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Link to published version (if available): 10.1177/1098612X17693490

Link to publication record in Explore Bristol Research

PDF-document

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ABSTRACT

Objective: To report the haematological parameters and coagulation times for cats with a congenital portosystemic shunt (CPSS) and the influence of surgical shunt attenuation on these parameters. To identify any association between prolongation in coagulation profiles and incidence of peri-operative haemorrhage.

Methods: Retrospective clinical study using client owned cats with a CPSS. Signalment, shunt type (extrahepatic or intrahepatic), degree of shunt attenuation (complete or partial), haematological parameters, PT and aPTT test results and occurrence of any peri-operative clinical bleeding complications were recorded for cats undergoing surgical treatment of a CPSS at the Royal Veterinary College between 1994 and 2011.

Results: Forty-two cats were included. Thirty-six cats (87.5%) had an extrahepatic CPSS and six (14.3%) had an intrahepatic CPSS. Pre-operatively, mean cell volume (MCV) and mean cell haemoglobin (MCH) were below the reference interval in 32 (76.2%) and 31 (73.8%) cats.
respectively. Red blood cell count (RBC) and mean cell haemoglobin concentration (MCHC) were above the reference interval in 10 (23.8%) and eight (19.1%) cats respectively. Postoperatively, there were significant increases in HCT ($P = 0.044$), MCV ($P = 0.008$) and MCH ($P = 0.002$). Despite the significant increase in MCV post-operatively, the median MCV post-operatively was below the reference interval indicating persistence of microcytosis. Preoperatively, PT was above the upper reference interval in 14 cats (87.5%), and aPTT was above the upper reference interval in 11 cats (68.7%). No cat demonstrated a peri-operative clinical bleeding complication.

**Conclusions**: Cats with a CPSS are likely to present with a microcytosis, but rarely present with anaemia, leukocytosis or thrombocytopenia. Surgical attenuation of the CPSS results in a significant increase in the HCT and MCV. Coagulation profiles in cats with a CPSS are likely to be prolonged, irrespective of shunt type, but do not appear to be associated with an increased risk of clinical bleeding.

**MANUSCRIPT**

**Introduction**

A congenital portosystemic shunt (CPSS) is an aberrant connection between the portal and systemic circulations, where venous blood from the gastrointestinal tract, pancreas and spleen does not filter through the hepatic parenchyma and sinusoids. This results in an underdeveloped and poorly functioning liver. As the liver has an important role in the production of the majority of the coagulation factors, animals with impaired liver function are thought to be at increased risk of developing a coagulopathy. Most studies assessing coagulation in dogs with a CPSS or other hepatic disease have investigated for the presence of hypocoagulability, and one study has identified hypercoagulability in some dogs with a CPSS.
Previous studies of dogs with CPSS have shown that 35-84% had microcytosis and 16-70% were anaemic, whilst 7-53% had a prolonged prothrombin time, and 5-64% had a prolonged activated partial thromboplastin time (aPTT). A leukocytosis is variably present with documented prevalence of between 15.4-40%. A prospective study of dogs with CPSS showed that pre-operatively, when compared with healthy dogs, they had lower platelet counts, prolonged aPTT and lower activity of some coagulation factors. Immediately post-operatively, the platelet counts decreased, the PT was prolonged and activity of coagulation factors previously reduced were increased. Six weeks post-operatively, dogs with no further shunting had improved coagulation times and further increased activity of coagulation factors.

In a number of studies of dogs with a CPSS, aPTT and PT are variably prolonged, however, this rarely results in clinical bleeding, and these changes have not been shown to be predictive of the ability to attenuate the shunt. Incidences of haemorrhage, as a result of coagulopathy, in dogs undergoing surgery for CPSS attenuation have been documented but are rare in the literature.

The red blood cell parameters for cats with CPSS are reported in four studies including 130 cats in total with 25-54% having a microcytosis, and 0-15% being anaemic. In one study, 33% of cats had microcytosis without a concurrent anaemia. There is less information regarding coagulation parameters in cats with a CPSS with, to the authors’ knowledge, only one study reporting the haematology and coagulation parameters of a series of six cats with portal vein thrombosis, three of which were ultimately diagnosed with CPSS. Results were not reported for individual cats making interpretation of these results with relation to the CPSS difficult.

Dogs with a CPSS variably have a leukocytosis, which is postulated to be multifactorial. Factors theorised to be involved include chronic stress, and inflammation as a result of hepatic encephalopathy, and inadequate hepatic clearance of bacteria and endotoxin. A recent study has shown that surgical attenuation of a CPSS in dogs reduces the inflammation associated with hepatic encephalopathy, reflected as a significant reduction in the neutrophil and monocyte counts.
Information regarding leukocyte parameters in cats with a CPSS is lacking in the literature.

The objectives of this study were to report the haematological (red and white blood cell) parameters, PT and aPTT of cats with a CPSS and evaluate the influence of surgical correction of the shunt on these parameters. We also examined the data for any association between prolongations in coagulation times or abnormalities in platelet count, and risk of peri-operative clinical haemorrhage. Our study hypotheses were that cats with a CPSS would have prolongations in PT and aPTT, microcytic anaemia and leukocytosis with similar prevalence to that reported for dogs and that these abnormalities would improve following attenuation of the CPSS. In addition, we hypothesised that these parameters would be similar between cats with extrahepatic and intrahepatic CPSS and not be predictive for the ability to completely attenuate the shunt. We further hypothesised that any abnormalities in coagulation parameters would correlate with the incidence of peri-operative bleeding complications.

**Materials and Methods**

The medical records of cats referred to the Queen Mother Hospital for Animals (QMHA) for surgical attenuation of a CPSS between November 1994 and June 2011 were retrospectively reviewed. Cats were treated with either partial or complete suture ligation of their CPSS depending on objective and subjective assessment of portal hypertension. A mesenteric vessel was catheterised and connected to a water manometer, allowing direct portal pressure measurement. The authors limited the increase in portal pressure to less than 10cmH₂O/8mmHg, or less than double the base pressure prior to occlusion. Additionally, the central venous pressure and systemic arterial pressure were monitored during ligation, as well as changes in the colour of splanchnic viscera, as further indicators of changes in portal pressure. Only cats with haematology profiles submitted to the diagnostic laboratory at the authors’ institution were included in this study. Some cats also had coagulation
profiles assessed, but this was at the attending clinician’s discretion. Clinical data collected included sex, age at time of surgery, breed, CPSS type (extrahepatic or intrahepatic), degree of CPSS attenuation at surgery (complete or partial) and details of any peri-operative clinical bleeding complications.

Pre-operative and, where available, follow up post-operative haematological and coagulation parameters were recorded. This included complete blood count (CBC) data, red blood cell count (RBC), haemoglobin (Hb), haematocrit (HCT), mean cell volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), red blood cell distribution width (RBCDW), platelet count (PLT), white blood cell count (WBC), neutrophils, lymphocytes, monocytes, eosinophils, basophils, PT and aPTT. For haematology blood was taken and placed in an EDTA tube and analysed the same day. Haematology was performed using an Abbott Cell-Dyn 3500 (Abbott Diagnostics Limited, Berkshire, UK) as previously described. At least a 100-white blood cell manual differential count was undertaken to establish the concentrations of neutrophils, monocytes, lymphocytes, eosinophils and basophils. Blood smears were evaluated according to the diagnostic laboratory protocol, with review by a Board-certified veterinary clinical pathologist where further assessment was necessary. For coagulation tests, blood was placed in a sodium citrate tube and immediately transferred to the laboratory for evaluation without delay. Coagulation tests were performed between 1994 and 1998 using an Amelung Coagulometer (Burkard Scientific Ltd, Middlesex, UK) and between 1998 and 2011 using a STart 4 Hemostasis Analyzer (Diagnostica Stago UK Ltd, Theale, UK).

**Statistical Evaluation**

Analysis was performed using IBM SPSS Statistics 20.0.0 software package (Education SPSS (UK) Limited IBM). Continuous data were assessed for normality visually and with the Kolmogorov-Smirnov test. Mean and standard deviation were reported for parametric data, which were compared with a Paired Sample T test. The median and range were reported for skewed data, which
were compared with a Wilcoxon Signed Rank test. Percentages were reported for categorical data, which were compared with a Fisher’s Exact test. For all tests significance was set at the 5% level (\( P \leq 0.05 \)).

**Results**

**Study Population**

Forty-two cats were included in the study. Twenty-eight cats (66.7%) were male, and 14 were neutered (33.3%). Fourteen cats (33.3%) were female, with eight (19%) being spayed. Twenty-one cats (50.0%) were pedigree breeds including British short hair (5), Ragdoll (4), Persian (4), Siamese (2), Tonkinese (2), and one each of American Short Hair, Birman, Burmilla and Maine Coon. There were 18 domestic shorthair and three domestic longhair cats. The median age at time of surgery was 9 months (range 3-115 months).

Thirty-six cats (85.7%) had an extrahepatic CPSS and six (14.3%) had an intrahepatic CPSS. Twenty-seven cats (64.3%) had partial CPSS attenuation and 15 cats (35.7%) had complete CPSS attenuation. There was no significant difference in the degree of attenuation based on the type of shunt with 2/6 cats (33.3%) with an intrahepatic CPSS and 13/36 cats (36.1%) with extrahepatic CPSS tolerating complete attenuation (\( P = 1.00 \)). There were no incidences of peri-operative haemorrhage in any cat.

**Complete Blood Counts (CBC)**

CBCs were available for all cats pre-operatively (table 1). The mean values of the study population for red blood cell parameters were below the reference interval for MCV and MCH. MCV and MCH were below the reference interval in 32 (76.2%) and 31 (73.8%) cats respectively. Both were below the reference interval in 28 cats (66.7%). There was no difference in the proportion of cats with microcytosis based on the type of CPSS or the degree of attenuation at surgery. All cats had normal platelet counts confirmed on a fresh blood smear. Only one cat had a HCT below the reference interval. The mean or median values for all white blood cell parameters were within the reference
intervals. Only one cat had an increased total white blood cell count (2.4%). Lymphocytes were below the reference interval in eight (19.1%) cats.

Twenty-one cats (50.0%) had follow-up blood samples for CBC taken a median of four months after surgery (range 1-72 months). Nineteen cats (90.5%) had an extrahepatic CPSS and two (9.5%) had an intrahepatic CPSS. Nineteen cats (90.5%) had been treated with a partial attenuation and two (9.5%) had been treated with a complete attenuation. Paired pre and postoperative CBC are summarised in table 2. There were significant increases in mean or median study population values for haematocrit (HCT) ($P = 0.044$), mean cell volume (MCV) ($P = 0.008$) and mean cell haemoglobin (MCH) ($P = 0.002$).

Coagulation profiles (table 3)
Sixteen cats (38.1%) had pre-operative assessment of PT and aPTT at the discretion of the surgeon, independent of their clinical presentation. Thirteen cats (81.2%) had an extrahepatic CPSS and three (18.8%) had an intrahepatic CPSS. Eleven cats (68.7%) had partial shunt attenuation, whilst five cats (31.3%) had complete shunt attenuation. The PT was normal in two cats (12.5%) and prolonged in fourteen cats (87.5%). The aPTT was normal in three cats (18.7%), shortened in 2 cats (12.5%) and prolonged in eleven cats (68.8%). The PT was not greater than 1.5 times the maximal reference limit in any cat. The aPTT was greater than 1.5 times the maximal reference limit in five cats (31.3%).

Six cats had follow-up assessment of coagulation profiles a median of 5.5 months (range 2-69 months) after surgery. Five cats (83.3%) had an extrahepatic CPSS, that were treated by partial shunt attenuation. One cat (16.7%) had an intrahepatic CPSS that was treated by complete shunt attenuation. Five of six cats (83.3%) had prolonged PT and aPTT. Only two of these cats had paired pre and postoperative samples. In these two cats both PT and aPTT were increased before and after surgery.
Discussion

This is a novel study reporting haematological and coagulation profiles in a series of cats undergoing surgical attenuation of a CPSS.

Non-regenerative anaemia is a common finding in dogs with CPSS, with the literature documenting a prevalence of between 16%-46.2%.\textsuperscript{1, 6, 8-10} In contrast only one cat (2.4%) with a CPSS had a haematocrit below the reference interval in this study, which is a similar reported prevalence as that found in previous studies on cats with CPSS.\textsuperscript{16, 18, 19} The reason for this difference in presentation is unknown, but a significant increase in haematocrit (within the normal interval) was documented within 4 weeks of surgical attenuation of the CPSS in this population of cats, even though the majority had only been treated with partial attenuation. Follow up coagulation profiles were not performed for abnormal pre-operative results in this population. The exact pathophysiology of anaemia in dogs with CPSS has not been ascertained.\textsuperscript{24} However, it is typically microcytic and hypochromic, and low serum iron concentrations have been identified in several dogs with CPSS, all of which suggests iron metabolism may be involved in the aetiology.\textsuperscript{6, 7, 25} Similarly, the exact reason why microcytosis develops in animals with CPSS is unknown, but in dogs it is postulated to be a result of impaired iron transport due to the inability of the liver to produce enough transferrin, resulting in increased iron sequestration in Kupffer cells and decreased serum iron levels.\textsuperscript{21, 25}

Additionally, animals with CPSS have abnormal lipid metabolism, which can result in alterations in erythrocyte membrane triglycerides and cholesterol content, causing the erythrocyte to become smaller.\textsuperscript{6} Further studies have failed to clearly identify an anaemia of inflammatory or chronic disease.\textsuperscript{6, 26} The exact mechanism of anaemia in dogs with CPSS is probably multifactorial and requires further investigation. No feline specific literature exists.

Microcytosis, with or without anaemia, is a common finding (33%-84.6%) in dogs with a CPSS,\textsuperscript{1, 6, 8, 27} and was seen in 76.2% of the cats in this study. This is a greater prevalence than 27-54% previously
reported for cats with CPSS, and the reasons for this are unclear, although it is obvious from the wide ranges reported in the previous dog and cat studies that much variation is possible and the higher rate reported in this study is within the range reported for dogs. As has been reported for dogs with a CPSS, the MCV significantly increased after surgical attenuation. Pre-operatively, 32 cats (76.2%) had an MCV below the reference interval, compared to 12 of 21 cats (57.1%) post-operatively, with nine of 21 cats (42.9%) having an MCV within the reference interval. However, the median of our study population remained below the reference interval despite the increase in erythrocyte size. This improvement was associated with similar improvements in HCT suggesting that this abnormality is reversible with improvements in portal blood flow. The presence of microcytosis was not associated with shunt type or predictive of the ability to completely attenuate the shunt, in this study, although the number of cats was relatively small.

A decrease in MCH was seen in this population of cats prior to surgery which is likely related to the low MCV, rather than a reflection of decreased haemoglobin concentrations in these cells as the MCHC was within normal limits. The increase in MCHC seen in this study is artefactual, and is typically associated with haemolysis within the sample. No gross haemolysis was seen in any of the cats. An increase in the RBC count was documented in 23.8% of our cats, however the significance of this in the face of a normal HCT is unknown. Further studies on the haematology of cats with CPSS is required to investigate these findings.

The majority of cats with a CPSS that were tested (n= 16) had prolonged PT (87.5%) and aPTT (68.8%) prior to surgery. In comparison, some reports in dogs with a CPSS show PT and / or aPTT tests were significantly increased compared with a control population. Conversely, two studies in dogs with CPSS document both PT and aPTT within reference intervals. These contradictory results highlight both the importance of approaching each animal with a CPSS individually, and the necessity to further research more reliable methods of assessing coagulation status in both dogs and cats with
CPSS. Numbers were not considered adequate to allow statistical comparison of coagulation times based on the type of CPSS and the degree of attenuation.

None of the cats with CPSS in this study showed clinical signs of coagulopathy or developed a complication relating to haemorrhage through the period of hospitalisation for surgical attenuation of their shunt. Whilst the sample size in this study is small, it does suggest that the cats with prolonged PT and aPTT tests prior to surgery are not at increased risk of developing a clinical peri-operative bleeding complication. There are reports of dogs with CPSS suffering serious or fatal postoperative haemorrhage, but overt bleeding is overall an uncommon complication in animals with a CPSS, severe liver disease or failure. One possible theory for why many of these animals do not become hypocoagulable is that the pro-coagulant system is not affected in isolation. The liver’s role in the coagulation system is complex, with significant roles in both the pro- and anti-coagulant systems. The liver also produces inhibitors of coagulation and fibrinolysis, as well as fibrinolytic proteins, and is responsible for clearing proteins of both systems from the circulation to prevent them from having a prolonged effect. aPTT and PT assays only evaluate secondary haemostasis in-vitro, and provide no information on primary haemostasis or the anti-coagulant system, giving the clinician minimal information on haemostasis as a whole. In addition, whilst they can identify clinically significant hypocoagulable states they are not able to identify hypercoagulable states, nor are they predictive of procedural bleeding. More thorough evaluation of coagulation can be made through the use of viscoelastic testing, e.g. thromboelastography (TEG). Viscoelastic testing allows measurement of all stages of coagulation in-vitro, including the anti-coagulant and fibrinolytic systems, giving a more complete view of coagulation status. In addition it allows determination of hyper-coagulability. A study investigating the use of TEG in dogs with CPSS revealed that whilst 52% of dogs had a prolonged PT and none had a prolonged aPTT compared with a control population, the TEG results showed a significantly shorter K value in all 21 dogs with a CPSS, although only 2 dogs were below the reference interval. Additionally there was an increased angle, MA and G value in 2/21, 6/21 and
9/21 dogs respectively, all of which are consistent with a hypercoagulable state. This suggests that some dogs with a CPSS may be hypercoagulable and highlights the importance of assessing the entire coagulation system, both pro and anticoagulation pathways. Studies on the use of TEG in healthy cats have demonstrated variable results, with some producing reliable, reproducible results, indicating that this may be a useful technique for the assessment of the coagulation cascade in cats. Another study has shown less reliability with the method, after excluding 15 of 40 samples from the final analysis due to > 20% variability for ≥ 2 variables. There are no reports yet of the use of TEG in cats with CPSS and this will be important to include in future studies.

In the current study the median values of all white blood cell parameters were within the reference interval. A lymphocytosis was present in one cat (2.4%) and eight cats (19.1%) had a lymphopenia. There is limited information on white blood cell parameters in cats with CPSS. Previous studies have identified a lymphocytosis in 8.3-25% of cats and a lymphopenia in 12.8-25% of cats, which is similar to our findings. These findings in cats are different to dogs with CPSS, where a leukocytosis, as a result of neutrophilia and/or a lymphocytosis, is a more common finding, being present in 15.4-40% of dogs. This leukocytosis in dogs is thought to be related to inflammation due to inadequate hepatic clearance of lipopolysaccharide (LPS) and chronic stress. A recent study showed evidence of reduced inflammation following CPSS attenuation in dogs in the form of reduction in neutrophil concentration, monocyte concentration and C-reactive protein. It is unclear why cats with CPSS do not demonstrate increased white blood cell counts similar to dogs. It is also interesting that a greater proportion of cats show a lymphopenia. This may be related to species differences in the response to stress.

The retrospective nature of the project carries inherent issues with small study size and data collection. There were only two paired samples for pre and postoperative coagulation profiles, preventing assessment of improvement in coagulation times, and inability to draw conclusions
regarding whether the shunt is able to be attenuated or not. Similarly, the time period between surgery and collection of the post-operative blood sample was inconsistent across the study population. This makes it difficult to conclude how quickly haematological and coagulation abnormalities normalise after surgical attenuation. The lack of a control group (not possible in this clinical setting with client owned cats) means we do not have a population of healthy cats undergoing surgery but unaffected by a CPSS to compare our results to, which makes it difficult to accurately conclude that the changes seen were due to CPSS attenuation itself. The coagulation system was assessed in cats using PT and aPTT as this was the routine method employed during the study period. These have been shown to have poor correlation with clinical bleeding, in certain circumstances. As such, further investigation in to newer techniques, such as TEG, in cats with CPSS would be beneficial. Despite the limitations of the retrospective nature of this study, the data for feline CPSS is novel, and interesting differences and similarities are noted for haematological parameters and coagulation profiles compared with those reported in dogs with a CPSS.

**Conclusions**

Unlike dogs, cats with a CPSS are unlikely to be anaemic even though the majority will have microcytosis. Despite this, the HCT of cats with a CPSS significantly increased following surgical attenuation, as did the microcytosis, demonstrating that these changes are potentially reversible when hepatic portal flow is improved. Microcytosis was not associated with CPSS type or ability to completely attenuate the CPSS in this population of cats. Based on the current study, coagulation (PT and aPTT) profiles in cats with a CPSS are likely to be mildly prolonged. PT and aPTT tests in cats with a CPSS appear to give limited information with regards to the risk of a clinical bleeding complication during surgery.

**Conflict of Interest**
The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

**Funding**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.
References

18. Center S, Magne M, editors. Historical, physical examination, and clinicopathologic features of portosystemic vascular anomalies in the dog and cat. Seminars in veterinary medicine and surgery (small animal); 1990.


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Table 1. Pre-operative haematological values for CPSS cats
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<td>5.5-19.5</td>
<td>10.7</td>
<td>6.3-18.7</td>
<td>9.3</td>
</tr>
<tr>
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<td>-----</td>
</tr>
<tr>
<td><strong>Neutrophils (x10^9/dL)</strong></td>
<td>21</td>
<td>2.5-12.5</td>
<td>7.0</td>
<td>3.3-11.6</td>
<td>4.7</td>
</tr>
<tr>
<td><strong>Lymphocytes (x10^9/dL)</strong></td>
<td>21</td>
<td>1.5-7.0</td>
<td>3.0</td>
<td>0.6-6.3</td>
<td>3.34</td>
</tr>
<tr>
<td><strong>Monocytes (x10^9/dL)</strong></td>
<td>21</td>
<td>0.0-1.5</td>
<td>0.4</td>
<td>0.0-0.7</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Eosinophils (x10^9/dL)</strong></td>
<td>21</td>
<td>0.0-1.5</td>
<td>0.3</td>
<td>0.0-1.6</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Basophils (x10^9/dL)</strong></td>
<td>21</td>
<td>0.0-0.4</td>
<td>0.0</td>
<td>0.0-0.2</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Table 2.** Paired pre and postoperative haematological data for cats that underwent surgical attenuation of a CPSS
<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of cats</th>
<th>Reference interval</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Number lower than reference interval (%)</th>
<th>Number higher than reference interval (%)</th>
<th>Complete attenuation (%)</th>
<th>Partial attenuation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin time – PT (seconds)</td>
<td>16</td>
<td>7.0-11.0</td>
<td>12.3</td>
<td>1.7</td>
<td>0 (0)</td>
<td>14 (87.5)</td>
<td>6 (42.9)</td>
<td>8 (57.1)</td>
</tr>
<tr>
<td>Activated partial thromoboplastin time – APTT (seconds)</td>
<td>16</td>
<td>13.0-20.0</td>
<td>24.7</td>
<td>9.6</td>
<td>2 (12.5)</td>
<td>11 (68.8)</td>
<td>4 (36.4)</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td><strong>Postoperative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin time – PT (seconds)</td>
<td>6</td>
<td>7.0-11.0</td>
<td>12.0</td>
<td>0.7</td>
<td>0 (0)</td>
<td>5 (83.3)</td>
<td>1 (20)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Activated partial thromoboplastin time – APTT (seconds)</td>
<td>6</td>
<td>13.0-20.0</td>
<td>29.3</td>
<td>10.5</td>
<td>0 (0)</td>
<td>5 (83.3)</td>
<td>1 (20)</td>
<td>4 (80)</td>
</tr>
</tbody>
</table>

**Table 3.** Pre and postoperative PT and aPTT results for cats that underwent surgical attenuation of a CPSS

Complete attenuation: number of cats with prolonged PT or APTT that underwent complete attenuation

Partial attenuation: number of cats with prolonged PT or APTT that underwent partial attenuation