reported here are similar to those of a previous report, with a $CV_I : CV_G$ ratio of 1.27 in both studies.[22] Although the mean concentrations of CRP and Spec cPL reported here show substantial agreement with previous reports, the critical difference for CRP is higher than that reported previously (71.7 and 60.4% for 1- and 2-sided, respectively). Another report of biological variation of CRP in dogs by Martinez-Subelia et al[30] found lower apparent variation than that reported here, but their results are reported in terms of mg/L change. The authors of this 2nd study cautioned that their results are likely less variable than those expected in clinical practice.[30] Possible contributors to the discrepancies observed between this study and those cited earlier include the longer period of measurement in the present study (12 versus 5 weeks) and the use of purpose-bred, laboratory-housed dogs of a single breed in each of the previous studies. Dogs in the present study were allowed to participate in any activities permitted by the owner, introducing uncontrolled variables such as changes in ambient temperature, exercise, inconsistencies in diet, and exposure to the outdoor environment and other animals. However, these conditions are thought to be more representative of a client-owned population than a laboratory colony. Dogs in the study described here exhibited increases in CRP that apparently were not linked to the presence of clinically detectable disease. By comparison, studies of biological variability of CRP in human beings, although showing high degrees of individuality, typically did not result in CRP concentrations greater than the reference range. In a study by Macy et al,[2] some individuals had high concentrations of CRP, but most samples (208 separate data points) were below the clinically applied upper cut off-value of 10 mg/L. In the study reported here, 14/150 samples from dogs were higher than the Gastrointestinal Laboratory's upper limit for this assay (7.6 mg/L). Why dogs show this pattern of increased variability and apparent sporadic increases in CRP is unknown at this time. Dogs have very different behaviors and interactions with their environments than do humans. Among many potentially important factors, dogs pick up and chew objects found outdoors, and cannot follow hygienic procedures that humans do. These differences make client-owned dogs more prone to mild injuries or infections that could lead to higher CRP concentrations.

Some of CV_G for both CRP and Spec cPL may be attributable to subpopulation characteristics such as age or reproductive status. Identification of a subpopulation of dogs with demonstrably different Spec cPL or CRP concentrations would allow for development of reference ranges for each subpopulation, narrowing and thus enhancing the clinical utility of the reference range for the analyte. However, no such subpopulations have been identified in studies reported to date. Serum CRP concentration has been shown to have no apparent diurnal or circadian pattern in dogs, does not appear to be breed dependent, and is not influenced by sex or reproductive status.[31,32] Dogs <3 months of age may have decreased CRP concentrations in inflammatory states when compared with older dogs, but no age-related differences in CRP have been noted in dogs >3 months of age.[33] No published data suggest that breed, sex, or reproductive status influence serum Spec cPL concentrations. Evaluations of diurnal variation for Spec cPL as well as longer-term patterns (ie, seasonal, annual) have not been reported for either Spec cPL and CRP in dogs.

Limitations of the present study include a relatively small number of subjects, reliance upon client-reported health status rather than extensive clinicopathological evaluation, and lack of standardization with regard to animal care and management. As noted previously, we believe the use of privately owned pet animals with variable husbandry and environmental conditions results in a more relevant model of biological variation in the client-owned dog population. The small sample size is more likely to affect measures of CV_G compared with CV_I, but the concordance of the $CV_I : CV_G$ ratio for CRP with previously published data suggests that the proportional relevance of each component of variability has been reliably estimated. Studies in humans have indicated that estimates of biological variation are largely independent of group size and time span of the study.[1,3]

Footnotes

[a] Monoject 6 mL Syringes and Red Top Tubes, Covidien, Mansfield, MA

[b] Canine C-Reactive Protein ELISA Kit, BD Biosciences, San Jose, CA

[c] Spec cPL, IDEXX Laboratories, Westbrook, ME. Performed by the Gastrointestinal Laboratory at Texas A&M University

[d] Berghoff N, Suchodolski JS, Steiner JM. Assessment of stability and determination of a reference range for C-reactive protein in serum. J Vet Int Med 2006;20:790 (abstract)

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Conflict of interest: Dr Ruaux is employed as a consultant for the GI Laboratory, Texas A&M University. This lab provides the Spec cPL and CRP assays as "for fee" services.

Dr Steiner has an ongoing financial and consultative relationship with IDEXX Laboratories, the manufacturer of the Spec cPL assay. Dr Steiner is also the director of the GI Laboratory, Texas A&M University. This lab provides the Spec cPL and CRP assays as "for fee" services.

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