

Summary from Dr. Sharon Centers talk on PSVA and MVD given 2/17/2007 in San Jose, CA in Conjunction with CTCA Roving Specialty

Liver Portosystemic Vascular Anomaly (PSVA) and Microvascular Dyplasia (MVD)

-Current information regarding the heritability of PSVA and MVD substantiated that they are related abnormalities, they are congenital, and are consistent with an ancient genetic mutation that occurred as small dog breeds were evolving (because so many breeds are affected).

-The first thing to consider is that we are in the process of discovering the underlying genetic cause and hoping to develop a useful test to help eliminate these traits: Don't do anything "rash."

- Some dogs with PSVA may drink a lot of water, eat abnormal substances, drool, do head pressing, have a cholesterol less than 150 mg/dl and microcytic (small red blood cells). However, not all dogs with PSVA or MVD have symptoms or are ill; in fact up to 20% of PSVA dogs may be asymptomatic which has resulted in some of these dogs being used for breeding.

Unlike dogs with PSVA, dogs with MVD usually do not manifest clinical signs, are not ill, and do not require medical or dietary treatments.

-The only test that is reliable for PSVA screening is bile acid testing because ammonia is so labile. -Blood ammonia is not a good or reliable indicator of PSVA or MVD (lots of false positives and the blood ammonia samples are very unstable). Ammonia measurements must be evaluated immediately, cannot be frozen, and environmental variables can vastly alter results. Ammonia measurements cannot be done using samples mailed to a laboratory. Ammonia challenge with administration of ammonium chloride given orally or per rectum optimizes the use of ammonia as a diagnostic test for shunting but can cause encephalopathic signs. In contrast, serum bile acids are stable, can be mailed, can be measured after extended refrigeration or sample freezing. A recent veterinary clinical publication touted the use of ammonia to detect shunts over bile acids; the study was biased by several confounding factors and compared ammonia concentrations only to fasting bile acids: **DO NOT USE SINGLE BILE ACID VALUES** to rule out shunting- that has long been established by rigorous investigation in our hospital and published in 5 peer reviewed scientific manuscripts.

- Serum bile acids should be collected Before and 2-hours After a meal (this serves as a provocative challenge initiating bile acid release from the gallbladder, intestinal reabsorption, passage into the portal vein to the liver, and rapid liver extraction from the portal blood). The term *Postprandial* refers to the after meal sample. Dogs **DO NOT** need to be fasted for 12-hours to conduct this test. The important issue is to test **BEFORE** and 2-Hrs after **FEEDING** to fully evaluate the dogs ability to extract bile acids from the portal circulation. Spilling of portal blood contents into the systemic blood is reflected by finding high Serum Bile Acid values > 25 umol/L in a sample collected from a leg vein or jugular vein.

-About 15-20% of dogs have a higher fasting than post-prandial bile acid values so using a random bile acid sample or a single bile acid sample is not optimal. **ALWAYS: USE PAIRED TESTS AROUND a MEAL.**

-The cut-off for abnormal results used by Dr. Center fasting **AND** for Postprandial values is greater than or equal to 25 micromole/L (normal dogs do not have bile acid values > 15 micromole/L at either interval). To avoid calling normal outliers abnormal, an indisputable cutoff was mathematically determined based on samples from hundreds of healthy dogs and dogs with liver disease in Dr. Center's laboratory.

-Both PSVA and MVD dogs have increased serum bile acid values; **BUT** you can't tell if a dog has PSVA or MVD based on bile acid results alone. It is true that dogs with PSVA often have at

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least one bile acid value > 200 umol/L, but not always. Some MVD dogs can develop bile acids at high as 200 umol/L also.

- The bile acid test is very reliable but the red blood cells MUST be separated from plasma (the clear part of blood) before they are sent to lab for analysis (centrifuged or spun to allow plasma separation from blood cells). Results can be falsely abnormal if the bile acid samples are lipemic (lots of fat IF the fat is not adequately removed by the laboratory analyzing the sample) or if hemolysis (burst red blood cells, makes the plasma red) occurs. The red color interferes with the color of the end point dye in the bile acid test. A clinician can tell if the sample is hemolyzed when they centrifuge the sample to separate the red blood cells from the plasma. If it is hemolyzed they should collect another sample. Drawing blood with a vacutainer needle into a vacutainer (suction of the tube facilitates the collection) may be too traumatic for some red blood cells augmenting hemolysis. Using a syringe and needle or syringe and butterfly needle appears to collect the best samples. After the blood is collected, the needle should be removed from the syringe and the top removed from the vacutainer so that the blood may be gently transferred to the vial. Results of the bile acid test should state if the samples were lipemic or if hemolysis occurred. In this case, the tests should be repeated

-Most dogs with PSVA will have Ammonia Biurate Crystals in their urine detected if 3 urine samples collected at different intervals are evaluated. Urine from these dogs has a peculiar light orange-brown color observed if the dogs urinate on a white surface. The color is derived from the gold-brown color of the tiny ammonium biurate crystals. A laboratory technician can check for these crystals on a sample of urine. MVD dogs will not have Urine-Ammonia Biurate Crystalluria so when the crystals are found you likely have a shunt in a Cairn Terrier. Unfortunately, any cause of severe liver disease can lead to the development of multiple portosystemic shunts and ammonium biurate crystalluria. Thus, in older dogs where finding the crystals is a new event, we will need to make sure what the underlying cause is. Ultrasound and liver biopsy may be necessary.

-If a dog has elevated bile acid values (either fasting or postprandial), determination of Protein C activity can help differentiate between PSVA and MVD (local vet can collect a citrate anticoagulated blood sample, separate the plasma for mailing, and send it to Cornell for analysis). This sample collected in a special citrate anticoagulated vial. Specifics of the test can be clarified by calling the Cornell Diagnostic Laboratory at 607-253-3900; the test is conducted by the Comparative Hematology / Coagulation Laboratory [Dr. Marjory Brooks].

-MVD dogs usually are not ill and do not require a special diet. Rarely, some of these dogs have had a problem with drug metabolism (e.g. antihistamines, certain anesthetics)

-Pursuing an asymptomatic dog with high bile acids and normal Protein C can result in costly and invasive testing; thus some MVD dogs are subjected to rigorous evaluations that may not be practically useful. Most of these dogs require no treatment yet often, a diet modification and even antioxidants are sometimes recommended. In most cases, these are unnecessary for the MVD dog based on Dr. Center's extensive experience with MVD.

- In the very large pedigree of Cairn Terrier's studied so far (>600 dogs) there is a 31% affectation rate of vascular malformations INCLUDING dogs with PSVA and dogs with MVD. Our data and linkage analyses support that these disorders represent two manifestations of the same genetic trait.

-PSVA dogs should not be bred until we gather more information on the genetic basis of the disorder. We do not know yet whether MVD represents a heterozygous situation or just a less severe trait manifestation. *It is too early to start culling all dogs with high bile acids- read the next paragraph to convince yourself why this may be ineffectual.*

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We know that some parents with normal bile acids have produced dogs with PSVA and MVD. Since we believe that PSVA and MVD represent disorders of angiogenesis, it is quite possible that not all dogs carrying the trait will have liver or portal vein involvement. Consider for example, that we have documented dogs with vascular malformations between the spleen and vena cava that have not influenced portal venous blood flow and thus did not cause high bile acid values. So, the trait may exist in some dogs with normal bile acid values. We also have some evidence that we may only see a subset of dogs with PSVA; we suspect there are embryonic deaths in severely affected dogs likely related to abnormal vasculature involving the placenta.

At present we recommend that all Cairn puppies undergo paired bile acid tests before they are adopted into homes (15 weeks or so). Why? Because you do not want a veterinarian to surprisingly find high bile acids when a dog is presented for illness. This results in aggressive testing that may include an expensive abdominal ultrasound and even a liver biopsy in a dog with MVD- consider for example a dog presented for vomiting after eating garbage. A high bile acid test would implicate the liver as being severely affected, and the clinician would be obligated to inform the client that the liver should be investigated. If they already knew the dog had high bile acids as a pup, consistent with MVD, then the medical investigations would be judiciously focused on the vomiting.