An evaluation of changes over time in serum creatine kinase activity and C-reactive protein concentration in dogs undergoing hemilaminectomy or ovariohysterectomy

B Nevill[a*], A Leisewitz[b], A Goddard[c] and P Thompson[d]

ABSTRACT
The extent of trauma in a patient can be difficult for a clinician to quantify. A prospective study was performed on 2 groups of dogs undergoing either ovariohysterectomy or hemilaminectomy. The serum activity of creatine kinase and serum concentration of C-reactive protein were evaluated preoperatively and then at 4, 6, 8, 12, 24 and 48 hours postoperatively in both groups. The results were compared statistically both within and between the 2 groups. A wide range of results was found at each time point for both analytes although there were no significant differences for either analyte between the 2 surgical groups preoperatively. Thereafter there were significant differences in creatine kinase activity levels between the 2 groups. C-reactive protein concentration results were very similar in the 2 groups with no statistical difference at any time point. The results of this study suggest that the evaluation of CK and CRP at any one time point in a traumatised animal is of limited value. However, the evaluation of the trend of these 2 analytes, even over a relatively short time period, may allow for useful prognostication in clinical cases.

Keywords: C-reactive protein, creatine kinase, hemilaminectomy, ovariohysterectomy, trauma.

Nevill B, Leisewitz A, Goddard A, Thompson P **An evaluation of changes over time in serum creatine kinase activity and C-reactive protein concentration in dogs undergoing hemilaminectomy or ovariohysterectomy**. *Journal of the South African Veterinary Association* (2010) 81(1): 22–26 (En.). Department of Companion Animal Clinical Studies, Faculty of Veterinary Science, University of Pretoria, Pivate Bag X04, Onderstepoort, 0110 South Africa.

INTRODUCTION

Trauma of diverse origins is a common reason for presentation of pets for treatment. It is often difficult clinically to objectively quantify the severity of any trauma suffered by an animal. One approach is to measure changes in the various serum constituents that are known to alter in response to trauma or inflammation. Creatine kinase (CK) is an enzyme found predominantly in skeletal muscle and significantly elevated serum activity is largely associated with muscle damage. It is an extremely sensitive indicator of muscle damage, but is not specific as to cause[14,27]. Serum elevations in dogs are associated with cell membrane leakage and will therefore be seen in any condition associated with muscular inflammation, necrosis or degeneration. Peak serum activity is expected between 3 and 12 hours after muscular insult and the elevation is roughly proportional to the amount of muscle tissue involved[1,5,27]. It is also possible to quantify the mass of muscle damage if the changes in CK values over time after a particular insult are plotted[1,3,4,27].

C-reactive protein (CRP) is a member of a large group of plasma proteins called acute phase proteins (APPs) which show elevated serum concentrations in response to a broad range of inflammatory stimuli. These proteins are integral to the acute phase response, which is the body's rapid initial systemic inflammatory reaction to any non-specific tissue injury[10,13,24,29]. Examples of other acute phase proteins are fibrinogen, serum amyloid A, haptoglobin and ceruloplasmin. Most of the APPs, including CRP, are positive in that they increase in serum concentration in response to inflammation. Others are negative, that is they show a decreased serum concentration in response to inflammation[10,25]. A well known negative APP is the plasma protein albumin. The synthesis of positive APPs is stimulated by various proinflammatory cytokines in response to tissue injury or infection. The main stimulatory cytokines are interleukin-1, interleukin-6 and tumour necrosis factor alpha[10,15,24,29]. The exact functions of the APPs are not completely understood, but it is known that they regulate and coordinate the body's response to tissue injury. The functions of CRP include suppressing microbial growth, clearance of damaged tissues and regulation of the inflammatory response[24,25].

Thoracolumbar disc disease is commonly seen in small animal practice. This is a degenerative condition of the intervertebral discs, often leading to disc extrusion. Most of the dogs seen are chondrodystrophic breeds, in particular Dachshunds[26]. At the Onderstepoort Veterinary Academic Hospital (OVAH), decompression of a thoracolumbar disc extrusion is achieved surgically by means of a hemilaminectomy or pediculectomy over the affected intervertebral space. The surgical approach involves extensive elevation and retraction of the epaxial musculature over the affected disc space resulting in surgical trauma primarily to skeletal muscle[23,26]. Ovariohysterectomies are performed routinely at the OVAH, generally on healthy pets under a year of age. The standard method of ovariohysterectomy is by means of a midline coeliotomy through the linea alba, with removal of the ovaries and uterus up to the cervix. The linea alba is a midline tendinous aponeurosis of the abdominal muscles. As such there is minimal skeletal muscle damage during the procedure, with surgical trauma confined to the genital tract.

Many parameters are used as measures of trauma. In humans, both CRP and CK have been employed in attempts to quantitatively compare the degree of tissue trauma between different surgical techniques[6,17,18]. CK has also been used to evaluate the extent and cause of muscle damage resulting from lumbar back surgery[19,20,22].

A prospective study was performed on

[a]Small Animal Surgery Section, [b]Small Animal Medicine Section and [c]Clinical Pathology Section, Department of Companion Animal Clinical Studies, Faculty of Veterinary Science, University of Pretoria, Pivate Bag X04, Onderstepoort, 0110 South Africa.

[d]Epidemiology Section, Department of Production Animal Studies, Faculty of Veterinary Science, University of Pretoria, Onderstepoort, 0110, South Africa.

*Author for correspondence.
E-mail: bruce@ovation.co.za

Received: July 2009. Accepted: January 2010.

2 groups of animals. The spay group underwent an ovariohysterectomy, representative of minor trauma, and the spine group underwent a hemilaminectomy, representative of major trauma. Serial evaluation of serum CK and CRP was performed both pre- and postoperatively on the 2 groups of patients in order to evaluate the potential use of the 2 analytes as measures of the severity of trauma. The hypotheses were as follows: (1) within the spay group, CRP and CK would both be within the normal reference ranges on presentation, would increase markedly after surgery and then decline to normal levels; (2) within the spine group, CRP and CK would both be elevated on presentation with CRP displaying a similar postoperative pattern to the spay group although with a more marked increase. In addition, CK would increase to very high levels postoperatively before declining, but remain elevated above the level of the spay group throughout the study.

MATERIALS AND METHODS

This project was a prospective descriptive study on dogs presented to the OVAH, Faculty of Veterinary Science, University of Pretoria, South Africa. The research protocol was approved by the University of Pretoria's Animal Use and Care Committee. Forty-three dogs presented between August 2006 and April 2007 were included in the study. Twenty-two dogs were presented for surgical treatment of thoracolumbar disc prolapse. A further twenty-one dogs were presented for elective ovariohysterectomy. All dogs admitted to the study were at least 7 months of age and had no history of trauma or any inflammatory process within the previous month, with the exception of the occurrence of the disc prolapse in the case of the spine group. No dogs were in season or pregnant. Dogs selected for the spine group were of either sex, entire or neutered.

Experimental procedure

All dogs admitted to the study underwent a thorough clinical evaluation, which included assessment of temperature, pulse and respiration and examination of a thin peripheral blood smear. Each dog had an intravenous catheter placed in the cephalic vein and premedication was administered intravenously. The dogs received intravenous fluids (Ringer's Lactate) at 10 mℓ/kg/h for the duration of the surgical procedure. General anaesthesia was induced with intravenous thiopentone and maintained with isoflurane in oxygen. An indwelling 16-gauge, over-the-needle catheter was placed in a jugular vein shortly after anaesthetic induction. Two millilitres of blood was collected from the jugular vein using the indwelling catheter shortly after induction, immediately after completion of the surgical procedure and thereafter at 4, 6, 8, 12, 24 and 48 hours postoperatively. The samples were centrifuged for 10 min at 1520 *g* and the serum harvested.

The CRP assay was performed as a batch at the end of the trial to avoid inter-assay differences. All CRP samples were stored at –80 °C until the assay was performed. Postoperatively and for the duration of the study, patients were housed in the intensive care unit of the OVAH. Postoperative care and housing was standardised as far as possible for all animals.

All surgery was performed by the same surgeon (the principal investigator) with operative procedures standardised as far as possible. Ovariohysterectomy was performed by means of a midline coeliotomy. Both ovaries and the uterus up to the level of the cervix were removed and ligated with chromic catgut. Clamping of the genital tract was avoided. In the case of the spine group, a dorsolateral surgical approach to the affected intervertebral space was made and the epaxial muscles retracted. A hemilaminectomy was performed over the affected disc space[23,26].

Observation

The blood samples collected were tested to determine the CRP and CK values at the predetermined intervals for both groups of dogs. CK activity in serum samples was measured using an automated colorimetric assay. The analysis was performed using an automated analyser (Nexct, Alfa Wasserman, The Netherlands) according to the manufacturer's instructions. The assay temperature was 37 °C and no reducing agent was used. The precision of the assay was 2.35 % and the assay was linear up to 1685 U/ℓ. Autodilution was performed as required according to the analyser programming with a diluent supplied by the manufacturer. CRP concentrations in serum samples were measured using an automated human C-Reactive Protein Turbidometric Immunoassay validated for use in dogs, (Bayer CRP TIA, Newbury, UK)[21].

Statistical analysis

All analyses were carried out using Stata 10.0 (StataCorp, College Station, TX, U.S.A.). Normality of the data was assessed by visual inspection of histograms and using the Shapiro-Wilk test. All data were then log-transformed to achieve near-normality. No identification or removal of outliers was performed. Log-transformed values of CK and CRP for spay and spine groups were plotted in order to examine the changes over time in each group. Within each group, geometric mean values at each time point were compared with the pre-operative geometric means using repeated measures analysis of variance and the Bonferroni-Holm multiple comparison test. Comparisons between groups were also done at each time point, adjusting for sex and body mass. Median times to maximum concentration of CK and CRP were compared between groups using the Wilcoxon rank-sum test. Log-transformed areas under the curve were compared between groups using multiple regression, adjusting for sex and body mass. A significance level of $\alpha = 0.05$ was used throughout.

RESULTS

The preoperative results for CK and CRP are represented by the histograms in Fig. 1 and Fig. 2 respectively. In both groups the results encompassed a wide range and were not normally distributed. Although the median CK activity on presentation was greater in the spine group, in both spay and spine groups the medians were greater than the upper limit of the OVAH reference interval (49-146 U/ℓ). A dog in the spay group had the highest CK activity of all the dogs in the study. The overall range of CRP concentration was similar in both groups and the medians both fell within the normal reference range of the OVAH (<35 mg/ℓ). A dog in the spay group had the highest CRP concentration.

Figure 3 shows the mean CK values for each time point for both spay and spine groups. Both groups had a similar basic trend of postoperative peak and subsequent decline. It is clear that the spine group had a greater and more sustained increase in activity compared with the spay group, with all postoperative time points being significantly different between the 2 groups ($P < 0.05$). Within the spay group, only the 4 hour postoperative mean was significantly elevated from the preoperative mean ($P = 0.015$). Within the spine group, all postoperative time point means were significantly elevated over the preoperative mean ($P = 0.015$). Median time to maximum CK activity was significantly greater in the spine group (12 h) than in the spay group (4 h) ($P < 0.001$). Adjusted for sex and body mass, the area under the curve for the spine group was significantly greater than that of the spay group ($P < 0.001$). Figure 4 shows the mean CRP values for each time point for both spay and spine groups. The results appear broadly similar in the 2 groups with an immediate postopera-

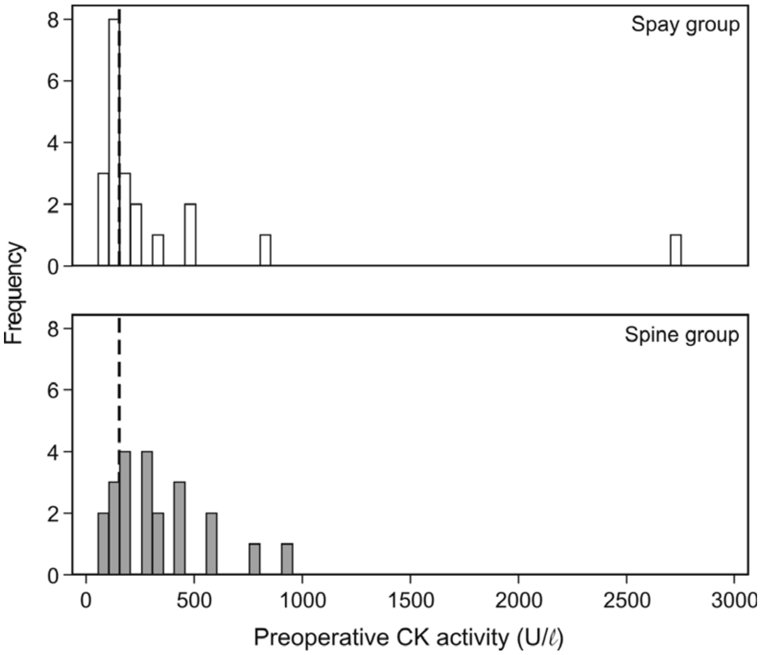

Fig. 1: **CK preoperative results for the spay and spine groups. The dashed line represents the upper limit of the OVAH reference interval.**

tive elevation, although the spay group tended to peak earlier. Median time to maximum CRP concentration was 12 hours in the spay group *vs* 24 hours in the spine group ($P = 0.066$). However, no significant differences were found between the 2 groups at any time point. All time points, except the immediate postoperative one, were found to be significantly different from the preoperative mean in both the spay and spine groups ($P < 0.05$).

DISCUSSION

The stated hypotheses were found to be supported with 2 exceptions. CK activity in dogs admitted for ovariohysterectomy was found to be greater at presentation than the upper limit of the OVAH reference interval and CRP concentration was not elevated in the spine group on presentation.

The high CK median obtained for the spay group on presentation was unexpected[2,3]. This study was comprised of a group of clinically normal animals and a median more in line with other reference values was expected. Individual animals may have been exposed to potentially confounding preanalytical events not ascertained by the history such as exercise, injections or trauma which may have influenced the results[2]. The same was of course also potentially true for the spine group. Adult levels of CK are reportedly reached in dogs by the age of 7 months[8]. However, other studies have found that dogs between 6 and 12 months of age had a significantly higher mean CK activity level (73 ±h SD 27 U/ℓ) compared with dogs over 1 year of age (46 ±h SD 22 U/ℓ)[2,3]. This may at least partially account for the high CK level on presentation in the spay group as they were on the whole much younger than the spine group, with 50 % of the spay group less than 1 year of age. Although the CK levels in both the spay and spine groups displayed a postoperative rise to peak and subsequent decline, it is interesting that in the spay group, only the 4 hour mean was significantly elevated from the preoperative levels. This suggests that the degree of muscle trauma in the spay group was not only relatively minor but also not sustained. The reason for this is probably that the surgical approach was made through the linea alba with minimal trauma to striated muscle. In addition, it is known that the soft tissues and smooth muscle in the genital tract contain very little CK[14].

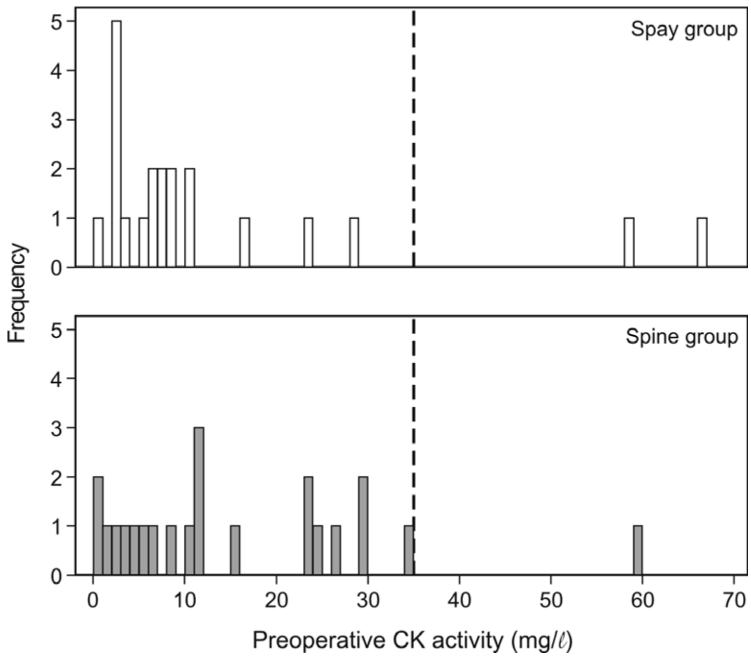

Fig. 2: **CRP preoperative results for the spay and spine groups. The dashed line represents the upper limit of the OVAH reference interval.**

The higher median CK seen in the spine group on presentation was in line with expectations, although statistically there was no significant difference between preoperative spine and spay group activity. The spine group showed an immediate postoperative rise and was significantly elevated over preoperative levels at all time points. The maximum CK activity levels were found at about 12 hours postoperatively. These were perhaps somewhat lower than might have been anticipated when one considers the nature of the surgical procedure, in particular the approach[23,26]. The greatest CK value in the spine group was below 10000 U/ℓ and only 4 results at any of the time points were over 5000 U/ℓ, with 3 of those from 1 dog. This should be considered against reports that a single intramuscular injection of chloramphenicol can result in CK elevations of greater than 60 times normal values and that in racing sled dogs, for instance, CK activity levels of less than 5000 U/ℓ have been regarded as not significant[3,5,12]. These events are of course not directly comparable, but should perhaps make clinicians question the value of isolated CK measurements. A study evaluating CK in dogs undergoing laparoscopic ovariohysterectomy supported this view, concluding that CK was not useful as a measure of surgical stress as the postoperative increases of CK in their patients differed widely, despite their undergoing a uniform procedure[7]. Other authors have further suggested that when utilising CK as a measure of

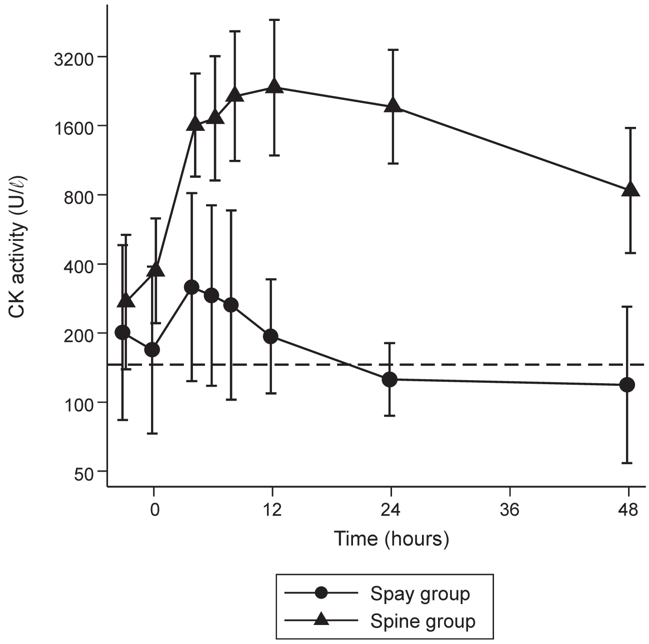

Fig. 3: **Mean CK values for each time point for both spay and spine groups. The dashed line represents the upper limit of the OVAH reference interval. Time 0 is the immediate postoperative time point. The means were significantly different at all time points between the 2 groups except preoperatively**.

trauma, isolated measurements of CK activity are of little use. The aim should rather be to obtain a more complete profile of CK activity over time so as to accurately estimate the Area Under the Curve (AUC)[11,12]. This calculation has been used to accurately quantify and compare muscle damage in dogs under various circumstances[1,5,12,27]. This approach perhaps improves CK as a tool, but it necessitates many more CK measurements over time and may be too cumbersome to apply in a clinical environment.

Both spay and spine groups exhibited a wide range in the CRP results on presentation. Although the CRP median for the spine group was higher than that of the spay group, for both groups it fell well within the normal OVAH laboratory range. This makes sense for the spay group where there were no anticipated reasons for increased levels. It is, however, more difficult to explain why the spine group's preoperative values were not more elevated. It may be that the insult experienced by the body is very localised and therefore that the actual trauma is comparatively minor, despite having potentially severe consequences. The wide range of preoperative values in this study suggests that, as for CK, single CRP measurements, even if elevated, need to be interpreted with caution. The highest preoperative CRP value was found in a clinically healthy dog from the spay group. However, the peak in mean postoperative CRP concentration was at a point between 12 and 24 hours for both groups as it was for CK in the spine group. This time period may thus be the most informative interval in which to monitor both CK and CRP levels in traumatised animals.

The similarity of the postoperative CRP results between the 2 groups was perhaps a little surprising (Fig. 4). In a recent review of acute phase proteins, the authors stated that postoperative CRP increases are approximately proportional to the intensity of surgical trauma[10]. Macroscopically, it seems that the surgical procedure for spinal decompression is much more traumatic than an ovariohysterectomy and that this should be reflected by higher CRP concentrations. CRP values were found to increase much more in orthopaedic surgery compared with ovariohysterectomy in 1 study, and the authors concluded that the rise in CRP was indeed proportional to the intensity of surgical trauma[29]. Another, larger study found the opposite, with the median CRP concentration 24 hours postoperatively being higher in dogs undergoing ovariohysterectomy than in dogs undergoing orthopaedic procedures[9]. In human studies, no correlation has been found between serum CRP concentration and severity of injury or survival[15]. In other words CRP appears to be a sensitive indicator of trauma but cannot be used as a reliable quantitative measure of trauma. Single time point values are, however, probably more applicable to CRP than to CK. CRP is used as an indicator of inflammation in human medicine and clinically relevant cut-off points have been used routinely for various conditions[16,21,28]. This has not yet reached the same level of sophistication in veterinary medicine, although the relatively rapid production and clearance of CRP should make it a relevant indication of the clinical situation in an animal at any given time, or at least provide proof of the presence or otherwise of an inflammatory process[10,13]. The same should be true for any traumatic process. CRP levels may thus be most applicable in the monitoring of cases where a particular inflammatory or trau-

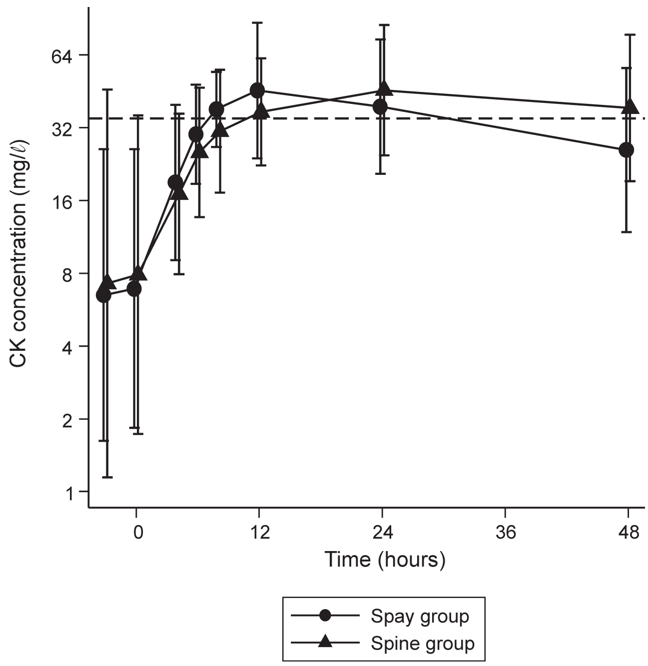

Fig. 4: **Mean CRP values for each time point for both spay and spine groups. Time 0 is the immediate postoperative time point. The dashed line represents the upper limit of the OVAH reference interval. There was no significant difference between the means of the 2 groups at any time point.**

matic condition is already known to be present. CRP cut off points could then be used prognostically, or the CRP trend used to monitor progress and efficacy of treatment[10,16].

The ability to quantitatively measure the degree of trauma in an injured animal would be useful therapeutically and prognostically. CRP and CK have both been used previously as measures of trauma and were thus evaluated and compared in this study. A wide range of results was obtained for each time point for both CRP and CK, although as groups they followed a predictable pattern over time after trauma. The results of this study suggest that measuring the serum levels of CK and CRP in a traumatised dog at a single time point, for instance on presentation, is of limited value. Establishing the maximal CK and/or CRP levels is similarly of little clinical use. The information gained does not necessarily accurately reflect the degree or severity of trauma suffered by the animal. The time interval 12–24 hours post-trauma is potentially the most informative for both analytes, especially if a baseline value is available for comparison. The trend over time, even a relatively short time period of 48 hours, will provide the most meaningful information.

REFERENCES

1. Aktas B M, Vinclair P, Autefage A, Lefebvre H P, Toutain P L, Braun J P 1997 *In vivo* quantification of muscle damage in dogs after general anaesthesia with halothane and propofol. *Journal of Small Animal Practice* 38: 565–569
2. Aktas M, Auguste D, Concordet D, Vinclair P, Lefebvre H, Toutain P L, Braun J P 1994 Creatine kinase in dog plasma: preanalytical factors of variation, reference values and diagnostic significance. *Research in Veterinary Science* 56: 30–36
3. Aktas M, Auguste D, Lefebvre H P, Toutain P L, Braun J P 1993 Creatine kinase in the dog: a review. *Veterinary Research Communications* 17: 353–369
4. Aktas M, Lefebvre H P, Toutain P L, Braun J P 1995 Disposition of creatine kinase activity in dog plasma following intravenous and intramuscular injection of skeletal muscle homogenates. *Journal of Veterinary Pharmacology and Therapeutics* 18: 1–6
5. Aktas M, Vinclair P, Lefebvre H P, Toutain P L, Braun J P 1995 *In vivo* quantification of muscle damage in dogs after intramuscular administration of drugs. *British Veterinary Journal* 151: 189–196
6. Atabekoglu C, Sönmezer M, Gungor M, Aytac R, Ortac F, Unlu C 2004 Tissue trauma in abdominal and laparoscopic-assisted vaginal hysterectomy. *Journal of the American Association of Gynecologic Laparoscopists* 11: 467–472
7. Austin B, Lanz O I, Hamilton S M, Broadstone R V., Martin R A 2003 Laparoscopic ovariohysterectomy in nine dogs. *Journal of the American Animal Hospital Association* 39: 391–396
8. Bender H 2003 Muscle. In Latimer K S, Mahaffey A M, Prasse K W (eds) *Veterinary laboratory medicine.* Iowa State Press, Ames: 260–269
9. Caspi D, Snel F W J J, Batt R M, Bennett D, Rutteman G R, Hartman E G, Baltz M L, Gruys E, Pepys M B 1987 C-reactive protein in dogs. *American Journal of Veterinary Research* 48: 919–921
10. Ceron J J, Eckersall P D, Martinez-Subiela S 2005 Acute phase proteins in dogs and cats: current knowledge and future perspectives. *Veterinary Clinical Pathology* 34: 85–99
11. Chanoit G P, Lefebvre H P 2004 Speaking out. *Journal of the American Animal Hospital Association* 40: 2–3
12. Chanoit G P, Lefebvre H P, Orcel K, Laroute V, Toutain P L, Braun J P 2001 Use of plasma creatine kinase pharmacokinetics to estimate the amount of exercise-induced muscle damage in beagles. *American Journal of Veterinary Research* 62: 1375–1380
13. Conner J G, Eckersall P D, Ferguson J, Douglas T A 1988 Acute phase response in the dog following surgical trauma. *Research in Veterinary Science* 45: 107–110
14. DiBartola S P, Tasker J B 1977 Elevated serum creatine phosphokinase: a study of 53 cases and a review of its diagnostic usefulness in clinical veterinary medicine. *Journal of the American Animal Hospital Association* 13: 744–753
15. Giannoudis P V, Hildebrand F, Pape H C 2004 Inflammatory serum markers in patients with multiple trauma. Can they predict outcome? *Journal of Bone and Joint Surgery, British volume* 86: 313–323
16. Holm J L, Rozanski E A, Freeman L M, Webster C R L 2004 C-reactive protein concentrations in canine acute pancreatitis. *Journal of Veterinary Emergency and Critical Care* 14: 183–186
17. Holub Z, Jabor A, Sprongl L, Kliment L, Fischlova D, Urbanek S 2002 Inflammatory response and tissue trauma in laparoscopic hysterectomy: comparison of electrosurgery and harmonic scalpel. *Clinical and Experimental Obstetrics and Gynecology* 29: 105–109
18. Iwanaka T, Arai M, Ito M, Kawashima H, Imaizumi S 2000 Laparoscopic surgery in neonates and infants weighing less than 5 kg. *Pediatrics International* 42: 608–612
19. Kumbhare D, Parkinson W, Dunlop B 2008 Validity of creatine kinase as a measure of muscle injury produced by lumbar surgery. *Journal of Spinal Disorders and Techniques* 21: 49–54
20. Kumbhare D, Parkinson W, Dunlop B, Ryan E, Denkers M, Shah A, Bobba R, Adachi J 2007 Biochemical measurement of muscle injury created by lumbar surgery. *Clinical Investigative Medicine* 30: 12–20
21. Kjelgaard-Hansen M, Jensen A L, Kristensen A T 2003 Evaluation of a commercially available human C-reactive protein (CRP) turbidometric immunoassay for determination of canine serum CRP concentration. *Veterinary Clinical Pathology* 32: 81–87
22. Kotil K, Tunckale T, Tatar Z, Koldas M, Kural A, Bilge T 2007 Serum creatine phosphokinase activity and histological changes in the multifidus muscle: a prospective randomized controlled comparative study of discectomy with or without retraction. *Journal of Neurosurgery. Spine* 6: 121–125
23. Lubbe A M, Kirberger R M, Verstraete F J M 1994 Pediculectomy for thoracolumbar spinal decompression in the dachshund. *Journal of the American Animal Hospital Association* 30: 233–238
24. Murata H, Shimada N, Yoshioka M 2004 Current research on acute phase proteins in veterinary diagnosis: an overview. *Veterinary Journal* 168: 28–40
25. Petersen H H, Nielsen J P, Heegaard P M 2004 Application of acute phase protein measurements in veterinary clinical chemistry. *Veterinary Research* 35: 163–187
26. Sharp N, Wheeler S 2005 Thoracolumbar disc disease. In *Small animal spinal disorders. Diagnosis and surgery.* Elsevier Mosby, Edinburgh: 121–159
27. Strain G M, Kerwin S C, Tedford B L, Johnson R P 1998 Creatine kinase level changes following electromyography in the normal anaesthetized dog. *Veterinary Journal* 156: 231–233
28. Verma S, Szmitko P E, Ridker P M 2005 C-reactive protein comes of age. *Nature Clinical Practice Cardiovascular Medicine* 2: 29–36
29. Yamamoto S, Shida T, Miyaji S, Santsuka H, Fujise H, Mukawa K, Furukawa E, Nagae T, Naiki M 1993 Changes in serum C-reactive protein levels in dogs with various disorders and surgical traumas. *Veterinary Research Communications* 17: 85–93