Why do some greyhounds bleed and others clot excessively? Deciphering the hemostatic teeter-totter

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Sighthounds in general, and greyhounds in particular, have evolved over the past 6,000 to 7,000 years to follow their prey by sight. Hence, they have developed numerous physiologic and hematologic adaptations specific to the breeds.[1]

In retired racing greyhounds (RRGs), the packed cell volume (PCV), hemoglobin concentration, red blood cell (RBC)

count, and whole blood viscosity are higher, while the white blood cell count, neutrophil count, and platelet count are lower than in other dogs (reviewed in 2). The serum total protein, globulin, alpha-globulin, and beta-globulin concentrations are also lower than in non-greyhound dogs.[3-5] Interestingly, platelet aggregation under high shear, as determined with the platelet function analyzer 100 (PFA-100), is significantly higher in RRGs than in non-greyhound dogs.[6] The latter is particularly noteworthy, since lower platelet counts typically lead to prolonged closure times when using PFA.[7]

There was anecdotal information suggesting the hemostatic system in greyhounds is also different. After losing a greyhound patient due to unexplained bleeding in early 2003, I embarked in a saga to determine why greyhounds bleed spontaneously. Shortly thereafter, I also discovered that some actually clot excessively. This review article summarizes my clinical and research experience during the past 15 years trying to decipher hemostasis in greyhounds.

Hemostasis for clinicians

Under normal conditions, injury to a blood vessel leads to immediate vascular changes (*e.g.* vasoconstriction) and rapid activation of the hemostatic system. Changes in axial blood flow lead to exposure of circulating blood to subendothelial collagen, resulting in rapid adhesion of platelets to the affected area. The adhesion of platelets to the subendothelium is mediated by adhesive proteins, such as von Willebrand factor (vWF) and fibrinogen, among others. After adhering to the area of endothelial damage, platelets aggregate and form the primary hemostatic plug, which is short-lived and unstable. The primary hemostatic plug serves as a framework in which secondary hemostasis occurs because most of the clotting factors "assemble" the thrombus or clot on the platelet plug (reviewed in 8).

Although the intrinsic, extrinsic, and common coagulation pathways have been well characterized and are still used to teach physiology of hemostasis, coagulation *in vivo* does not necessarily follow these distinct pathways. For example, factors XII and XI do not appear to be necessary for the initiation of coagulation (*e.g.* dogs and cats with factor XII deficiency do not have spontaneous bleeding tendencies). It is generally accepted the physiologic mechanism responsible for clotting *in vivo* is primarily tissue factor (TF) activation of factor VII. TF is ubiquitous, and it is present in most every cell surface, with the exception of resting endothelium. Disruption or "damage" to the endothelial cells causes exposure of circulating blood (containing factor VII) to TF, and rapid activation of the

coagulation cascade via the traditional extrinsic system. Thrombin plays a pivotal role in both the activation and inactivation (through thrombomodulin) of the hemostatic mechanisms (reviewed in 9). In the past two decades, the traditional coagulation cascade has been thought of as a common pathway from early in the process; the traditional intrinsic, extrinsic, and common pathways are now known to be interrelated.[9-11]

The stimuli that activate coagulation also trigger the fibrinolytic and kinin pathways. Fibrinolysis is an extremely important safeguard mechanism because it prevents excessive clot or thrombus formation. When plasmin lyses fibrinogen and fibrin, it generates fibrin degradation products (FDPs), which impair additional platelet adhesion and aggregation in the site of injury. Once fibrin has been stabilized by complexing factor XIII, plasmin biodegradation generates D-dimers instead. The activation of plasminogen into plasmin results in the destruction (lysis) of an existing clot (or thrombus) and interferes with the normal clotting mechanisms (inhibition of platelet aggregation and clotting factor activation in the affected area). Therefore, excessive fibrinolysis usually leads to spontaneous bleeding. Two main molecules stimulate plasminogen activation into plasmin: tissue plasminogen activator (tPA) and urokinase-type plasminogen activator. Three plasminogen activator inhibitors (PAI) termed PAI-1, -2, and -3 inhibit fibrinolysis, leading to thrombosis (reviewed in 8).

Other systems opposing blood coagulation also become operational once intravascular clotting has occurred. The best characterized ones include antithrombin (AT), a protein synthesized by hepatocytes that is a cofactor for heparin and inhibits the activation of factors IX, X, and thrombin. AT also inhibits tPA. Proteins C and S are two vitamin K-dependent anticoagulants also produced by hepatocytes. These three factors are some of the natural anticoagulants that prevent excessive clot formation (reviewed in 8).

The thrombelastograph (TEG) is a whole blood coagulation analyser that evaluates cell/protein interaction; it allows for a global analysis of the hemostatic system, including primary and secondary hemostasis, and the fibrinolytic system.[12,13] The TEG parameters reported by the instrument are as follows: The "R-time" is the time from addition of the agonist (CaCl2 or TF) to the citrated whole blood in the cup, until the clot formation reaches detectable levels and represents the enzymatic portion of coagulation. The "K-time" is the time from detection of the endpoint "R-time" until the clot reaches a determined firmness, a measure of the speed to reach a certain level of clot strength, representing the clot kinetics. The angle ("alpha") is related to the fibrinogen concentration (and function) and the rapidity of fibrin formation and cross-linking, also related to the kinetics of clot formation. The

"MA" is the maximum amplitude or ultimate strength of the fibrin clot and represents primarily the contribution of platelet aggregation to clot formation. "G" provides a measure of clot strength viscoelastographically and is calculated from the MA. Finally, LY60 represents the percent or proportion of clot lysis (*i.e.* clot retraction and fibrinolysis) or decrease in amplitude from the MA at 60 minutes, under the area of the tracing.[12,13] In a recent study, we demonstrated thromboelastographic features in RRGs are different from those in other dogs; mainly the maximum amplitude and clot strength are significantly lower than in other breeds.[13]

Surgery and hemostasis

Surgery typically induces a hypercoagulable state.[14] A recent study in humans demonstrated a continuous increase in clot firmness, as determined by TEG, two to six days after surgery; however, there were no changes in one-stage prothrombin time (OSPT) or activated partial thromboplastin time (APTT) that suggested hypercoagulability.[14] The proposed mechanism of this hypercoagulability is associated with local tissue trauma, release of tissue factor from damaged vessels, decreased blood flow, activation of inflammation, and compromised fibrinolysis.[14,15]

Intraoperative and immediate postoperative bleeding can be due to local surgical technique (*i.e.* surgical bleeding) or to systemic abnormalities (*i.e.* nonsurgical bleeding).[16] The latter includes primary hemostatic defects, such as thrombocytopenia, platelet dysfunction, or von Willebrand disease (vWD), as well as secondary hemostatic defects, including hypofibrinogenemia, hypoprothrombinemia, hemophilia A or B, factor VII deficiency, or combined clotting factor deficiencies.[16] Coagulopathy due to trauma must also be considered in such patients.[17] Finally, systemic endothelial damage or dysfunction after postoperative septic complications or hypertensive crises can result in thrombocytopenia and generalized bleeding, as described in women with hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome associated with preeclampsia and in children with hemolytic-uremic syndrome.[18] Delayed postoperative bleeding is more likely due to abnormal fibrin stabilization, factor XI deficiency, or enhanced fibrinolysis.[19]

Delayed postoperative bleeding in greyhounds and other sighthounds

In the early 2000s, we observed what appeared to be a high tendency for bleeding after minor trauma or a simple surgical procedure, such as gonadectomy, dewclaw removal, skin mass biopsy, or laparotomy in RRGs. Some affected dogs required multiple blood transfusions, and several died or were euthanized. In the majority of the patients, the one-stage prothrombin time, activated partial thromboplastin time, and platelet counts (PLTs) were within the reference intervals for the breed.

We therefore conducted a web-based health survey that documented the prevalence of diseases and major causes

We therefore conducted a web-based health survey that documented the prevalence of diseases and major causes of death in RRGs in North America.[20] Bleeding disorders were one of the four most prevalent causes of death reported, accounting for eight percent of all deaths. Overall, hematologic diseases had a prevalence of 3.3 percent, with stroke and spontaneous or postoperative bleeding accounting for 46 percent of these.[20]

We subsequently conducted a prospective study of 88 RRGs that underwent gonadectomy, and evaluated most clinically relevant hemostatic parameters before surgery, and after a bleeding episode in both "bleeders" and "nonbleeders."[21] The following tests were used to evaluate primary hemostasis: platelet count, platelet function with PFA-100 closure time (CT), von Willebrand factor antigen concentration (vWF:Ag) and von Willebrand factor activity using the collagen binding assay (vWF:CBA). Secondary hemostasis was evaluated with APTT, OSPT, fibrinogen concentration (FIB), antithrombin (AT) activity, and factor XIII. The fibrinolytic pathway was evaluated by measuring plasminogen activity (Plmg), antiplasmin activity (AP), and D-dimer concentration.

Although at the time there was no standardized scale to evaluate the severity of bleeding in dogs, we proposed a system with scores ranging from "0 "to "4," adapted from the one proposed by Buchanan and Adix[22] for children with idiopathic thrombocytopenic purpura. The final bleeding score assigned to each RRG corresponded with the highest score recorded during the postoperative period. In dogs with clinical evidence of bleeding (*i.e.* bleeding score 1 to 4), the assays of hemostatic function performed at baseline were repeated when the bleeding was detected. These assays were also performed in a group of sex-matched greyhounds that underwent surgery at the same time and did not have postoperative bleeding (*i.e.* bleeding score 0-control dogs).[21]

None of the dogs developed intraoperative or immediate postoperative bleeding; however, 26 percent of the dogs (23/88) had delayed postoperative bleeding 36 to 48 hours after surgery. The signs of bleeding consisted of cutaneous bruising that extended from the area of the surgical incision toward the periphery (Figure 1). There was no bleeding from mucosal surfaces or in areas distant from the surgical site. None of the dogs required transfusion of blood components and the bleeding was self-limiting; bruising was still present at the time the dogs were discharged four to five days after the surgery.[21] There were no significant differences between "bleeders" and "non-bleeders" preoperatively for any of the conventional hemostasis assays.

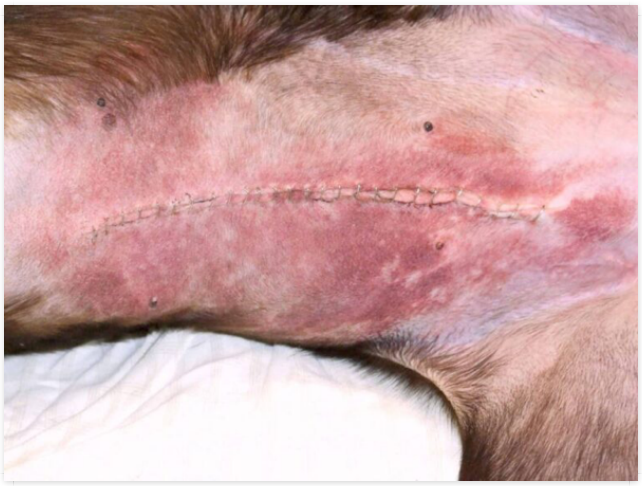

Figure 1: Postoperative bleeding 48 hours after ovariohysterectomy in a greyhound (bleeding score 3).

The AP and AT activities, although within the reference interval, were significantly lower in the "bleeder" group than in the "non-bleeders" ($p<0.001$ and $p=0.007$, respectively). There were no significant postoperative differences between "bleeders" and the control group for any of the hemostatic parameters evaluated.

In that prospective study, we documented for the first time the development of delayed postoperative bleeding after gonadectomy in RRGs, with a prevalence of 26 percent. In both groups, platelet counts and platelet function were within the reference ranges for the breed and were not significantly different between "bleeders" and "non-bleeders." Selective or combined clotting factor deficiencies were ruled out on the basis of normal fibrinogen concentration, OSPT, and APTT in the "bleeders." Factor XIII deficiency was also ruled out on the basis of normal factor XIII assay.[21]

Both von Willebrand disease and von Willebrand syndrome (vWS) were excluded on the basis of normal vWF and CBA.[23] Greyhounds commonly have a high-velocity aortic murmur due to relative aortic stenosis.[24] Type 2 vWS —a depletion of high-MW vWF multimers secondary to high shear—has been described in humans with aortic valve mineralization, and in dogs with aortic and subaortic stenosis.[25,26] We ruled out type 2 vWS based on the fact the vWF:Ag/vWF:CBA ratio was below two.

At the time of the study, we suggested the delayed onset of bleeding (*i.e.* 36 to 48 hours) in the affected greyhounds could be due to enhanced fibrinolysis, since "bleeders" had lower AP than "non-bleeders" prior to surgery, suggesting activated fibrinolysis and hence, a hypocoagulable state.[21] Subsequent studies revealed fibrinolysis does not appear to play a role in the delayed postoperative bleeding of greyhounds.[27] Using TEG, fibrinolysis is assessed by the LY30 and LY60 parameters that measure the decreases in MA once fibrinolysis "loosens up" the clot in the cuvette. In a pilot study of 21 dogs, we found no differences in LY60 between "bleeders" and "non-bleeders."[27] Only the TEG variables that represent the fibrin cross-linking of the clot (*i.e.* angle) and the fibrin to platelet interaction or the strength of the clot (*i.e.* MA and G) were predictors of the outcome. Hence, we proposed failure to strengthen the clot after surgery was primarily responsible for the bleeding events.

However, recent evidence suggests conventional TEG may not be sensitive enough to detect abnormalities in fibrinolysis.[28,29] Fletcher et al[28] described an *in vitro* model of TEG using tPA and kaolin activation. Subsequently, the same team further validated this assay in dogs receiving epsilon aminocaproic acid (EACA).[30]

Considering a routine spay or neuter in a RRG frequently results in hemostatic complications that may lead to readmission to the clinic for treatment, identifying the patients at risk, and/or developing a simple protocol for preventing or minimizing this complication will be extremely valuable. With a prevalence of bleeding of 26 percent

preventing or minimizing this complication will be extremely valuable. With a prevalence of bleeding of 20 percent, as many as 3,500 to 5,000 RRGs may be readmitted to the clinic and treated after routine surgery every year in the U.S.[31]

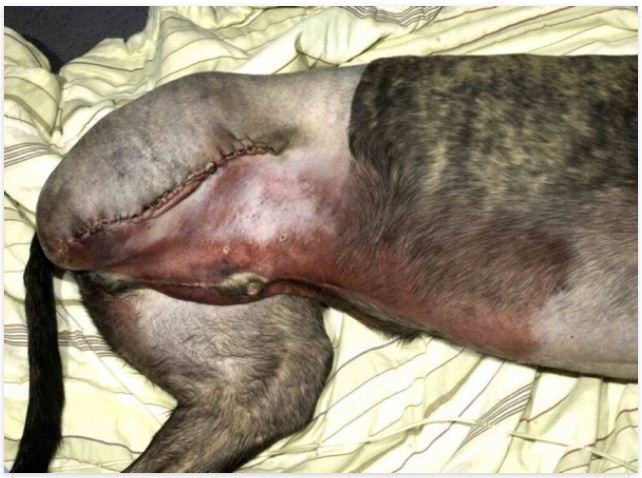

Figure 2: Severe postoperative bleeding 48 hours after a rear limb amputation in a greyhound with osteosarcoma.

Furthermore, osteosarcoma (OSA) is the most common form of cancer in RRGs, representing 45 percent of all tumors and accounting for approximately 25 percent of the deaths in the breed.[20] The standard of treatment in dogs with OSAs is limb amputation followed by postoperative adjuvant chemotherapy; thus, owners of RRGs with OSA who elect amputation face the potential complications, grief, and expenses related to blood component therapy and intensive care for hemostatic complications.[31] Figure 2 depicts typical postamputation bleeding in a greyhound. In a retrospective study, we documented 13 of 46 (28 percent) RRGs undergoing amputation for bone tumors bled excessively after surgery, and most required administration of fresh frozen plasma, cryoprecipitate, and or packed red blood cell transfusions.[31]

Antifibrinolytic agents

Fibrinolytic inhibitors such as epsilon aminocaproic acid (EACA) and tranexamic acid (TXA)[28,32-35] have proven to be effective in human patients and horses where bleeding complications are associated with enhanced fibrinolysis, but they have also been beneficial in patients with systemic bleeding due to other mechanisms.[32] Theoretically, EACA and TXA prevent activation of plasminogen into plasmin on the fibrin surface by preventing the binding of plasminogen to C-terminal lysine residues on partially degraded fibrin, thus blocking the plasminogen binding site, which is essential for efficient plasmin formation (reviewed in 33). Interestingly, EACA neutralizes bleeding states created experimentally in dogs by infusion of plasmin or a plasminogen activator.[34]

EACA can either block enhanced fibrinolytic activity, or rapidly restore hyperfibrinolytic states to normal, thus impeding the dissolution of fibrin clots and thereby decreasing RBC transfusion requirements in human patients undergoing surgery.[35] EACA has a wide therapeutic index; no relevant adverse effects were reported in toxicologic studies in dogs with doses as high as 0.5 g/kg.[36]

Since we had anecdotal evidence suggesting EACA had a positive effect in minimizing bleeding, we evaluated the prevalence and severity of postoperative bleeding in 100 RRGs undergoing orchiectomy (OHE) that received either

EACA or placebo in a prospective, double-blinded, randomized study. In addition, we aimed to evaluate EACA's effects on selected TEG and fibrinolysis parameters.[33]

Dogs were randomized to receive either EACA (500 mg PO q8 hours for five days starting the night of the surgery) or placebo (lactose). The clinicians were blinded as to the type of drug administered. We used the bleeding score previously reported to classify dogs as "bleeders" or "non-bleeders."[33]

Venous blood samples were obtained at 24, 48, and 72 hours after surgery for TEG analysis as previously described;[13] the residual blood samples were centrifuged and plasma aliquots were used for other hemostasis assays (OSPT, APTT, FIB, plasminogen, and antiplasmin).[33]

Similar to our previous studies, none of the dogs experienced intraoperative or immediate postoperative bleeding; however, 15 out of 50 RRGs (30 percent) in the placebo group had delayed postoperative bleeding 36 to 48 hours after surgery, compared with five out of 50 RRGs (10 percent) in the EACA group (P=0.012); the use of EACA decreased the odds of bleeding by 79 percent (OR = 0.21, P=0.011). The R and K time shortened (*i.e.* "hypercoagulability") over time in the EACA group, while they lengthened (*i.e.* "hypocoagulability") in the placebo group (Figure 2). In addition, the angle, MA, and G increased postoperatively over time in the EACA group (*i.e.* "hypercoagulability"), while they decreased in the placebo group (*i.e.* "hypocoagulability"). We therefore concluded the clot kinetics were enhanced in dogs receiving EACA when compared with the placebo group.[33]

Our results are similar to what Hamada et al described in 1995 in 30 human patients undergoing upper abdominal surgery that randomly received placebo or carbazochrome sodium sulfonate (CS) and TXA, a drug similar to EACA.[37] They also found significant differences between pre-surgical and postsurgical TEG variables in both groups, and all the patients became hypercoagulable after surgery. The beneficial effects of lysine analogues in bleeding patients were recently reviewed by Hunt.[38]

Since our early findings, several papers on the use of EACA or TXA have been published in dogs,[28,30,39-45] and EACA or TXA are now commonly used in practice. After extensive studies, we concluded administration of EACA at approximately 15 mg/kg, PO, q8h (typically 500 mg per dogs per dose) for five days beginning on the day of the surgery significantly decreases the prevalence of delayed postoperative bleeding in RRGs undergoing surgery by amplifying and strengthening the fibrin clot. We routinely use EACA in greyhounds undergoing major surgery and in those that bleed postoperatively. For major surgeries, we use the EACA preemptively; for minor surgeries (laceration, dental extractions, biopsies, etc.), we send the patient home with a prescription for EACA, and instructions to its owner administer it if the dog bruises in the area or bleeds from the mouth. EACA in tablet or

capsule form has become increasingly difficult to obtain or is overly expensive in the U.S. Although, no data on pharmacokinetics or pharmacodynamics are available to my knowledge, I have been using the injectable EACA administered orally at the same dosage via syringe—this appears to be as effective as tablet or capsule form.

As a final note, we have recognized a similar syndrome of delayed postoperative bleeding in deerhounds and in Italian greyhounds (Figure 6), and have anecdotal reports of postoperative bleeding in whippets, Afghan hounds, Borzois, and some other sighthound breeds.

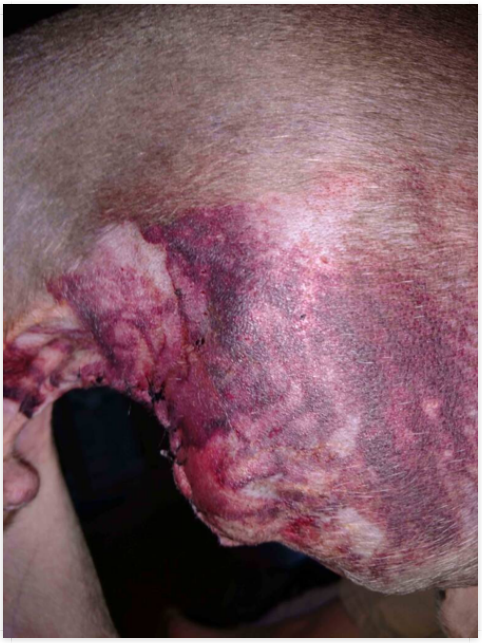

Figure 6: Delayed postoperative bleeding after surgical removal of a small mast cell tumor in a six year-old Italian greyhound.

Thrombosis

The terms "thrombus' and "embolism" were coined by Rudolph Virchow in the 1850s (reviewed in 46). A thrombus (from the Greek *thrombos*) is defined as a clot of blood formed within a blood vessel that remains attached to its place of origin; an embolus (from the Greek *embolus* or wedge-shaped object) is an abnormal particle, such as an air bubble or piece of thrombus, circulating in the blood. Thromboembolism (TE) is defined as formation of a clot (thrombus in a blood vessel) that breaks loose and is carried by the blood stream to occlude another vessel. As a general rule, venous thrombi are low-flow, fibrin-rich structures, whereas arterial thrombi are high-flow, platelet-rich clots (2014). Thrombosis can be due to local factors (*e.g.* stagnant blood flow) or systemic hypercoagulability.

Numerous hemostatic and hemorrheologic mechanisms can contribute to hypercoagulability (reviewed in 47 and 48). In human medicine, the term "thrombophilia" is used to describe conditions that predispose to venous and arterial thrombosis by impairing hemostasis.[47] Hyperviscosity due to a high circulating red blood cell mass is one

that leads to marked increases in the hematocrit (HCT); in some dogs, the HCT during or immediately after a race can be as high as 80 percent.[51,52] Although an optimal increase in HCT (and hence, hemoglobin concentration) typically enhances aerobic performance and buffering during exercise, HCT above this value result in high viscosity[53,54] and markedly decreased cardiac output.[54-56] However, a high HCT also has a beneficial effect on endothelial cells, leading to the release of nitrous oxide (NO), and subsequent vasodilation.[57-59] To my knowledge, there are no published reports of red blood cell deformability in greyhounds; in human athletes, the release of high

numbers of young RBCs results in increased deformability and compensates for the higher HCT.[54]

A high HCT and its associated increased viscosity lead to hypercoagulability, due to unknown mechanisms.[49] As Virchow proposed in 1855, "circulating blood does not clot" (reviewed in 46,60. Hence, it is quite likely that greyhounds and other sighthounds have developed adaptational mechanisms to deal with this risk factor for thrombosis, thus becoming somewhat "hypocoagulable." Interestingly, fibrinogen concentrations decrease in human athletes in association with training.[49] Most greyhounds have fibrinogen concentrations below the reference intervals for dogs (reference intervals 89-180 mg/dL compared to 100-384 mg/dL in non-greyhound dogs.[2]

Thrombosis and TE are common in cats with hypertrophic cardiomyopathy, but are uncommon in dogs.[61] However, we reported that almost four percent of greyhounds had hemostatic disorders, including hypo- and hypercoagulability, resulting in eight percent of the deaths in the survey.[20] Some reports of greyhounds and other sighthounds with central nervous system (CNS) TE have appeared in the literature[62,63] Several greyhounds with aortic and iliac thrombosis[64-69] and another one with pulmonary TE[70] were also reported recently. Although some of the non-greyhound dogs in these reports had underlying disorders, such as cancer or heart disease, most of the greyhounds and sighthounds affected were otherwise healthy.

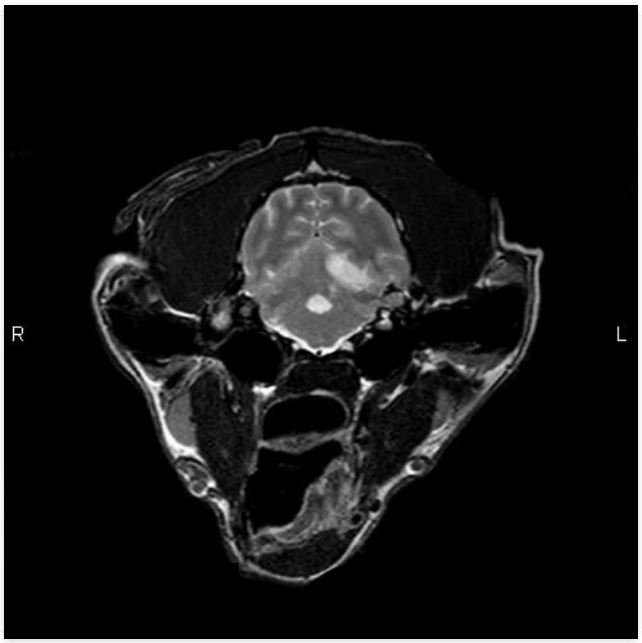

Figure 3: MRI T2W image of a brain infarct in a nine-year-old female, spayed greyhound showing a hyperintense lesion.

In my experience, CNS TE is common in greyhounds and other sighthounds, and it resembles human ischemic strokes. The typical presentation is that of an older (eight to 10-year-old) dog, with peracute onset of CNS signs consisting of ataxia, salivation, nystagmus, seizures, or any combination of neurologic signs; in my experience, most dogs present with central vestibular signs. Results of magnetic resonance imaging (MRI) typically reveal a well-defined lesion that is hyperintense in T2W and T2W-fluid-attenuated inversion recovery sequences, hypointense in T1W sequences, has minimal to no enhancement after IV administration of paramagnetic contrast agents, results in minimal mass effect, and involves predominantly the gray matter in the vascular territory of main cerebral or cerebellar arteries or a perforating branch of such arteries.[63] Figure 3 depicts the MRI image of an infarct 24 hours after the development of clinical signs in a nine-year-old, female spayed greyhound.

Most dogs have a single lesion. In a recent retrospective study of 21 greyhounds with ischemic strokes,[63] they were located in the cerebellum (n = 9), caudate, and lentiform nuclei and the intervening internal capsule (3), thalamus (6), or piriform lobe of the cerebrum (1). On the basis of the anatomic location of the lesions, the arterial supply that was presumed disrupted included the rostral cerebellar artery (n = 9), lenticulostriate artery (3), another perforating artery (6), or distal branch of the middle cerebral artery (1). Interestingly, most affected greyhounds we have evaluated and those reported by Kent et al[63] have normal parameters of hemostasis, including TEG tracings.

We have also identified a subset of young actively racing greyhounds that develop peracute spinal cord signs within 50 to 75 m of starting the race. Most trainers and veterinarians refer to them as fibrocartilaginous emboli (FCE), despite the fact that, to my knowledge, no imaging or pathologic studies have documented the lesions. Although we have limited data from advanced imaging, most affected dogs that underwent MRI had evidence of arterial thrombosis. In most dogs, the response to antiplatelet agents (see below) is rapid (hours), suggesting a thrombus as opposed to FCE. Interestingly, these episodes seem to coincide with the purported splenic contraction secondary to catecholamine release that rapidly increases the hematocrit to almost 80 percent.[71] In addition to the arterial thrombosis mentioned above, we have seen peracute thrombosis of the spinal venous sinuses in pet greyhounds as young as 18 months of age.

I manage affected dogs with antiplatelet agents, since they are likely arterial (*i.e.* platelet-rich) thrombi. In my experience, aspirin at a dosage of 40.5 mg (half of an 81-mg aspirin) per dog, PO, q24h, is effective in most dogs treated shortly after the development of clinical signs. Indeed, in some dogs, administration of aspirin at home by their owners frequently results in marked improvement or even resolution of most neurologic signs by the time the patient arrives at the clinic. We continue this treatment indefinitely, and thus far, I have documented only two dogs who relapsed. Interestingly, in the largest study of CNS infarcts in greyhounds, response to therapy was not reported.[63]

Using platelet function analysis (PFA-100) and TEG platelet-mapping, we documented that 40.5 mg of aspirin given PO once daily significantly decreases platelet aggregation in greyhounds (data not shown). We were unable to demonstrate decreases in platelet aggregation in a small number of greyhounds in which we used clopidogrel (Plavix); this may be due to the fact the latter is a cytochrome P450- (CYP-) dependent drug. Anecdotally, however, clopidogrel may be beneficial in greyhounds (S. Shropshire, DVM, DACVIM, Colorado State University, personal communication). Greyhounds have lower activity of selected CYP enzymes than other dogs,[72,73] so these drugs should be used with caution in the breed.

In a recent study of 100 dogs with aortic thrombosis, greyhounds represented the second most common breed, with 14 percent of the cases; Labrador retrievers were the most common breed, representing 16 percent of the cases.[74] Most greyhounds did not have clear underlying causes of hypercoagulability.

Greyhounds with aortoiliac thromboembolism (AITE) usually present for intermittent, progressive unilateral rear limb lameness that frequently starts in one limb and gradually becomes bilateral. In most dogs, the distal aorta and/or the external iliac arteries are involved; internal iliac arterial thrombosis is uncommon. Swelling and bruising of the affected limb are common (Figure 4).

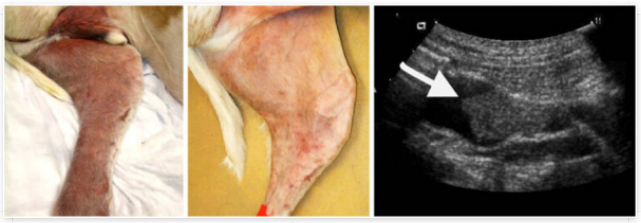

Figure 4: Gross and ultrasonographic appearance of a seven-year-old greyhound with osteosarcoma and a right hind limb amputation that developed thrombosis of the aorta several months later. [Left] At presentation. [Center] Six days after aspirin and warfarin (3 mg q24h) treatment. [Right] Ultrasonographic image—note the thrombus in the aortic bifurcation (arrow).

In most dogs, physical examination also reveals disparity in the femoral pulses between both limbs. Ultrasonography is the preferred imaging method of diagnosis, as it reveals and echogenic intra-arterial structure with decreased blood flow, as determined by Doppler (Figure 5).[68,69]

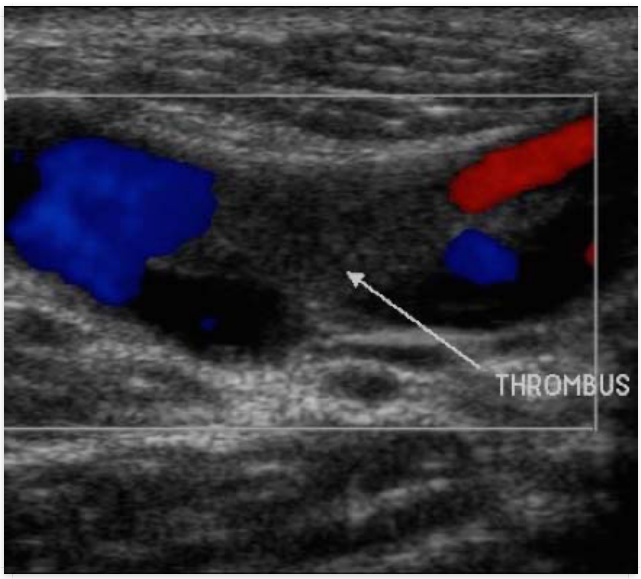

Figure 5: Color flow imaging of a six-year-old female, spayed greyhound with progressive rear limb claudication of over four months. Note echogenic thrombus interfering with blood flow (arrow).

In dogs with AITE who do not respond to aspirin therapy or who have severe edema/bruising, I have successfully used warfarin (0.05-0.2 mg/kg, q24h), adjusting dosages as reported by Winter et al[69]; as discussed above, warfarin is also a CYP-dependent drug, so it should be used with caution in greyhounds. The rationale behind using heparin is to decrease additional clot formation, and hopefully allow for the endogenous fibrinolytic (and other clot-

opposing mechanisms) to work.

In most patients I have managed, underlying hypercoagulable syndromes were not identified. Affected greyhounds had results of OSPT, APTT, fibrinogen concentration, and TEG within the reference interval for the breed. Interestingly, old studies have suggested greyhounds and other sighthounds may have tortuous arteries or arteriosclerosis, or they may develop atheromas.[75-78] This could explain the high prevalence of AITE in these breeds.

In summary, greyhounds (and likely other sighthounds) do not follow the rules when it comes to hemostasis; some bleed and some thrombose, despite having normal test results. Fortunately, the recognition of the delayed postoperative bleeding and the clinical studies of EACA, and better knowledge of the fact greyhounds are at risk for thrombosis, along with implementation of aspirin therapy, have led to decreased morbidity and mortality.

Guillermo Couto, DVM, dipl. ACVIM, specializes in internal medicine and oncology. He has coauthored the bestselling textbook, Small Animal Internal Medicine *(Elsevier), now on its sixth edition, has published more than 150 scientific articles in peer-reviewed journals, as well as 150 book chapters. Dr. Couto has 40 years' experience in clinical and comparative hematology, oncology, transfusion medicine, and clinical pathology, and is an expert in greyhound and sighthound medicine.*

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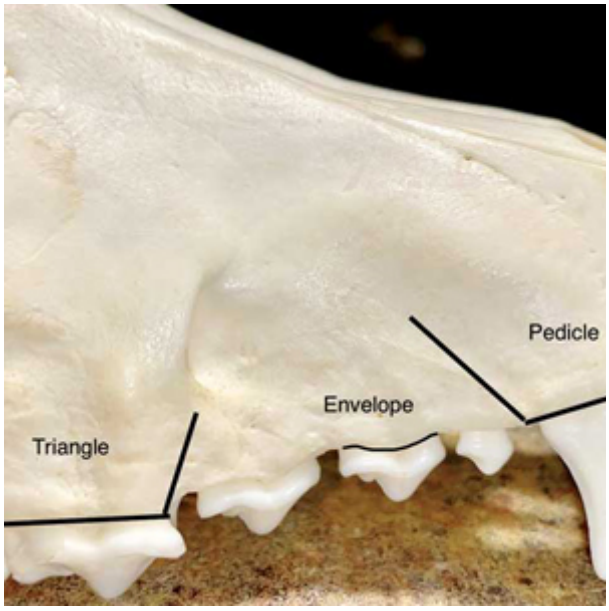

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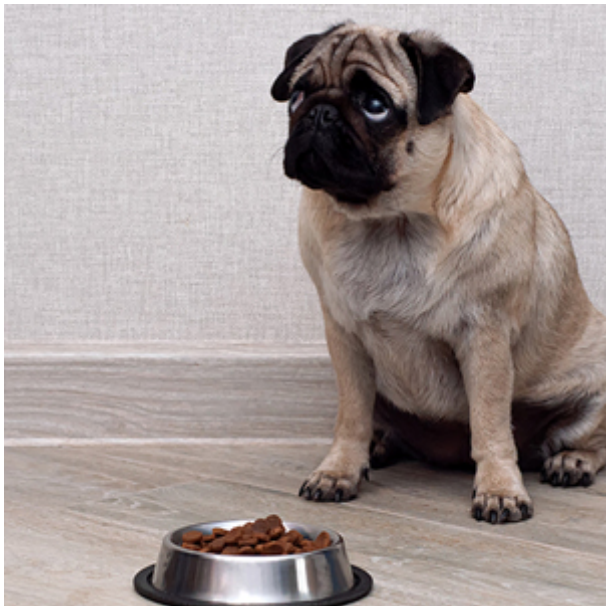

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