Evaluation of hemostatic and fibrinolytic markers in dogs with ascites attributable to right-sided congestive heart failure

Andrea Zoia, DVM; Monica Augusto, DVM; Michele Drigo, DVM, PhD; Marco Caldin, DVM, PhD

Objective—To determine whether dogs with ascites secondary to right-sided congestive heart failure (CHF) have bleeding disorders associated with hypofibrinogenemia and discordant plasma fibrin-fibrinogen degradation products (FDPs) and D-dimer assay results (ie, a circulating concentration of FDPs higher than the reference range and a circulating concentration of D-dimer within the reference range).

Design—Retrospective case-control study.

Animals—80 client-owned dogs.

Procedures—Dogs with ascites secondary to right-sided CHF (group 1; n = 20), unhealthy dogs without cardiac disease (group 2; 40), and dogs with left-sided CHF (group 3; 20) were included in the study. Urine bile acids-to-creatinine concentration ratios were calculated as a marker of liver function. Differences among groups regarding coagulation profile analysis results and prevalence of discordant FDPs and D-dimer assay results were determined.

Results—No significant differences were detected among the 3 groups regarding urine bile acids-to-creatinine concentration ratios. Plasma fibrinogen concentration was significantly lower for group 1 versus groups 2 or 3. Prevalence of discordant FDPs and D-dimer assay results was significantly higher for group 1 versus groups 2 or 3. Eighteen group 1 dogs had discordant FDPs and D-dimer assay results. Ten of these dogs had concurrent hypofibrinogenemia, 2 of which had clinical signs of bleeding. Only 10 dogs in groups 2 or 3 had discordant FDPs and D-dimer assay results; none of these dogs had hypofibrinogenemia or clinical signs of bleeding.

Conclusions and Clinical Relevance—Dogs with right-sided CHF and ascites may be at increased risk for primary hyperfibrinogenolysis (ie, hypofibrinogenemia and discordant FDPs and D-dimer assay results). (J Am Vet Med Assoc 2012;241:1336–1343)

Many humans with cardiomyopathy have systemic hypercoagulability.1,2 Results of other studies3,4 suggest that dogs and cats with cardiomyopathy may also have systemic hypercoagulability. Hypercoagulability in humans with heart failure may be associated with platelet activation, increased thrombin activity, and endothelial dysfunction.5 Moreover, hypercoagulability in humans with hypertrophic cardiomyopathy may be caused by left atrial enlargement, whereas hypercoagulability in humans with DCM may be caused by left ventricular enlargement and dysfunction.6 Both of those diseases are associated with formation of thromboembolisms. Although controversial, cats6 and humans7 with cardiac failure or left ventricular systolic dysfunction are sometimes treated with anticoagulants. Platelet aggregation inhibitors and warfarin are used as anticoagulant drugs in humans with heart failure.7 A major complication of anticoagulant treatment is hemorrhage. Despite the systemic hypercoagulable state in humans with cardiomyopathy,1,2 humans with severe heart disease who are treated orally with anticoagulant drugs have an increased risk of bleeding.8 However, to the authors’ knowledge, ascites attributable to right-sided CHF has not been investigated as a risk factor for bleeding in such patients.

Fibrinolysis results in dissolution of fibrin, and hyperfibrinolysis (which compromises blood clot in-

Abbreviations

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<th>Abbreviation</th>
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<tr>
<td>aPTT</td>
<td>Activated partial thromboplastin time</td>
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<td>CHF</td>
<td>Congestive heart failure</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CKCS</td>
<td>Cavalier King Charles Spaniel</td>
</tr>
<tr>
<td>DCM</td>
<td>Dilated cardiomyopathy</td>
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<tr>
<td>DIC</td>
<td>Disseminated intravascular coagulation</td>
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<tr>
<td>FDP</td>
<td>Fibrin-fibrinogen degradation product</td>
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<td>PHF</td>
<td>Primary hyperfibrinogenolysis</td>
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<td>PT</td>
<td>Prothrombin time</td>
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tegrity) develops when the rate of fibrinolysis is greater than the rate of fibrin formation. Hyperfibrinolysis is classified as primary or secondary. Primary hyperfibrinolysis develops independently of intravascular activation of coagulation, and plasmin is formed without concomitant formation of thrombin. Lysis of preformed fibrin and fibrinogen will then occur. In addition to causing increased degradation of fibrinogen and preformed fibrin (if present), spontaneous formation of plasmin causes degradation of coagulation factors V, VIII, IX, and XI. Primary hyperfibrinogenolysis is a rare condition that develops in humans in association with acute conditions such as shock, surgical procedures, liver transplantation, acute leukemia, or administration of thrombolytic drugs. It can also be caused by chronic conditions, such as neoplasia or chronic liver disease. During PHF, production of FDPs is increased but production of D-dimer is not increased. Secondary hyperfibrinolysis is a consequence of activation of a coagulative process, often caused by DIC, which stimulates endothelium to increase production of tissue plasminogen activator, causing activation of plasminogen to form plasmin. Lysis of cross-linked fibrin during secondary hyperfibrinolysis generates FDPs and D-dimer. To the authors' knowledge, PHF has been reported only once in the veterinary medical literature, and it has never been associated with congestive cardiac diseases in humans or other animals. Standard criteria for diagnosis of PHF have not been reported. Nevertheless, discordant FDPs and D-dimer assay results may be an indicator of PHF and such criteria have been used in a clinical setting to diagnose PHF in humans. We identified a 9-year-old sexually intact male CKCS (index dog) with a 2-week history of exercise intolerance and ascites attributable to right-sided CHF that was referred to the Small Animal Hospital of Glasgow University, Glasgow, Scotland, because of a progressively enlarging neck hematoma that developed following jugular venipuncture for blood collection. Results of the coagulation profile analysis were characterized by severe hypofibrinogenemia, prolonged aPTT and PT, discordant results between FDPs and D-dimer assays, and mild thrombocytopenia. Therefore, we conducted a retrospective study to determine whether other dogs with right-sided CHF and ascites had such hemostatic abnormalities. The objectives of this retrospective case-control study reported here were to determine whether dogs with right-sided CHF and ascites had such hemostatic abnormalities. The objectives of this retrospective case-control study reported here were to determine whether dogs with right-sided CHF and ascites had such hemostatic abnormalities. The objectives of this retrospective case-control study reported here were to determine whether dogs with right-sided CHF and ascites had hypofibrinogenemia, prolonged aPTT and PT, and discordant plasma FDPs and D-dimer assay results (ie, a circulating concentration of FDPs higher than the reference range and a circulating concentration of D-dimer within the reference range) and to determine whether such assay results were associated with bleeding rather than the more commonly reported thrombotic events in those dogs.

Materials and Methods

Animals—The electronic medical records database of the San Marco Veterinary Clinic, Padua, Italy, was searched to identify dogs with ascites and right-sided CHF (group 1 dogs) evaluated between April 1, 2005, and May 31, 2008. Only dogs with complete medical records including history and results of physical examination, CBC (including blood smear examination), serum biochemical analysis, urinalysis, coagulation profile analysis, echocardiography, ECG, and abdominal ultrasonography were included in group 1. Thoracic radiographs had been obtained for one of the dogs (the first dog identified at the Small Animal Hospital of Glasgow University with ascites secondary to right-sided CHF and a hemorrhagic disorder characterized by severe hypofibrinogenemia, prolonged aPTT and PT, discordant results between FDPs and D-dimer assays [ie, a circulating concentration of FDPs higher than the reference range and a circulating concentration of D-dimer within the reference range], and mild thrombocytopenia; index dog). Information regarding pleural effusion was acquired from echocardiographic reports. Ascites had been confirmed via abdominal ultrasonography and cytologic examination, and biochemical analysis of abdominal fluid was performed in all cases. Only dogs with right-sided CHF (determined on the basis of a history and results of echocardiography consistent with structural cardiac or pericardial disease severe enough to cause right-sided CHF) were included in group 1. Dogs with evidence of concurrent disease (ie, neoplasia, renal or relevant primary hepatic disease, or systemic inflammatory disease) that could have caused ascites or affected results of coagulation profile analysis were excluded from group 1. Dogs were considered to be free of primary hepatic disease if none of the following abnormalities had been found: history or clinical signs consistent with hepatic disease other than ascites (ie, polyuria, polydipsia, vomiting, diarrhea, jaundice), results of serum biochemical analyses suggestive of reduced liver function (ie, increased serum bilirubin concentration or decreased serum urea or glucose concentrations), and ultrasonographic signs of liver parenchyma abnormalities or intra- or extrahepatic cholestasis. Via the database search, 165 dogs with ascites were identified. Effusion had been determined to be secondary to right-sided CHF in 24 of those dogs. Five of these dogs were excluded because of concurrent disease (sepsis [n = 1], primary hepatopathy [1], atrial mass [1], endocarditis [1], or adrenal mass [1]) that may have contributed to development of ascites or affected results of coagulation profile analysis. Therefore, 20 dogs with ascites and right-sided CHF (including the index dog) met the criteria for inclusion in the study. Two groups of control dogs were included in the study. Dogs evaluated at the clinic between April 1, 2005, and May 31, 2008, were identified via a search of the electronic database of the San Marco Veterinary Clinic and selected for inclusion in control groups. Forty unhealthy dogs without clinical evidence of cardiac disease or abdominal, pleural, or pericardial effusion were included as control dogs (group 2); these dogs were individually matched to group 1 dogs for age, sex (including neuter status), and breed. These dogs were selected as closely as possible to the admission date of the corresponding dogs of group 1 to reduce variations in results of laboratory analyses attributable to changes in performance of analyzers. When 2 or more dogs met these criteria, the dog included in the group was selected via a randomization procedure with a computer system. Only dogs with complete medical records in-
Clinicographic evidence of CHF and a history and echocardiographic evidence indicative of structural cardiac disease severe enough to cause left-sided CHF. Dogs included in group 3 did not have abdominal, pleural, or pericardial effusion or evidence of concurrent diseases that could have affected results of coagulation profile analysis. Only dogs with complete medical records including history and results of physical examination, CBC (including blood smear examination), serum biochemical analyses, urinalysis, and coagulation profile analysis were included in group 3. Dogs that had received anticoagulant treatments or any type of blood product during the 2 months prior to examination were excluded.

Coagulation profile analysis—Coagulation profile analysis had been performed for all dogs and included determination of aPTT, PT, platelet count, and plasma concentrations of fibrinogen, FDPs, and D-dimer. A whole blood sample (3.5 mL) had been collected from each dog via cephalic or jugular venipuncture. Blood samples had been immediately placed in plastic tubes containing K₂-EDTA for determination of platelet count and plastic tubes containing 3.2% sodium citrate (final ratio of volume of anticoagulant to volume of blood, 1:9) for measurement of all other coagulation variables. Tubes containing sodium citrate were centrifuged (1,500 \( \times \) g) for 5 minutes, plasma was harvested, and coagulation profile analysis was performed within 1 hour after blood sample collection (except for the index dog, for which coagulation profile analysis was performed within 15 hours after blood sample collection). Plasma concentrations of fibrinogen, FDPs, and D-dimer were determined via quantitative assays with an automated analyzer. Plasma concentrations of FDPs were determined with a semiquantitative plasma latex agglutination kit validated for use with canine blood. Plasma D-dimer concentrations were determined via a validated immunoturbidimetric quantitative assay with an automated analyzer. Platelet counts were determined by use of a hematology analyzer for all dogs except the index dog. Platelet concentration had been estimated via analysis of a blood smear for the index dog; therefore, that value was not included in further analysis. Platelet counts determined by use of the hematology analyzer were used for statistical analysis only if no platelet clumps were detected via examination of blood smears.

Liver function was assessed to determine whether liver damage secondary to right-sided CHF may have contributed to coagulation disorders in the dogs of the present study. A urine bile acids-to-creatinine concentration ratio of 0.25 was used to distinguish dogs with impaired liver function from dogs with clinically normal liver function. A cutoff value higher than the upper limit of the urine bile acids-to-creatinine concentration ratio reference range (0.03 to 0.20) was used to increase specificity for detection of hepatic insufficiency.

Statistical analysis—Normality of data was assessed with the Kolmogorov-Smirnov test. Data were compared among groups of dogs via ANOVA (plasma fibrinogen concentrations and platelet counts), Kruskall-Wallis test (aPTT, PT, plasma D-dimer concentrations, and urine bile acids-to-creatinine concentration ratios), or \( \chi^2 \) test (plasma concentrations of FDPs). Posttest analyses were performed with least squares means or Mann-Whitney tests. Additionally, differences in the prevalence of PHF (defined as discordant results between plasma FDPs and D-dimer assays) among the groups of dogs were evaluated with the \( \chi^2 \) test. For all statistical analyses, values of \( P < 0.05 \) were considered significant.

Results

Group 1 (dogs with ascites and right-sided CHF) included 13 male (12 sexually intact and 1 neutered) and 7 female (3 sexually intact and 4 spayed) dogs. Mean ± SD age of group 1 dogs was 8 ± 3.3 years (range, 2 to 14 years). Seven of the dogs were crossbred, and 13 were purebred (4 German Shepherd Dogs, 2 Labrador Retrievers, 2 Boxers, 1 Bernese Mountain Dog, 1 Saint Bernard, 1 Cocker Spaniel, 1 Golden Retriever, and 1 CKCS [index dog]). Causes of right-sided CHF included idiopathic pericardial effusion (6), DCM (4), and tricuspid valve insufficiency (10); diagnoses of idiopathic pericardial effusion had been determined in accordance with published guidelines. Two of the dogs had pleural effusion. After diagnosis, the index dog was treated with pimobendan (0.35 mg/kg [0.16 mg/lb], PO, q 12 h), benazepril (0.36 mg/kg [0.16 mg/lb], PO, q 24 h), furosemide (2.85 mg/kg [1.30 mg/lb], PO, q 24 h), and spironolactone (1.78 mg/kg [0.81 mg/lb], PO, q 24 h) for CHF and fresh frozen plasma (230 mL, IV), and tranexamic acid (25 mg/kg [11.36 mg/lb], IV, q 24 h, for 5 days) for its coagulation disorder. Ascites had resolved in that dog within 3 days after the start of treatment. By that time, the dog's plasma fibrinogen concentration was within reference range and it was discharged from the hospital 11 days after admission. The hematoma, coagulation disorder, and signs of CHF had all resolved, suggesting a temporal association between a return of clotting times to within reference ranges and the resolution of ascites.

Group 2 (unhealthy dogs without cardiac disease) included 26 male (24 sexually intact and 2 neutered) and 14 female (6 sexually intact and 8 spayed) dogs. Mean ± SD age of group 2 dogs was 8 ± 3.4 years (range, 2 to 14 years). Fourteen of the dogs were crossbred, and 26 were purebred (8 German Shepherd Dogs, 4 Labrador Retrievers, 4 Boxers, 2 Bernese Mountain Dogs, 2
Saint Bernards, 2 Cocker Spaniels, 2 Golden Retrievers, and 2 CKCSs). Causes of sickness included neoplastic disease (n = 8), sepsis (7), gastrointestinal disorders (4), inflammatory or immune-mediated disease (3), orthopedic problems (3), fibrocartilaginous emboli or compression of the spinal cord by intervertebral disks (3), endocrinopathy (3), polytrauma secondary to road traffic accident (2), liver diseases (2), and other (5).

Group 3 (dogs with left-sided CHF) included 13 male (10 sexually intact and 3 neutered) and 7 female (3 sexually intact and 4 spayed) dogs. Mean ± SD age of group 3 dogs was 10.3 ± 4.2 years (range, < 1 to 15 years). Eight of the dogs were purebred, and 12 were crossbred (2 CKCSs, 2 Doberman Pinschers, 2 Yorkshire Terriers, 1 Maltese, 1 Cocker Spaniel, 1 German Shepherd Dog, 1 Border Collie, 1 Shih Tzu, and 1 Dachshund). Causes of left-sided CHF included primary mitral valve insufficiency (n = 17), patent ductus arteriosus (2), and DCM (1).

Urine bile acids-to-creatinine concentration ratios were available for all dogs except the index dog. Median (range) urine bile acids-to-creatinine concentration ratios for groups 1, 2, and 3 were 0.20 (0.09 to 13.53), 0.12 (0.02 to 6.17), and 0.10 (0.03 to 0.92), respectively. When the urine bile acids-to-creatinine concentration ratio was considered as a categorical variable (on the basis of a cutoff value of 0.25) for evidence of liver dysfunction, no significant (P = 0.176) differences were detected among the 3 groups. In group 1, values for 11 dogs were < 0.25 and values for 9 dogs were > 0.25. In group 2, values for 21 dogs were < 0.25 and values for 9 dogs were > 0.25. In group 3, values for 15 dogs were < 0.25 and values for 5 dogs were > 0.25. Despite having postsinusoidal portal hypertension, 7 dogs in group 1 had urine bile acids-to-creatinine concentration ratios within the reference range. Nevertheless, six of these 7 dogs had ≥ 1 value outside the reference ranges for aPTT (n = 6 dogs), PT (2), and plasma fibrinogen concentration (4).

The aPTT was significantly (P < 0.001) higher for group 1 (median, 13.9 seconds; range, 11.4 to 121.0 seconds) versus groups 2 (median, 12.0 seconds; range, 9.9 to 17.1 seconds) and 3 (median, 12.0 seconds; range, 9.7 to 14.5 seconds; reference range, 10.2 to 12.6 seconds; Figure 1). The PT was significantly (P < 0.001) higher for group 1 (median, 8.9 seconds; range, 7.4 to 81.0 seconds) versus groups 2 (median, 7.7 seconds; range, 6.8 to 12.6 seconds) and 3 (median, 7.3 seconds; range, 6.7 to 8.3 seconds; reference range, 6.8 to 8.7 seconds; Figure 2). The aPTT was not significantly (P = 0.47) different between groups 2 and 3, but the PT was significantly (P = 0.01) higher for group 2 than it was for group 3. Plasma fibrinogen concentration was significantly (P = 0.001) lower for group 1 (mean ± SD, 154.9 ± 107.2 mg/dL; 95% CI, 109.6 to 212.3 mg/dL) versus groups 2 (mean ± SD, 374.0 ± 250.9 mg/dL; 95% CI, 293.8 to 454.3 mg/dL) and 3 (mean ± SD, 347.1 ± 159.1 mg/dL; 95% CI, 272.6 to 421.6 mg/dL; reference range, 130 to 242 mg/dL; Figure 3). Plasma fibrinogen concentration was not significantly (P = 0.63) different between groups 2 and 3.

Examination of blood smears did not reveal platelet clumps in any of the blood samples. The platelet count was significantly (P = 0.017) higher for group 3 (mean ± SD, 416.2 ± 164.0 × 10^9 platelets/L; 95% CI, 339.4 ± 10^9 platelets/L to 492.9 × 10^9 platelets/L) versus groups 1 (mean ± SD, 284.2 ± 123.5 × 10^9 platelets/L; 95% CI, 307.2 ± 10^9 platelets/L to 429.5 × 10^9 platelets/L).
224.7 × 10⁹ platelets/L to 343.7 × 10⁹ platelets/L) and 2 (mean ± SD, 336.8 ± 139.6 × 10⁹ platelets/L; 95% CI, 292.2 × 10⁹ platelets/L to 381.5 × 10⁹ platelets/L; reference range, 176 × 10⁹ platelets/L to 479 × 10⁹ platelets/L; Figure 4). Platelet counts were not significantly (P = 0.19) different between groups 1 and 2.

Plasma D-dimer concentrations were significantly lower for group 3 (median, 0.02 μg/mL; range, 0.01 to 1.83 μg/mL) versus groups 1 (median, 0.13 μg/mL; range, 0.01 to 0.51 μg/mL; P = 0.034) and 2 (median, 0.08 μg/mL; range, 0.01 to 0.82 μg/mL; P = 0.045; Figure 5). Plasma D-dimer concentration was not significantly (P = 0.40) different between groups 1 and 2. Plasma D-dimer concentrations higher than the reference range (0.01 to 0.33 μg/mL) were detected in samples obtained from 1 dog in group 1, 5 dogs in group 2, and 2 dogs in group 3.

The number of dogs in each group with plasma concentrations of FDPs of < 5, ≥ 5 to < 20, and ≥ 20 μg/mL were summarized (Table 1). Plasma concentrations of FDPs were significantly (P < 0.001) higher for group 1 versus groups 2 and 3. Plasma concentrations of FDPs were not significantly (P = 0.37) different between groups 2 and 3. Plasma concentrations of FDPs were higher than the reference range (< 5 g/mL) in samples obtained from 19 dogs in group 1, 7 dogs in group 2, and 6 dogs in group 3.

Discordant plasma FDPs and D-dimer assay results were detected for 18 dogs in group 1, 5 dogs in group 2, and 5 dogs in group 3. Prevalence of discordant plasma FDPs and D-dimer assay results was significantly (P < 0.001) higher for group 1 versus groups 2 and 3. Prevalence of discordant plasma FDPs and D-dimer assay results was not significantly (P = 0.39) different between groups 2 and 3. Of the 18 dogs in group 1 with discordant plasma FDPs and D-dimer assay results, 10 had concurrent hypofibrinogenemia. Two of these 10 dogs had clinical signs of impaired coagulation: the in-
Discussion

Results of the present study indicated group 1 dogs had higher aPTT and PT, lower plasma fibrinogen concentrations, and a higher prevalence of discordant plasma FDPs and D-dimer assay results versus group 2 and 3 control dogs, suggesting that group 1 dogs may have had PHF.10,12,13 Some of the assay results detected for dogs of group 1 are also typically detected in dogs with secondary hyperfibrinolysis caused by DIC.5 However, DIC was considered unlikely in group 1 dogs, including the index dog, because group 1 dogs did not have evidence of a disease expected to cause DIC, 19 of the dogs had plasma D-dimer concentrations within the reference range, they did not have severe thrombocytopenia, and schistocytes were not detected.10,15 In addition, the coagulation disorder in the index dog improved after administration of tranexamic acid, an anti-fibrinolytic drug that can cause thrombosis in patients with DIC.9,10,19,20

The finding that aPTT and PT were prolonged for group 1 dogs of the present study may have been attributable to hypofibrinogenemia. However, not all group 1 dogs had hypofibrinogenemia and these results could have been caused by low circulating concentrations of coagulation factors other than fibrinogen. Such low circulating fibrinogen and coagulation factor concentrations could have been caused by decreased synthesis attributable to liver damage secondary to right-sided CHF. Although some of the dogs with right-sided CHF may have had decreased synthesis of fibrinogen and other coagulation factors because of liver damage, this seemed unlikely because group 1 dogs had high plasma concentrations of FDPs and plasma D-dimer concentrations were in the reference range for 19 of the 20 dogs in that group (suggesting that group 1 dogs had high catabolism rather than decreased synthesis of fibrinogen) and had urine bile acids-to-creatinine concentration ratios similar to control group dogs. In addition, 6 of the 7 dogs in group 1 with urine bile acids-to-creatinine concentration ratios within the reference range (indicating these dogs had clinically normal liver function) had ≥1 value outside the reference ranges for aPTT, PT, and plasma fibrinogen concentration. These findings suggested that coagulation disorders in those dogs were not caused by liver dysfunction. Urine bile acids-to-creatinine concentration ratios were used as a marker of liver function in the present study because the variable could be determined for all dogs except the index dog, it is a better indicator of liver function than other biochemical analysis variables (eg, circulating bilirubin, urea, albumin, and glucose concentrations), and the sensitivity of this variable for detection of liver insufficiency in dogs is similar to that of serum pre- and postprandial bile acids assays.21

In patients with portal hypertension, ascitic fluid is essentially an ultrafiltrate of plasma. Therefore, such fluid contains proteins involved in coagulation in an environment where the actions of those proteins are not well regulated. Results of a study22 in which fibrinolytic activity was determined for humans with cirrhosis and ascites (n = 15), humans with cirrhosis and without ascites (15), and humans without liver disease and with ascites (2) indicated that activation of coagulation and fibrinolysis (ie, high D-dimer and FDPs concentrations and low fibrinogen and plasminogen concentrations) had developed in ascitic fluid of all patients with abdominal effusion, regardless of the cause of the ascites. In addition, signs of systemic (ie, intravascular) fibrinolysis (as indicated by a high plasma D-dimer concentration with or without decreased plasma plasminogen or fibrinogen concentrations) were detected in 93% of the patients with cirrhosis and ascites, 33% of the patients with cirrhosis and without ascites, and neither of the patients with ascites and without liver disease. The authors of that study22 concluded that ascitic fluid is inherently fibrinolytic.

The conclusion of those other authors that ascitic fluid is inherently fibrinolytic is supported by the clinical finding that clots rarely form in abdominal or pleural effusion fluid in vivo and by results of another experimental study.23 Therefore, systemic hyperfibrinolysis or hyperfibrinogenolysis may be attributable to reabsorption of plasminogen activator, plasmin, or plasmin-like factors from ascitic fluid. The primary similarities between the dogs of the present study and the humans with cirrhosis and ascites of the other study22 were that both the dogs and the humans had ascites and several hemostatic abnormalities. It was therefore possible that the ascitic fluid in dogs of the present study may have had fibrinolytic-fibrinogenolytic activity. Although the mechanisms of development of ascites secondary to cirrhosis and right-sided CHF are similar (hepatic portal hypertension and post-hepatic portal hypertension, respectively), 18 of the 20 dogs with right-sided CHF and ascites in the present study had evidence of PHF (ie, a plasma D-dimer concentration within the reference range with concentrations of FDPs higher than the reference range), whereas humans with cirrhosis and ascites in that other study22 had evidence of secondary hyperfibrinolysis (ie, increased plasma D-dimer concentrations with or without decreased plasma plasminogen or fibrinogen concentrations). To explain this difference, 2 possibilities may be considered. Humans...
with cirrhosis and ascites\textsuperscript{22} may have had PHF (attributable to ascites) and secondary hyperfibrinolysis (attributable to concurrent DIC).\textsuperscript{9,24} Alternately, those patients\textsuperscript{22} may have had only PHF (attributable to ascites), in which case the increased plasma D-dimer concentrations in those patients could have been attributable to decreased hepatic clearance of D-dimer because of cirrhosis.\textsuperscript{8}

Bleeding episodes are uncommon in humans with ascites secondary to right-sided CHF but are more common in humans with ascites secondary to cirrhosis or other causes of hepatic portal hypertension.\textsuperscript{26,27} These findings may be attributed to high systemic venous pressures impeding reentry of ascitic fluid into the systemic circulation in humans with right-sided CHF; whereas ascitic fluid may freely reenter the venous circulation in humans with cirrhosis. High systemic venous pressures may have also limited systemic reabsorption of ascitic fluid in dogs of the present study and may have been the reason that 18 dogs with right-sided CHF had coagulation profile analysis results suggestive of PHF; whereas only 2 dogs had clinical signs of bleeding. However, clinical signs of bleeding may be more common in humans with ascites attributable to liver disease than they are in humans with right-sided CHF because of other mechanisms.

A primary limitation of the present study was that values for some variables that could have been used to detect systemic PHF and activation of coagulation and fibrinolysis in ascitic fluid of the dogs were not determined. Activation of coagulation and fibrinolysis could have been identified in dogs via increased abdominal fluid concentrations of FDPs and D-dimer and decreased abdominal fluid fibrinogen concentration. Primary hyperfibrinogenolysis could have been identified in dogs via increased plasma plasma−α2 antiplasmin complex concentrations and plasma thrombin-antithrombin complex concentrations within the reference range.

To the authors’ knowledge, ascites secondary to right-sided CHF has not been previously reported as a risk factor for bleeding in dogs. Results of the present study indicated that 18 of the 20 dogs with right-sided CHF and ascites may have had PHF. These results and the results of another study\textsuperscript{8} that indicate that humans with cardiac disease have an increased risk of bleeding due to ascites suggest that further investigation regarding PHF as a potential cause of bleeding in humans and other animals with cardiac disease may be warranted.

\begin{thebibliography}{99}
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\end{thebibliography}
Effects of meloxicam on values of hematologic and plasma biochemical analysis variables and results of histologic examination of tissue specimens of Japanese quail (*Coturnix japonica*)

Kristin M. Sinclair et al

**Objective**—To determine the effects of meloxicam on values of hematologic and plasma biochemical analysis variables and results of histologic examination of tissue specimens of Japanese quail (*Coturnix japonica*).

**Animals**—30 adult Japanese quail.

**Procedures**—15 quail underwent laparoscopic examination of the left kidneys, and 15 quail underwent laparoscopic examination and biopsy of the left kidneys. Quail in each of these groups received meloxicam (2.0 mg/kg, IM, q 12 h; n = 10) or a saline (0.9% NaCl) solution (0.05 mL, IM, q 12 h; control birds; 5) for 14 days. A CBC and plasma biochemical analyses were performed at the start of the study and within 3 hours after the last treatment. Birds were euthanized and necropsies were performed.

**Results**—No adverse effects of treatments were observed, and no significant changes in values of hematologic variables were detected during the study. Plasma uric acid concentrations and creatine kinase or aspartate aminotransferase activities were significantly different before versus after treatment for some groups of birds. Gross lesions identified during necropsy included lesions at renal biopsy sites and adjacent air sacs (attributed to the biopsy procedure) and pectoral muscle hemorrhage and discoloration (at sites of injection). Substantial histopathologic lesions were limited to pectoral muscle necrosis, and severity was greater for meloxicam-treated versus control birds.

**Conclusions and Clinical Relevance**—Meloxicam (2.0 mg/kg, IM, q 12 h for 14 days) did not cause substantial alterations in function of or histopathologic findings for the kidneys of Japanese quail but did induce muscle necrosis; repeated IM administration of meloxicam to quail may be contraindicated. (Am J Vet Res 2012;73:1720–1727)