Evaluation of inflammatory and hemostatic surgical stress responses in male cats after castration under general anesthesia with or without local anesthesia

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Objective—to characterize acute inflammatory and hemostatic surgical stress responses following castration in cats and to evaluate whether the addition of local anesthesia to the anesthetic protocol attenuates these responses.

Animals—39 male cats.

Procedures—Cats undergoing castration were randomly assigned to 2 groups: both groups underwent surgery with general anesthesia, and 1 group additionally received a local anesthetic (lidocaine [2.0 mg/kg in total, divided intratesticularly and SC]) prior to incision. Blood samples were collected after anesthetic induction (baseline) and 1, 5, and 24 hours later. Thromboelastography and coagulation variables (activated partial thromboplastin time [aPTT] and prothrombin time [PT]) were analyzed; fibrinolysis was assessed with plasma D-dimer concentrations. The acute-phase response was evaluated via measurement of plasma fibrinogen and serum amyloid A (last time point, 28 hours) concentrations. Hematologic variables were analyzed at baseline and 1, 5, and 24 hours later.

Results—Evidence of hemostatic and inflammatory activation after surgery was detected in both groups. Maximum amplitude and G (global clot strength) were significantly increased at 24 hours, and significant, but not clinically relevant, decreases were detected in aPTT at 5 and 24 hours and in PT at 24 hours, compared with baseline values. Serum amyloid A concentrations were significantly higher at 24 and 28 hours than at baseline, and plasma fibrinogen concentration was significantly increased at 24 hours; WBC and RBC counts and Hct were significantly increased at multiple time points. No differences between groups were detected for any variables.


Elective neutering of dogs and cats comprises the most commonly performed surgical procedures in veterinary practice. Castration of male cats is perceived as a minimally invasive, routine surgery because of the short duration of the procedure and the small incisions required, and little attention has traditionally been paid to postoperative sequelae that potentially affect homeostatic mechanisms in these cats.

Postoperative inflammatory and hemostatic surgical stress responses in humans have been widely reported. Surgery and immobilization are considered some of the risk factors for hypercoagulability (ie, increased tendency toward blood clotting) and thrombosis. Similar hemostatic responses, characterized by decreased antithrombin activity and increased D-dimer concentrations, have been reported in horses; in pigs, decreases in thrombin time and antithrombin activity after surgery have been described.
We have previously demonstrated postoperative hypercoagulability in dogs after ovariohysterectomy. This response was characterized by increased MA measured via thromboelastography and thus increased G (global clot strength), combined with decreases over time of von Willebrand factor and factor VIII and shortened PT and thrombin time. Increased circulating D-dimer concentrations after surgery were also detected.

Cats with cardiomyopathies or other systemic diseases, including inflammatory conditions, often have hypercoagulability, but to the authors’ knowledge, no studies to date have evaluated hemostatic responses to surgery in cats. Serum amyloid A is a major acute-phase protein in cats, and SAA concentration has been shown to increase in female cats after spaying. However, the acute-phase response in male cats following castration has not been characterized.

Results of previous studies have indicated that castration is moderately painful and warrants the use of perioperative analgesia. Local anesthetics are typically inexpensive and provide a simple method to block afferent neural stimuli from the surgical site, and use of these drugs has been shown to reduce endocrine-metabolic responses to surgery but not inflammatory responses in humans. Several authors have reported evidence of analgesia and improvement in clinical signs following administration of local anesthetics in nonhuman animals, including pigs, lambs, calves, dogs, and cats, but information about the potential modifying effect of local anesthetics on the surgical stress response in these species is scarce.

Monitoring of hemostasis has traditionally focused on measuring PT and aPTT. Thromboelastography has been widely used in human medicine and, more recently, has also gained popularity as a method to monitor hemostasis in veterinary patients. The method allows for a global assessment of hemostatic function from initiation of clotting through amplification and propagation of clot formation to fibrinolysis, including the interaction of platelets with coagulatory plasma proteins, and is therefore considered a valuable addition to the monitoring of plasma variables alone. Thromboelastography has been used in other studies in cats, but little information is available on the use of this technique for the evaluation of hypercoagulability in feline surgical patients.

The purpose of the study reported here was to characterize the acute inflammatory and hemostatic surgical stress responses following castration, considered a minor surgery, in cats and to determine whether the addition of local anesthesia to the anesthetic protocol would modify these responses.

Materials and Methods

Animals—Thirty-nine client-owned sexually intact male cats admitted to the Department of Small Animal Clinical Sciences for routine castration were prospectively enrolled in the study. These included 34 domestic shorthair and domestic longhair cats and 1 each of Balinese, Oriental, Bengal, Maine Coon, and British Shorthair breeds. All cats underwent a thorough clinical examination. Inclusion criteria for entering the trial were that cats were healthy, had received no medication or vaccinations during the preceding month, were between 6 months and 3 years of age, and had apparently normal testicular anatomy. Written owner consent was obtained before enrollment. The study was approved by The Animal Experiments Inspectorate of Denmark (Dyreforsøgstilsynet) and the Research and Ethics Committee at the Department of Small Animal Clinical Sciences, Faculty of Life Sciences, Copenhagen University, Copenhagen.

Study design—The study was a prospective, randomized, blinded clinical trial and was performed at the Department of Small Animal Clinical Sciences between February and July 2008. Laboratory analyses were performed at the Department of Small Animal Clinical Sciences Central Laboratory.

Cats were each assigned consecutive numbers at enrollment and were randomly assigned to 1 of 2 groups after anesthetic induction. Cats in one group (n = 19) were assigned to undergo routine castration under general anesthesia only; cats in the other group (20) were assigned to undergo routine castration under general anesthesia with local anesthetic administration (intratesticularly and SC) prior to incision. Forty sealed envelopes containing cards indicating general or general and local anesthesia (20 each) were prepared and randomly numbered from 1 to 40. The envelope with the number corresponding to the number assigned to the cat at enrollment was opened after induction of general anesthesia.

Induction and maintenance of anesthesia—A 20-gauge IV catheter was aseptically placed in a cephalic vein. Cats were premedicated with midazolam (0.25 mg/kg, IV) and ketamine (2.5 mg/kg, IV) and anesthetized with propofol (4.0 mg/kg, IV). To facilitate intubation, lidocaine (0.5 mg, diluted with sterile saline [0.9% NaCl] solution to a 10% concentration) was instilled into the larynx. A cuffed endotracheal tube (size range, 3.0- to 4.0-mm internal diameter; selected according to the size of cat) was placed, and anesthesia was maintained with isoflurane in oxygen and air at an end-tidal concentration of 1.6%. Cats were automatically ventilated with 10 to 11 breaths/min at 15 to 20 cm H₂O. Ventilator settings were regulated to maintain end-tidal CO₂ between 33 and 50 mm Hg. All cats were administered a crystalloid solution (10 mL/kg/h, IV) throughout anesthesia and surgery. Blood pressure was measured with oscillometry. If the mean arterial blood pressure was < 60 mm Hg, systolic arterial blood pressure was < 90 mm Hg, or if diastolic arterial blood pressure was < 40 mm Hg, a bolus of the crystalloid solution was administered.

Cats that were randomly assigned to receive the local anesthetic were given lidocaine (2.0 mg/kg in total, divided intratesticularly and SC at each incision site) by the anesthetist using a 25-gauge, 1-inch needle 5 minutes prior to incision. In cats undergoing surgery with general anesthesia only, the anesthetist palpated the testicles and the surgeon waited 5 minutes before creating an incision.

If signs of insufficient anesthetic depth (pulse rate > 200 beats/min, MAP > 120 mm Hg for 2 minutes, or
muscle activity) were detected, rescue anesthesia was provided. This protocol consisted of ketamine administration (1 mg/kg, IV) and incremental (0.2%) adjustments of the isoflurane concentration to effect. Cats requiring rescue anesthesia were excluded from further participation in the study.

Following completion of the surgery, cats were weaned off of the ventilator. After spontaneous breathing resumed, all cats received an injection of medetomidine (2 µg/kg, IV) to prevent muscle rigidity during anesthetic recovery.

Surgery and postoperative analgesia—One surgeon (ERM) performed all of the castrations. The study was performed in a blinded manner, and only the anesthetist was aware of the group assignment of each cat. The protocol was chosen on the basis of a preliminary investigation with 9 cats (data not shown) that was performed to evaluate whether surgeons blinded to treatment groups could determine which testicles had been injected and which had only been palpated; results revealed that they could not. In addition, to avoid any influence from the monitoring equipment, this was muted and positioned so that it was facing away from the surgeon. Intraoperative monitoring included pulse rate, and positioned so that it was facing away from the surgeon.

In addition, to avoid any influence from the monitoring equipment, this was muted and positioned so that it was facing away from the surgeon. Intraoperative monitoring included pulse rate, noninvasive blood pressure measurements, and ECG, in addition to oxygen saturation and capnography.

The scrotum was clipped of hair and aseptically prepared for surgery, and castration was performed according to the technique described by Fossum et al. Cats were hospitalized in a quiet room for approximately 28 hours after surgery. Immediately after surgery, all cats received injections of buprenorphine (15.0 µg/kg, IM) and ketoprofen (2.0 mg/kg, SC). Ketoprofen (1.0 mg/kg, PO, q 24 h) was administered for the next 3 days.

Blood sample collection—Immediately after anesthetic induction, a 20-gauge, 32-mm peripheral IV catheter was aseptically placed in a saphenous vein and a baseline blood sample was collected. The catheter was then flushed with 1 mL of sterile saline solution and bandaged in place. Blood samples were collected in the same manner 1, 5, and 24 hours later; the first 1 mL of blood was discarded at each sample collection time. Sterile saline solution was used to flush the catheter between blood sample collections. After baseline and the 1-hour sample collection, the catheter was flushed once. After 5 hours, it was flushed immediately after blood collection and then once overnight by a staff member at approximately 10:00 PM. The IV catheter was removed after the 24-hour sample was obtained, and at 28 hours, blood for SAA concentration measurements was collected via right jugular venipuncture. At each of the first 4 time points (baseline and 1, 5, and 24 hours), 5 mL of blood was collected in a syringe and transferred to 1 separator tube, 2 tubes containing 3.2% sodium citrate, and 1 tube containing EDTA, in that order. The EDTA- and sodium citrate–containing tubes were inverted carefully 5 times to ensure adequate mixing of the sample. At 28 hours, 2 mL of blood was collected in a separator tube. At baseline and at 1, 5, and 24 hours, hematologic and hemostatic analysis was performed in addition to thromboelastography and SAA concentration determination. At 28 hours, only SAA concentration was analyzed.

Laboratory analysis—All blood samples were immediately transported to the laboratory after collection. Citrated samples were stored at room temperature (approx 22°C) for 30 minutes before analysis, and the serum separator tubes were stored in an upright position at room temperature for 1 hour before the samples were centrifuged. Serum samples were divided; one sample was analyzed, and the other sample was stored in a freezer at −80°C. The EDTA-treated blood samples were analyzed for hematologic variables consecutively.

Thromboelastography—Thromboelastography of citrated whole blood was performed with diluted recombinant human tissue factor as the activator by use of a computerized thromboelastography analyzer according to the method described by Winnberg et al; all analyses were performed by 1 operator. The analyses were run for approximately 100 minutes, and data were continuously transferred from the analyzer to a computer. Four thromboelastography variables were analyzed: R (reaction time), K (clot formation time), α angle, and MA. Global clot strength was then calculated with the formula G = 5,000 × MA/(100 – MA). Reaction time constitutes the distance in millimeters from the start of the tracing to the point where a preset fibrin clot is achieved (this is measured as a 2-mm increase in amplitude of the tracing). Clot formation time is measured in millimeters from the end of R until amplitude reaches 20 mm. The α angle represents the speed at which fibrin forms and cross-links (ie, clot formation). Maximum amplitude is a measure of the strength of the fibrin clot; MA and G provide the same information because G is a mathematical transformation of MA.

Coagulation, fibrinolysis, and acute-phase response—Citrated plasma was collected via pipette after centrifugation at 4,400 g for 3 minutes. All coagulation tests were performed with an automated coagulation analyzer. The following variables were measured: aPTT, PT, and fibrinogen concentration. Available pooled plasma samples from healthy cats that had not undergone surgery were used as reference standards.

As a measure of fibrinolysis, plasma D-dimer concentrations were measured with a point-of-care reader that uses an immunometric flow-through principle. Serum amyloid A concentration was determined via a turbidometric immunoassay.

Hematologic and biochemical analysis—Hematologic analysis comprised WBC (total leukocyte), RBC, granulocyte, lymphocyte, monocyte, eosinophil, basophil, and platelet counts and measurement of total hemoglobin concentration and Hct. At baseline, serum biochemical and electrolyte analysis was also performed to confirm the cats’ health. This included assessment of alanine aminotransferase, alkaline phosphatase, γ-glutamyl transferase, amylase, and lipase activities and measurement of glucose, BUN, creatinine, cholesterol, total bilirubin, albumin, total protein, fructoseamine, bile acids, calcium, magnesium, phosphate, sodium, and potassium concentrations.
Statistical analysis—All analyses were performed with a statistical software package. Associations between age or body weight and treatment group were assessed by comparing mean ± SD for variables between the 2 groups. Variables were initially tested for normality and pairwise correlations. Log transformation was performed when data did not follow a normal distribution. Linear mixed models, including a random intercept for cat, were applied to detect differences between the treatment groups and between time points for each of the outcome variables. Normality of residuals was assessed via a normal quantile plot. If logarithmic transformation failed to normalize variable distribution, quantile regression was performed because this procedure does not rely on assumptions of normality. The exception was the variable D-dimer concentration, which was dichotomized with a cutoff at < 0.2 and analyzed via a random effects logistic regression model, with cat added as a random effect. Median and range data were reported when data did not follow a normal distribution. A conservative value of $P \leq 0.01$ was considered significant, in an attempt to control for multiple comparisons.

Results

One cat in the general anesthesia group was excluded from the study because of exaggerated hemodynamic responses and movement during anesthesia and the resultant use of rescue anesthesia. The remaining 18 cats in the general anesthesia group and 20 cats in the general and local anesthesia group completed the study. There was no significant difference in age between the general (11.06 ± 5.1 months) and general

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<td>11.2 (7.4–13.5)</td>
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<td>2.48 ± 0.78*</td>
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<td>SAA (mg/L)</td>
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<td>2.7 (0–60.9)*</td>
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<td>28</td>
<td>2.1 (0–63.1)*</td>
<td>3.0 (0–39.7)*</td>
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</table>

Data are reported as mean ± SD or median (range). Baseline (time 0) values were obtained immediately after induction of general anesthesia and remaining times were measured from baseline. Some samples were excluded at certain time points because of technical problems. Pooled plasma samples from healthy cats were used as a reference standard for hemostatic variables. Reference intervals were obtained from the Central Laboratory at the Department of Small Animal Clinical Sciences, Faculty of Life Sciences, University of Copenhagen.

*Values are significantly ($P < 0.05$) different from baseline.

$G =$ Glut con. sloth. $K =$ Clotting time. $NA =$ Reference interval not available. $R =$ Reaction time.
and local (11.05 ± 4.3 months) anesthesia groups; body weight was also comparable between the 2 treatment groups at 4.0 ± 0.7 kg and 4.1 ± 0.8 kg, respectively. Results of baseline hematologic and serum biochemical analysis in all cats were within the laboratory reference intervals, and baseline values for evaluated variables did not differ significantly between groups.

There was no difference between the 2 treatment groups for any variables at any time point. However, significant changes over time were detected within groups for several variables. Mean ± SD or median and range values for each time point were calculated for each treatment group (Tables 1 and 2). Some measurements were missing for certain time points because of measurement errors or coagulated blood samples; the number of samples for each variable and each time point were summarized.

The degree of clustering within cat was high for all variables, with intraclass correlation coefficients (ρ) ranging from 0.3 for R to 0.69 for plasma fibrinogen concentration. Strong correlations (ρ > 0.7) existed between several related variables, as expected, with the strongest correlation observed between α angle and K (ρ = 0.98). The correlation between fibrinogen concentration and MA was 0.34.

**Thromboelastography variables**—For MA and thus G, a significant (P < 0.01) increase was detected at 24 hours, compared with baseline values. For the other thromboelastography variables, there was no change over time.

**Coagulation, fibrinolysis, and acute-phase response indicators**—Values were significantly decreased from baseline for aPTT at 5 (P = 0.002) and 24 hours (P = 0.003). The PT data were not normally distributed after logarithmic transformation and were analyzed via quantile regression. The PT was also significantly (P = 0.01) decreased at 24 hours, compared with the baseline value.

For plasma D-dimer concentration, the odds of having a value of ≥ 0.2 were analyzed via random effects logistic regression because of highly skewed data, with 84 of 143 (59%) measurements being 0.1 mg/L, 26 (18%) being 0.2 mg/L, and the remainder being between 0.3 and 20 mg/L. There was no change over time for this variable.

The SAA concentration was significantly (P < 0.001) increased at 24 and 28 hours, compared with baseline values (assessed as logarithmically transformed variables). Plasma fibrinogen concentration at 24 hours was also significantly (P < 0.001) increased, compared with baseline.

**Hematologic variables**—The WBC counts were significantly increased from baseline at 1 (P < 0.001), 5 (P < 0.001), and 24 (P = 0.003) hours. For granulocyte counts, there was a significant (P < 0.001) increase at all time points after baseline, and monocytes were significantly (P < 0.001) increased at 5 hours. The RBC counts at 5 (P = 0.002) and 24 (P < 0.001) hours, hemoglobin concentration at 24 hours (P = 0.001), and Hct at 5 (P = 0.003) and 24 (P < 0.001) hours were significantly increased, compared with baseline values.

**Discussion**

In the study reported here, inflammatory and hemostatic responses following castration (ie, surgical
This was consistent with the findings of Sasaki et al7 that in the present study was used, the range of SAA in SAA values reported after spaying of female cats7 were approximately 24 hours after surgery before declining, in SAA concentrations in cats after surgery, peaking approximately in human23,24 and veterinary patients2,3,25 from other studies. The discovery of postoperative hypercoagulability in cats of the present study is consistent with findings of local anesthesia to the anesthetic protocol did not attenuate the surgical stress response following castration. The discovery of postoperative hypercoagulability in humans13,24 and veterinary patients2,3,25 from other studies.

Serum amyloid A is one of the major acute-phase proteins in mammals, and concentration of this protein increases markedly during early stages of the acute-phase response.10,25 Serum amyloid A has been shown to be a more sensitive acute-phase marker than C-reactive protein in cats,29 and it may potentially help to differentiate between healthy cats and cats that have experimentally induced inflammation or various diseases or have undergone surgery.7,29 Different authors have reported different ranges for SAA in healthy cats. This is probably attributable to differences in methodology and the lack of standardization for SAA assays.20 In a study by Hansen et al26 in which the same assay as that in the present study was used, the range of SAA in healthy cats was 0.0 to 3.9 g/L, with a median of 0.4 g/L. This was consistent with the findings of Sasaki et al.7 whereas Kajikawa et al26 reported substantially higher values. The latter 2 studies29 revealed steep increases in SAA concentrations in cats after surgery, peaking approximately 24 hours after surgery before declining, consistent with the findings of the present study. The SAA values reported after spaying of female cats were somewhat higher than those found in the present study after castration; however, this is not surprising because ovariohysterectomy is a more invasive surgical procedure than is castration. It may thus be possible that SAA concentrations reflect the degree of surgical trauma in cats.

As is characteristic of its role as an acute-phase protein,28 plasma fibrinogen concentration significantly increased over time in cats of the present study, with a 2-fold increase at 24 hours, compared with the baseline value. It is evident that SAA and plasma fibrinogen concentrations varied similarly with time in cats that underwent castration. The increased fibrinogen concentration was probably the result of increased hepatic production (induced by inflammation at the surgical site) obscuring the decrease that would be expected due to consumption. Plasma fibrinogen concentrations are significantly associated with a risk of thrombotic ischemic disease in humans, although the degree of this risk has not been determined.31 The predictive value of fibrinogen concentration for thrombosis in domestic animals has yet to be established. In recent years, the use of fibrinogen concentration as an acute-phase marker in dogs and cats has been largely superseded by assays such as those for SAA and C-reactive protein concentrations, which typically have greater and more rapid responses to stimulation than the 2- to 4-fold increase that is commonly detected in fibrinogen concentrations.

Prothrombin time in the present study was significantly decreased at 24 hours, compared with baseline, in cats that were castrated under general anesthesia with or without receiving a local anesthetic (lidocaine [2 mg/kg, intratesticularly and SC]) prior to incision. The PT data were not normally distributed, and quantile regression could not take the effect of repeated measurements from the same cat into account. The results should thus be interpreted cautiously because of the lack of independence between observations. Also, the median values at all time points were within the reference range established for cats. It is thus unlikely that the difference in PT at 24 hours was of statistical or clinical relevance.

Fibrinolysis was difficult to evaluate because of severe skewness of the D-dimer variable, and no significant change in concentration over time could be detected for this variable. Although useful in dogs,32 D-dimer concentration has previously been shown to have suboptimal results when evaluating hypercoagulability in cats, and diagnostic performance is known to vary among kits used for D-dimer concentration determination.33,34 Both immunoturbidimetric and latex agglutination tests appear to be of limited value in measuring feline D-dimer concentration,34,35 and this may explain the results. Clinically evident venous thrombosis in cats is rare; pulmonary thromboembolism in 1 study3 had a very low prevalence (0.06%) during a 24-year period, despite evidence indicating that cats with cardiomyopathies or other systemic and inflammatory diseases frequently have hypercoagulability.36 Hyperfibrinolysis could be one of the reasons for this paradox, but findings from the present study could not be used to evaluate that assumption.

The marked increase in WBC counts over time in the present study could be explained by several factors. Even though castration is considered to result in relatively minor tissue trauma (compared with other types of surgery), inflammation is induced at the surgical site and granulocytosis is a well-known feature of the acute-phase response.38 A stress leukogram characterized by increased circulating concentrations of neutrophils and lymphocytes is commonly recognized in cats after surgery37 and is attributed to the release of catecholamines secondary to stress or pain. These factors could also have contributed to the increases in Hct and circulating hemoglobin concentration after surgery in cats of the present study, considering that previous studies38 of dogs have shown this phenomenon to occur as a result of splenic contraction caused by adrenergic stimulation. The increase in Hct and hemoglobin concentration could have been further augmented by mild dehydration because most of the cats were unwilling to eat or drink when hospitalized.

Several factors may influence the acute-phase, inflammatory, and hemostatic stress responses to surgery. Cats are prone to stress in clinical environments. In humans, mental stress has been shown to exert an effect on hemostatic and inflammatory variables, circulating concentrations of C-reactive protein, fibrinogen, and D-dimer, and the degree of platelet activation has been
shown to increase in response to stress, whereas aPTT and PT are not significantly affected.39,40 Stress-related mechanisms could account for the fluctuations of some variables in the study reported here. Stress in hospitalized cats remains a challenge for clinicians and is difficult to avoid completely. The blood sample collection technique used in the present study also has the potential to influence hemostatic variables, and peripheral cannulas may not be ideal for this purpose because of contact activation.41 However, because of the minor degree of surgical trauma associated with castration, use of a central line was considered too invasive and also to have the potential of becoming a confounding variable by increasing the surgical stress response. The findings of hypercoagulability and an activated acute-phase response in cats of the present study corroborated previous findings in other species,2,3,23–25 so it is likely that these limitations were of little importance.

It cannot be excluded that the choice of anesthesia and analgesia influenced results of the present study to some degree. The administration of crystalloids may influence results of the present study.28,29

The incorporation of local anesthetic techniques into the anesthetic protocol has gained widespread acceptance in small animal practice in recent years as a cost-effective and effective method for blocking acute surgical pain.37 Regional anesthesia with local anesthetics can alleviate hemostatic and inflammatory responses in humans, but the mechanism remains unclear.37,45 In the present study, results did not indicate that blocking the intraoperative nociceptive response with local administration of lidocaine modified postoperative inflammatory and hemostatic surgical stress responses. Infiltrational local anesthesia, which commonly affects a smaller area than do regional techniques, was used in all cats; this may explain the differences in results. The minor surgical trauma imposed on these cats by castration could possibly also make it difficult to differentiate between the 2 anesthetic treatments used in the study. In humans, hemostatic activation has been shown to be less marked when minimally invasive surgical techniques such as laparoscopic procedures are used.24,46 Likewise, the results of 1 study in humans revealed that orthopedic surgery has a more pronounced effect on hemostatic variables than does abdominal surgery. This effect has also been reported in a study in dogs, supporting the hypothesis that the surgical stress response is greatly influenced by the invasiveness of the surgical insult. Future studies should be directed toward the effect of regional anesthesia on the surgical stress response to more traumatic surgical procedures (eg, orthopedic surgery) in cats.

References

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