DIAGNOSTIC APPROACH: PORTOSYSTEMIC VASCULAR ANOMALIES (PSVA)

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Key Points:

- PSVA/MVD syndrome is a complex polygenic trait causing hepatic portal hypoperfusion. PSVA and MVD usually cannot be distinguished by liver biopsy alone.
- PSVA associates with historical & clinicopathologic features lacking in MVD: low RBC MCV, cholesterol, BUN, creatinine, urine SG, and ammonium biurate crystalluria and uroliths
- PSVA associates with low Protein C activity (100% I-PSVA, 79% E-PSVA) unlike MVD
- Liver biopsy done to document the PSVA/MVD syndrome, requires samples from 3 liver lobes avoiding the caudate lobe (receives first branch of the portal vein even in many PSVA)
- Excellent definitive imaging can be done using contrast enhanced multisector CT with 3 dimensional reconstruction for definitive identification of PSVA and surgical planning.
- For a yes/no shunting query: microbubble ultrasound study (splenic injection) or colorectal or per-splenic technetium pertechnetate study are less subjective than colorflow ultrasonography.

Diagnosis of portosystemic vascular anomalies (PSVA) can be straight forward in young dogs with classic historic or clinicopathologic features, but may be challenging in minimally symptomatic dogs and in small breed dogs where microvascular dysplasia must be discriminated. Furthermore, dogs with PSVA must be differentiated from dogs with anicteric acquired portosystemic shunting (APSS) typically associated with juvenile fibrosing liver disease (ductal plate malformation), non-cirrhotic portal hypertension, and hepatic arteriovenous malformations. Data cited in these notes reflect observations on > 500 dogs with PSVA (450 with Extrahepatic-PSVA (E-PSVA), 102 with Intrahepatic -PSVA (I-PSVA) and 112 anicteric dogs with APSS (AI-APSS) seen at the Cornell University Hospital for Animals (CUHA).

A spectrum of historical, behavioral, and clinicopathologic features associate with PSVA that reflect shunting severity. Day-to-day variability in clinical signs of dogs with portal atresia (nonsurgical PSVA) has been documented in dogs transiently or permanently sharing the author's home (months to years). In addition, information additional to CUHA case material has been derived from our genetic mapping initiative of the PSVA-E/MVD trait in 9 small breeds of dogs. A scheme categorizing canine PSVA that integrates anomalous vasculature, histological features, presence/absence of ascites, and response to surgical ligation is provide in **Table 1**.

There is no gender predilection and no consistent association of cryporchidism with PSVA. While significant difference in age (yr) at presentation between PSVA-E (1.5 [0.1-12.5) and PSVA-I (0.5 [0.17-12) and AI-APSS (4 [0.17-13] exists, the breadth of overlapping ranges limits its diagnostic utility. Minimally symptomatic PSVA may be serendipitously diagnosed in elderly dogs (PSVA-E ~16% are $\geq$ 6 yrs of age, PSVA-I ~3% are $\geq$ 6 yrs, and AI-APSS ~43% are $\geq$ 6 yrs of age). An older presentation for Miniature Schnauzers ~ 30% being $\geq$ 6 yrs of age is similar to one report where 23% (n=31) were > 7 yrs. Significant difference in body weight (kg) between PSVA-E and PSVA-I correlates with the long recognized propensity for PSVA-E to occur in small breed dogs and PSVA-I in large breed dogs. However, weight of PSVA-I and AI-APSS overlap (PSVA-I (15 [0.91-44.9], AI-APSS (15 [0.79-48]) and because some small breed dogs also develop PSVA-I, and a variety of dog breeds may develop AI-APSS, weight does not have definitive diagnostic utility. PSVA-E is far more common than PSVA-I. Breed prevalence for PSVA-E implicates high risk in Yorkshire Terrier (19-31%) and several other small breeds including: Shih Tzu, Maltese, Pug, Miniature Schnauzer, West Highland

White Terrier, Bichon Frise, Border Terriers, Jack Russell Terriers, Miniature and Toy Poodles, Havanese, Cairn Terriers, and Silky terriers, and mixtures of these breeds. While breed predilection varies with intercontinental location of reports (local breed popularity), inheritance in 9 dog breeds has been implicated by genetic studies. The most prevalent breed with PSVA-I is the Labrador Retriever, followed by mixed breed dogs and Siberian Huskies in our hospital and inheritance is implicated in Irish Wolfhounds. Breed predilection for AI-APSS include the Cocker Spaniel, Shetland Sheepdog, and Doberman Pinscher.

Historical features of PSVA include small body stature (runt of the litter), pediatric hypoglycemia (toy breeds especially), episodic inappetence, vomiting, salivation, ill defined pain or lameness, polyuria/polydipsia, pyrexia, and signs associated with ammonium biurate urolithiasis (hematuria, stranguria, urethral obstruction). Many small breed dogs with PSVA are impossible to house break owing to their PU/PD and apparent learning disabilities and attention deficit. Owners may notice a peculiar brown-golden urine color attributable to ammonium biurate crystalluria and even passage of small dark brown-green calculi on urine pads. Neurobehavioral signs of hepatic encephalopathy (HE) may be inapparent in asymptomatic or minimally symptomatic dogs or because of naiveté of a first time dog owner. In some dogs, HE may manifest only as mild episodic lethargy or inappetence. Overt HE may include ataxia, obsessive circling, head pressing, or inappropriate vocalization, amaurosis, vestibular signs, or apparent neck pain. Vomiting, diarrhea, and inappetence leading to dehydration and pre-renal azotemia as well constipation can augment onset and severity of HE. Dogs with frequent dysregulation and general illness on medical management are what I refer to as "brittle" dogs. The most common clinical scenario leading to obvious HE is consumption of a red meat or fish (less common egg) containing meal or oral bleeding (tooth eruption) or enteric hemorrhage / inflammation (hookworms, inflammatory bowel disease, parvovirus, foreign body). In some cases, sedation or anesthetic use (certain drugs) results in protracted recovery due to reduced hepatic metabolism or first pass hepatic extraction.

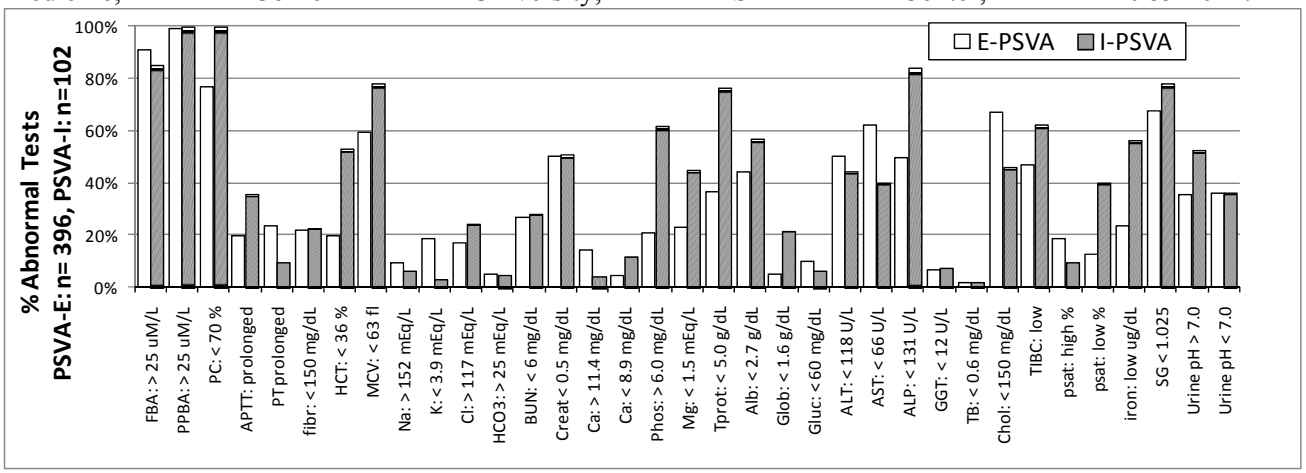
Physical assessment may disclose few abnormalities with the exception of notable small body size compared to breed standards, a large urinary bladder (PU/PD), palpable kidneys, and obvious neurobehavioral signs. In young adult dogs, remarkable tooth calculi may be observed, seemingly associated with hyeprammonemia. The presence of abdominal effusion suggests AI-APSS or the most severe form of PSVA (Table 1, Type 5) associated with intrahepatic and extrahepatic portal atresia or arterial-venous malformations (more common in Havanese).

Clinicopathologic Tests: In our cohort of dogs with PSVA and AI-APSS, *fasting bile acids (FBA)* are normal in 71/610 dogs whereas *postprandial bile acids (PBA)* are normal in only 6/610 dogs. With paired *SBA* tests (samples collected before and 2-hrs after meal ingestion), no PSS remains undetected. As reported previously, FBA > PBA occurs in ~15% of dogs making evaluation of single SBA tests less sensitive for PSS detection. *Low Protein C activity* (<70% is the cutoff) is observed in ~ 80% of dogs with PSS. This test reflects the severity of shunting. We have observed ~ 21% of PSVA-E with values just within the normal range, ostensibly reflecting a small shunt index. We speculate that either small size of the shunting vasculature or positional effects (i.e. viscera compressing shunting vasculature with postural change) influence this finding. The inability to visualize E-PSVA in dogs in different recumbent postures is consistent with this hypothesis. All E-PSVA dogs with a normal Protein C have been able to receive 100% surgical ligation. Furthermore, following the trend in Protein C after surgical shunt attenuation appears to reflect improved hepatoportal perfusion whereas bile acids may

remain persistently increased owing to non-correctable MVD. All I-PSVA dogs tested to date have had low Protein C activity (< 70% activity cutoff); Protein C activity in I-PSVA is significantly lower than in E-PSVA, reflecting the comparably larger shunt fraction in I-PSVA. In AI-APSS ~81% have a low Protein C activity (< 70% activity cutoff).

Considering all routine tests completed in our hospital, dogs with I-PSVA have lower Protein C, Antithrombin, PCV, iron indices, concentrations of total protein, albumin, and globulin, higher cholesterol and glucose, and more prolonged APTT than dogs with E-PSVA. Liver enzymes are not helpful in differentiating type of PSVA with the exception that a significantly younger age at presentation for PSVA-I (due to comparatively greater shunting fraction and symptomatology) results in a significantly higher ALP (bone growth). Each PSVA group has significantly lower MCV, iron indices, liver enzyme activities, and concentrations of BUN, creatinine, and globulin compared to AI- APSS. Although significant differences in electrolytes and bicarbonate are identified between PSVA & AI-APSS, this lacks diagnostic relevance as values remain within reference ranges. There are no differences in urine SG, pH, or appearance of biurate crystalluria between groups. Biurate crystalluria occurs in ~ 33% of E-PSVA, ~23% of I-PSVA, and ~11% of AI-APSS. However, the tertiary referral status of our hospital complicates assessment of this finding on first presentation for PSS because medical management has often been initiated before referral. Dogs with PSVA have a high GFR that normalizes on successful shunt attenuation. Subnormal MCV is identified in 75% of all dogs with PSVA compared to ~37% of dogs with AI-APSS. This large data set corroborates previously reported information in smaller PSVA cohorts indicating that a subset of routine clinicopathologic features can increase suspicion of PSVA, with no test providing a definitive diagnosis. The most reliable test for detection of PSS (Figure 1) are paired FBA & PBA (100% detection), >79% demonstrate low Protein C activity, and >60% show RBC microcytosis, low total protein and cholesterol concentrations, and a urine SG < 1.025.

Table 2: Comparison of common clinicopathologic tests in 550 dogs with PSVA. College of Veterinary Medicine, Cornell University, SA Center, 1985-2011.



Differentiating PSVA from MVD in Small Breed Dogs

Many small breed dogs with PSVA have concurrent MVD. Pedigree analysis and mapping data support that the PSVA/MVD syndrome is a complex polygenic trait. The term MVD represents abnormal hepatic microvasculature that variably/inconsistently affects liver lobes. Histologic features usually cannot be differentiated from those associated with PSVA: arterialization of

portal triads (coiled hepatic arteries cross sectioned, increased arterial twigs), small often binucleated hepatocytes, lobular atrophy, prominent hepatic veins with segmentally thickened smooth muscle (throttling muscule, hepatic veins sectioned longitudenially), prominant lymphatic distention around the hepatic vein and within the portal triad). In some dogs, inappropriate close proximity of the hepatic vein and portal triad suggests direct intrahepatic shunting. *Portal hypoplasia* is an inappropriate term that has been applied to this lesion. It is noteworthy that interruption of portal venous perfusion, at any age, can provoke similar histologic features (hypoplasia denotes lack of development, not an acquired effect). More appropriate terminology is *portal hypoperfusion.* It is important to remember that *Liver biopsy alone usually cannot differentiate PSVA from MVD.* This inherited syndrome has differing extents of vascular maldevelopment, with the most severe phenotype being PSVA. Variability of MVD among liver lobes (some lacking portal perfusion and others receiving portal perfusion) necessitates collection of biopsies from several liver lobes for histologic characterization; we usually collect biopsies from 3 liver lobes. Samples from the caudate lobe are not recommended as this lobe receives the first branch of the extrahepatic portal vein and often is perfused in dogs with PSVA.

MVD is not associated with signs of illness, HE, nor ammonium biurate crystalluria or uroliths, and usually associates with a normal Protein C activity. The SBA are usually not as high as those associated with PSVA, yet there is broad overlapping in SBA values thwarting clear distinction between these two phenotypes. Differentiation of MVD from asymptomatic PSVA thus requires definitive imaging. Yet, this is NOT recommended for most dogs, but is rather addressed on a case by case basis considering historical and clinicopathologic features. We use the Protein C test to determine the propriety of triage for more extensive and expensive PSVA imaging. That means that ~20% of asymptomatic PSVA dogs could be missed if case nuances are dismissed. Some MVD dogs with concurrent inflammatory bowel disease develop a Zone 3 progressive hepatopathy associated with persistently increased liver enzyme activity. Thus, dogs undergoing liver biopsy for suspected hepatic vascular malformations with history of persistent high liver enzyme activity ($\geq$ 3 fold) should have small intestinal biopsies collected in addition to biopsy of 3 different liver lobes. Dogs with MVD do not need dietary protein restriction, antioxidants, or hepatoprotectants unless they are in the unique subset having a progressive hepatopathy associated with IBD. Repetitious SBA testing is not recommended as the physiologic variables associated with the test will result in "bouncing" values confusing to owners and adding nothing to the patients diagnostic portfolio.

Imaging Studies The gold standard of radiographic contrast mesenteric portography has been retired and the inefficiency, subjectivity, and expense of routine or color flow assisted abdominal US replaced by more objective and definitive imaging modalities. If a "Yes" / "No" answer is desired regarding shunting, a transplenic microbubble study can deduce the presence of intrahepatic, extrahepatic and portoazygus shunting but cannot differentiate APSS from PSVA. Colorectal ^{99M}technicium scintigraphy similarly can deduce the presence of shunting without definitive identification of involved vasculature. This imaging modality however may disclose uneven isotope perfusion in liver lobes reflecting the MVD lesion. Trans-splenic portal scintigraphy has been favorably compared to per-rectal portal scintigraphy, requires a smaller isotope dose and may differentiate of APSS from PSVA and portoazygus shunting. However, contrast multisector CT imaging with 3-dimensional image reconstruction provides optimal comprehensive information for diagnosis and surgical planning for PSVA. This imaging

procedure can be rapidly completed (scanning in < 45 seconds) with imaging contrast delivered via manual injection into a peripheral vein. Image acquisition requires short term general anesthesia (use agents that maintain cardiac output and perfusion pressure to ensure contrast transport to splanchnic vasculature and liver), and manual hyperventilation to induce apnea immediately before image acquisition to reduce interference from chest motion. CT imaging also can disclose renoliths and cystoliths that may require removal during shunt attenuation surgery. MRI imaging methods also have been described but may take longer to acquire and require additional expense for ultrasonographic urolith detection.

Table 1: Types (arbitrary designation) of PSVA / MVD syndrome malformations according to vascular manifestations.

	Single PSVA-E	Two PSVA-E	MVD: attenuated intrahepatic portal tributaries (variably reduced flow to full atresia)	MVD: abnormal location & flow through hepatic venule: lobule outflow obstruction	Poorly developed extrahepatic portal vein (porta hepatis): extrahepatic portal hypoplasia	No extra-hepatic portal vein in porta hepatis: portal atresia	APSS	Ductus Venosus, R or L divisional branch	Projected Outcome: with successful surgical ligation "Cured" =**1** Improved, but high SBA=**2** Requires medical Rx, retains high SBA=**3** No Change = **4** Worsened =**5**
Type 1	+	+/-	-	-	-	-	-	-	1
Type 2	+	+/-	+	-	-	-	- (possible with ligation)	-	2 or 3
Type 3	+	+/-	+	+	-	-	+/- (+ with ligation)	-	2, 3, or 4
Type 4	+	+/-	+	-	+	-	+/- (+ with ligation)	-	3,4,5
Type 5	+	+/-	+/-	-	-	+	+	-	4,5
Type 6	-	-	-	-	-	-	-	+	1
Type 7	-	-	+	-	-	-	-	+	2 or 3
Type 8	-	-	+	-	-	-	+	+	4,5