Correlation Between Liver Volume, Portal Vascular Anatomy, and Hepatic Perfusion in Dogs With Congenital Portosystemic Shunt Before and After Placement of Ameroid Constrictors

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Objective: To correlate changes in hepatic volume, hepatic perfusion, and vascular anatomy of dogs with congenital extrahepatic portosystemic shunts, before and after attenuation with an ameroid constrictor.

Study Design: Prospective study.

Animals: Dogs (n = 22) with congenital extrahepatic portosystemic shunts.

Methods: CT angiography and perfusion scans were performed before and after attenuation of a portosystemic shunt with an ameroid constrictor. Changes in hepatic volume, hepatic perfusion, and vascular anatomy were measured. Portal scintigraphy was performed in 8 dogs preoperatively and 22 dogs postoperatively.

Results: Dogs with smaller preoperative liver volumes had greater increases in liver volume postoperatively compared with those with larger preoperative liver volumes. Hepatic arterial fraction was increased in dogs preoperatively and returned to normal range after shunt attenuation, and was correlated with increase in liver size and decreased shunt fraction. Three dogs with no visible portal vasculature preoperatively developed portal branches postoperatively.

Conclusions: Dogs with smaller preoperative liver volumes had the largest postoperative increase in liver volume. Hepatic arterial perfusion and portal scintigraphy correlate with liver volume and are indicators of successful shunt attenuation. Dogs without visible vasculature on CT angiography had visible portal vasculature postoperatively.

Congenital portosystemic shunts (CPS) cause a range of clinical signs and clinical laboratory abnormalities because a large proportion of portal blood bypasses the liver entirely, the liver volume is small, and metabolism is compromised.1-4 Small liver size and poor portal perfusion (high hepatic vascular resistance) led to development of surgical techniques designed to promote slow occlusion of the shunt, thus allowing the liver time to regenerate as the shunt closed and thereby avoid life-threatening portal hypertension.5-8 In a large series of dogs treated by use of ameroid constrictors for attenuation of their extrahepatic shunts, the mortality rate was only 5%, and almost 80% of survivors returned to normal liver function (based on serum biochemical analyses).7,9 Twenty-one percent of dogs had signs of ongoing portosystemic shunting, although the exact reasons were not clarified. Similar results were found in dogs that had slow shunt attenuation using cellophane bands.6,10 In another report, postoperative nuclear scintigraphy and portal venography confirmed that ongoing shunting may result from at least 3 events: development of acquired shunts, failure of the primary shunt to close, and failure of the surgeon to apply the attenuating device close enough to the systemic insertion to close all anomalous branches of the shunt.11

Increase in liver volume occurs soon after surgery in many dogs with the maximum increase in liver volume occurring within 1–2 weeks.10,12 The reason that some dogs undergo complete shunt occlusion and return to normal liver function, whereas others develop acquired shunts is not clear, and has been subject to much speculation. Pre-existing liver injury (as evidenced by hepatic steatosis) is known to affect the response to surgery and success after liver transplantation in people.13,14 Two studies of the histologic abnormalities detected using H&E staining of operative liver biopsy specimens in dogs with CPS failed to show any relationship between the severity of the changes and outcome after shunt attenuation.15,16 However, these studies were limited by the fact that the reasons for ongoing shunting (or liver dysfunction) were not clarified.
CT has been used as a noninvasive method of quantifying changes in liver volume and hepatic perfusion after surgery, and may be useful as a quantitative marker of return to normal liver function.\textsuperscript{10,17} CT has also been used to evaluate success of shunt attenuation by cellophane band.\textsuperscript{18} Although there has been speculation that the capacity of the liver to regenerate after CPS attenuation is determined by its preoperative size and development of its vasculature,\textsuperscript{1,3,4} there are no studies comparing liver volume, perfusion, and anatomy of the portal circulation before and after shunt attenuation, allowing objective evaluation of the impact of preoperative status on the surgical outcome in individual dogs.

Thus our hypotheses were: (1) that decreased hepatic arterial fraction, decreased shunt fraction, and increased liver volume will be associated with successful shunt attenuation; (2) that dogs with relatively small preoperative liver volumes will have greater proportionate increase in liver size than dogs with larger preoperative liver volumes; and (3) that the pre- and postoperative liver volume is relatively smaller in dogs that develop multiple acquired shunts than in those that do not.

MATERIALS AND METHODS

Dogs (n = 22) with single extrahepatic portosystemic shunts attenuated with ameroid constrictors were studied. These dogs are also the subject of another report of the \textit{in vivo} behavior of ameroid constrictors.\textsuperscript{5}

Surgical Attenuation

CPS were attenuated by ameroid constrictors sizes based on clinical judgment of the attending surgeon. Two AC types were used: conventional metal or a plastic AC possessing an external ring of polyacetal homopolymer (Delrin, Research Instruments NW, Lebanon, OR).

\textbf{CT Angiography}

Dual-phase computed tomography (CT) angiography was performed on each dog before and after portosystemic shunt attenuation. Imaging was performed on a Lightspeed 16 helical scanner (General Electric Co., Milwaukee, WI). All scans were performed under positive pressure breath hold at \(~\text{20 mm Hg}\). A dynamic scan was performed using a hand injection (<10 kg) or a power injector (Vistron CT, Medrad, Inc., Warrendale, PA) and an injection rate of 5 mL/s into the cephalic vein with 220 mg I/kg of non-ionic iodinated contrast medium (Isovue 370, Bracco Diagnostics, Inc., Princeton, NJ). Slice thickness for the dynamic scan was 5 mm with a 1 second tube rotation and interval, and a total of 60 images. The dynamic scan was located cranial to the right kidney near the porta hepatitis. Time-attenuation curves were used to plan the dual phase CT scan. The dual phase scan was performed with acquisition parameters of 880 mg I/kg at 3–5 mL/s (<10 kg) or 5 mL/s injection rate, 2.5 mm collimation in a soft tissue algorithm, 120 kVp, and 150 mA, and 0.625 mm reformatting as needed. Images in the arterial phase were obtained from the porta hepatis to the diaphragm, and in the portal phase from the caudal thorax to the pelvis.\textsuperscript{9}

\textbf{Nuclear Scintigraphy}

Per-rectal portal scintigraphy was performed using a gamma camera (Technicare Omega 500, Solon, Ohio, or IS2, Ottawa, Canada) and $^{99m}$Tc]technetium pertechnetate ($^{99m}$TcO$_4^-$; GE Healthcare, Sacramento, CA) deposited rectally in conscious dogs. A 128 x 128 matrix with 2 seconds frame rate was acquired for 120 seconds in lateral recumbency. Shunt status was determined by generating time activity curves of the heart and liver, with positive shunting defined by simultaneous arrival of radionuclide in the heart and the liver. Shunt fractions were calculated for each study (Mirage, Segami Corporation, Columbia, MD) although because of known variability as a quantitative technique, this value was not used to determine shunt status.

\textbf{Liver Volume and Perfusion}

Preoperative anatomy of the shunt was analyzed and liver volume calculated immediately before surgery using a planimetric method (GE Advantage Workstation, 4.4, Milwaukee, WI).\textsuperscript{10} Liver volume was determined again 8 weeks after surgery. Liver volume was corrected for an increase in body size after surgery by generating volume/kg bodyweight. Normal liver volume range used was $24.5 \pm 5.6 \text{cm}^3/\text{kg}$, determined in a previous study.\textsuperscript{10}

Liver perfusion was calculated using a liver tumor protocol (GE Advantage Workstation, 4.4). Regions of interest were placed in the aorta and portal vein, and corrected for respiratory motion. Hepatic arterial fraction (arterial blood flow/total blood flow), blood flow, blood volume, and permeability surface area product were measured using regions of interest on the generated perfusion maps. Arterial and portal vein diameters were measured at the porta hepatis. The presence of intrahepatic portal vein branches was also recorded.

\textbf{Shunt Anatomy}

Anatomy of the origin and termination of the shunt vessels was determined from the portal phase of the dual phase CT scan. A previously published anatomic classification scheme was used in typical shunts, and novel variations were described.\textsuperscript{19} Additional features evaluated were presence of residual flow through the ameroid constrictor after surgery and development of acquired portosystemic shunts.

\textbf{Shunting Status}

Postoperatively, dogs were considered to have continued shunting if 1 or more of criteria were fulfilled: the scintigraphic study was positive; there were multiple acquired shunts; intravascular contrast was visible beyond the ameroid...
constrictor that was because of persistent anomalous vessels or ameroid constrictor patency. All other shunts were considered closed.

Statistical Analysis

Statistical analysis was performed using software (Stata 11, Statacorp LP, College Station, TX). Descriptive statistics as well as ANOVA, Tukey’s test, Wilcoxon rank sum test, paired t-tests, linear regression and multinomial logistic regression were used to evaluate associations between measured variables and outcomes. Differences in liver volume before and after surgery, and between different groups, were calculated after correction for the dog’s weight (mL/kg). Data are reported as mean ± SD; *P < .05 was considered significant.

RESULTS

Dogs (15 female, 7 males) were aged 3 months to 6 years (median, 19 months) at initial imaging. Breeds were Yorkshire Terrier or Cross (9), Miniature Schnauzer (3), Shih Tzu or Shih Tzu Cross (4), Toy Poodle (1), Jack Russell Terrier (1), Maltese (1), Chihuahua (1), Golden Retriever (1), and Terrier Cross (1). Dog weight at initial scan ranged from 1.2 kg to 32.8 kg (median, 4.2 kg). Scan interval ranged from 54 to 105 days (mean, 65 days). Yorkshire Terriers and Miniature Schnauzers presented at a significantly younger age than other breeds (*P = .0015).

Surgical Attenuation

Surgical attenuation of the shunts was undertaken using ameroid constrictors (3.5 mm [n = 10], 5 mm [11], 6.5 mm [1]). Seventeen dogs had a plastic ameroid constrictor, possessing an external ring of polyacetal homopolymer (Delrin®) and 5 dogs, a metal ameroid constrictor.

Shunt Anatomy

A single extrahepatic portosystemic shunt was diagnosed in all dogs (7 splenic to phrenic, 6 splenocaval, 5 splenoazygos, 2 portocaval, 1 right gastric to caval, and 1 splenic and portal to caval). The 3 dogs with shunts that did not fit with the previous classification scheme 19 had origins directly from the portal vein and separate from the gastroduodenal vein and/or portal vein. One dog had 2 separate vessels, 1 arising from the portal vein and joining the caudal vena cava, and a 2nd arising from the splenic vein and joining the 1st shunt vessel.

Surgical Attenuation

All dogs survived surgery without major postoperative complications. None of the dogs has post-ligation neurologic disorder or evidence of life-threatening portal hypertension. All dogs were returned for follow up 7–16 weeks (median, 8 weeks) after surgery.

Presence of Continued Portosystemic Shunting

Continued shunting was detected in 7 dogs (Table 1). Postoperative technetium scans were positive in 3 dogs; in 2 dogs, postoperative CT revealed complete closure of the initial shunt and development of multiple acquired shunts and in 1 dog, there was substantial residual flow through a 6.5 mm AC that failed to change in diameter. This dog was removed from between group statistical analysis because no attenuation was achieved and therefore the liver’s response to surgical attenuation of the shunt could not be evaluated. Postoperative CT also revealed residual flow through the ameroid constrictor in 3 dogs; 2 had negative postoperative scintigraphic studies and 1 dog (described earlier) had multiple acquired shunts. Two other dogs with negative scintigraphic studies had persistent flow through an additional aberrant vessel, a splenic vein branch and left gastric vein branch, respectively, that joined the shunt cranial to the ameroid constrictor (between the ameroid constrictor and the systemic venous insertion of the shunt).

Shunt fractions were calculated in 8 dogs preoperatively, and in 21 dogs postoperatively. Mean ± SD preoperative shunt fraction (0.85 ± 0.12), was significantly higher than mean postoperative shunt fraction (0.21 ± 0.25; *P < .0001). Dogs with multiple acquired shunts had the highest shunt fractions postoperatively (0.91, 0.92), whereas those with shunting through persistent anomalous vessels, or residual shunting through the ameroid constrictor were in the normal range.

Changes in Liver Volume After CPS Attenuation

There was no association between preoperative liver volume and age, body size, breed, or gender.

Nine dogs had preoperative liver volumes below the normal range identified previously (Fig 1). 10 Dogs had a change in liver volume/kg between −0.19% and +130% (median 33%) after surgery (Table 1). There was a significant difference between liver volume/kg body weight preoperatively (mean, 20.32 ± 5.45 mL/kg) and postoperatively (mean, 28.98 ± 5.12 mL/kg; *P < .0001). Change in liver volume was highly associated with the preoperative liver volume (*P < .0001; F Ratio 52.2; Fig 1). Percentage increase in liver size after surgery was significantly higher in dogs that had subnormal size livers preoperatively (102 ± 7% versus 18.6 ± 6%; *P < .0001). Postoperative liver volumes fell within or above the normal range in all dogs.

Changes in Vasculature After CPS Attenuation

Most dogs (n = 19) had visible intrahepatic portal branches preoperatively. After successful shunt attenuation, the 3 dogs without preoperative portal branches had new portal branches visible on CT images. One dog with preoperatively visible portal branches had an additional portal branch visible after surgery. None of the 7 dogs with persistent shunting had new portal branches.

Both portal vein diameter and hepatic artery diameter were significantly associated with body weight (*P < .0001).
Table 1  Summary of Dogs With Extrahepatic Shunts Before and After Placement of an Occlusive Device on the Anomalous Vessel

<table>
<thead>
<tr>
<th>Dog</th>
<th>Age (Months)</th>
<th>Weight (kg)</th>
<th>Breed</th>
<th>Shunt Insertion</th>
<th>Liver Volume (cm³/kg Body Weight)</th>
<th>Shunt Fraction Postoperative</th>
<th>Postoperative Shunting</th>
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<tbody>
<tr>
<td>1</td>
<td>4</td>
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<td>Phrenic</td>
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<td>0.11</td>
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<td>28.5</td>
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<tr>
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<td>5</td>
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</tr>
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<td>24.7</td>
<td>0.15</td>
</tr>
<tr>
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<td>4</td>
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<tr>
<td>18</td>
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<td>Azygos</td>
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</table>

AC, ameroid constrictor; CVC, caudal vena cava.
Mean portal vein diameter before shunt attenuation was 0.28 ± 0.16 cm and after attenuation enlarged to 0.45 ± 0.12 cm; \( P < .05 \). Mean hepatic artery diameter when corrected for weight was not significantly different, preoperatively (0.24 ± 0.017 cm) and postoperatively (0.22 ± 0.017 cm; \( P = .62 \); Fig 2).

Dog 8 had thrombus formation in the left branch of the portal vein on the postoperative scan (Fig 3). Contrast medium was present in the shunt vessel on both sides of the amercoid constrictor, indicating ongoing shunting. The left liver lobe was small compared to the right, and on the arterial phase of the dual phase scan, there was marked increase in size and tortuosity of the hepatic arteries on the left side (ipsilateral to the thrombus). No thrombi were visible in the shunt vessel itself for any dog.

The attenuated shunt vessels of all dogs were filled with contrast to the level of the amercoid constrictor. Contrast in a defined vessel was not seen in the amercoid constrictor lumen in any dog with a plastic amercoid constrictor, and artifact prevented this assessment in those with a metal amercoid constrictors. Eight of 21 dogs included in the group analysis had visible vasculature after amercoid constrictor placement (4 phrenic, 4 azygos shunt terminations). The other 13 dogs had amercoid constrictor placement in close apposition to the caudal vena cava and could not be evaluated. Post-amercoid constrictor vasculature enhanced with contrast because of persistent anomalous vessels in 2 dogs (azygos termination), and because of incomplete amercoid constrictor closure in 1 dog (azygos termination). These were classified as persistent shunting. One dog with phrenic vein termination had additional normal vasculature draining into the phrenic vein and was not considered to have persistent shunting despite contrast post-amercoid constrictor. The other 3 dogs had minimal post amercoid constrictor vascular filling of normal size (2 phrenic vein termination) and no contrast filling post-amercoid constrictor (1 azygos termination). Backflow from the caudal vena cava was not observed in any dog.

**Relationship Between Liver Volume and Persistent Portosystemic Shunting**

Preoperative liver volume or the magnitude of change in liver volume (when corrected for weight) was no different in dogs that developed multiple acquired shunts versus those that did not. Indeed, dogs that developed acquired shunts (20.36 mL/kg, 25.48 mL/kg) tended to have larger preoperative liver volumes than dogs that did not (Fig 1). One dog that developed multiple acquired shunts had a decreased liver volume.
postoperatively (Fig 1). There was also no consistent relationship between the pre- and postoperative liver volume in dogs that had residual postoperative shunting through the ameroid constrictor or an additional anomalous vessel, but had negative postoperative technetium scans. These dogs had liver volumes within the normal range.

Hepatic Perfusion

The hepatic arterial fraction of total liver perfusion was significantly increased preoperatively (mean, 0.53 ± 0.21) compared with postoperatively (mean, 0.18 ± 0.13; \( P < .0001 \)). The hepatic arterial fraction was elevated\(^{17}\) in the preoperative group and normalized in most dogs after surgery. Dogs with attenuated shunts (\( P = .006 \)) and persistent shunting because of incomplete attenuation or an additional anomalous vessel (\( P = .045 \)) had significantly decreased hepatic arterial fraction compared with preoperative levels. The decrease in hepatic arterial fraction was associated with an increase in liver volume/kg body weight (\( P = .02 \); Fig 4). The 3 dogs with an absolute change in hepatic arterial fraction of <5% had postoperative hepatic arterial fractions above the normal range (0.40, 0.30, 0.49). Two of these dogs had small increases in hepatic volume (dogs 6, 11) and 1 had a large increase in volume (dog 4). None of these 3 dogs had persistent shunting.

There was a trend towards increased blood volume and blood flow in hepatic tissue after shunt attenuation; however, these were not significant. Permeability surface area product did not change significantly after surgery. Hepatic arterial fraction and shunt fraction were significantly correlated, and tended to decrease in similar proportions (\( P < .0001 \)). When separated into groups, there was high shunt fraction and hepatic arterial fraction in the pre-attenuation group, and lowered shunt fraction and hepatic arterial fraction in the occluded and incompletely occluded groups (Fig 5). The multiple acquired shunt group did not have enough data points for perfusion analysis.

DISCUSSION

We found that the magnitude of liver growth after CPS attenuation is primarily determined by the size of the liver (relative to body weight) before surgery. Small preoperative liver size had no discernable negative impact on the outcome after surgery; indeed, the 2 dogs that developed acquired shunts had preoperative liver volumes close to the normal range.\(^{10}\) This is surprising, given previous speculation that dogs with smaller preoperative liver volume may have less capacity for return to normal liver function. In addition, both hepatic arterial fraction and shunt fraction returned to normal range in all dogs with successful shunt attenuation and even when small amounts of residual shunting or small anomalous vessels persisted. Portal vein diameter increased significantly after surgery, and dogs without visible portal vasculature pre-surgically had visible portal vasculature after surgery.
These findings are counter-intuitive in light of previous observations that dogs with poor hepatic perfusion were less tolerant of shunt occlusion. This led to speculation that dogs with smaller livers (and hence higher hepatic vascular resistance) might be more disposed to development of multiple acquired shunts. Our results show that factors other than liver volume, portal vein diameter, and hepatic perfusion are important in development of multiple acquired shunts. This suggests that development of acquired shunts is due more to the capacity of the intrahepatic portal vasculature than the size of the liver. Observations in our dogs (which are also the subject of another report detailing the behavior of ameroid constrictors) confirm the findings of previous case series\textsuperscript{11,19} that persistent shunting after surgery for CPS can be because of factors other than development of acquired shunts, including surgical error and failure of the implant to completely occlude the shunt. This is highlighted by our study, in which analysis of preoperative factors on the basis of postoperative technetium scans would have grouped dog 8 (implant failure) together with dogs 14 and 15 (acquired shunts).

Review of the histopathology from dogs with known outcomes after shunt attenuation, with particular emphasis on development of the hepatic microvasculature, and signs of hepatic injury, may help to clarify the reasons for development of acquired shunts in some dogs. Multiple acquired shunts were considered the least desirable outcome and are likely to result in continuing clinical signs. Only a small proportion of dogs in our study developed acquired shunts; however, they were not dogs with small preoperative liver volumes or lack of portal vasculature, which have previously been considered risk factors.

Lack of preoperative visible portal vasculature in 3 dogs did not result in intolerance of shunt attenuation. Intrahepatic portal vasculature may not be seen angiographically under normal flow conditions. Temporary occlusion of the shunt for portography demonstrates that additional vessels may be seen under increased pressure.\textsuperscript{20,21} Because CT is performed at normal portal pressure, the lack of portal branches may not reflect the true status of the vasculature in shunting conditions. This should be contrasted with dogs with portal vein aplasia in which the portal vein does not reach the level of the porta hepatis, and are not surgical candidates.\textsuperscript{22} The number of dogs in this category was small; however, lack of visible vasculature on CT angiography did not seem to affect the post-surgical outcome.

The finding that all dogs with preoperative liver volumes below the normal range had an increase in hepatic volume such that their livers were within or above the normal range at postoperative evaluation suggests that most dogs with CPS have the potential for hepatic regeneration. The liver is subject to complex biological feedback mechanisms, including induction of vascular endothelial growth factor, cytokines and growth factors, with intracellular signaling and hepatocyte response occurring almost immediately after hepatectomy in experimental models.\textsuperscript{14,23} Hepatocyte proliferation must be accompanied by regeneration of the vasculature, as well as free exchange of nutrients, solutes, and lipid between the sinusoidal blood and liver parenchymal cells in order to achieve a
functional result. Experimental studies in dogs undergoing orthotopic liver transplants show body weight to be the main determinant of final liver volume. Livers from small dogs transplanted into larger dogs of approximately double the weight grew to a size appropriate to the recipient within 12 days. The maximum increase in liver size has been shown to occur within the 1st week after surgical attenuation of CPS in dogs.12 Experimental studies in pigs and dogs undergoing hepatectomy of >80% of the liver, or “small-for-size” liver transplants have shown that acute portal hypertension damages the sinusoidal epithelium. Whereas adequate portal blood flow is essential for maintaining the health of the liver and facilitating regeneration, the acute increase in pressure may be excessive, and animals in which the portal circulation is decompressed by means of a portosystemic shunt had better outcomes.3,4 A study of liver histology concluded that lack of portal veins and ductular reaction were associated with a decreased tolerance to complete intraoperative surgical attenuation.16 Although this might have an impact on the immediate postoperative outcome, they were not able to examine the long term prognostic significance of these changes, in particular, their influence on development of acquired shunts. Further research comparing portal veins and ductular reaction to objective outcome measures in a series of dogs with CPS is warranted.

Hepatic arterial fraction increases to compensate for decreased portal supply in experimental models as well as in dogs with portosystemic shunts.17,24 One of the aims of our study was to use CT to quantify the normalization of hepatic perfusion variables as the proportion of portal blood flow increased after surgery compared to shunt fraction and change in liver volume. Hepatic arterial fraction (HAF) normalized in most dogs with shunt attenuation, and the decrease of HAF correlated with increasing liver volume. The increased blood flow to, and blood volume in, the liver was not significantly different before and after surgery; however, portal vein diameter increased significantly. In addition, both HAF and shunt fraction were significantly decreased after attenuation. These measurements both quantify increased portal flow to the liver in different ways; hepatic arterial fraction documents portal blood supply (portal flow = 1 – HAF) and shunt fraction documents the proportion of portal blood bypassing the liver but does not include hepatic arterial flow. The level of correlation validates CT perfusion as a method of quantifying increased portal flow before and after surgery as compared to nuclear scintigraphy. However, the difference between the physiologic function being measured is slightly different. Dogs with incompletely attenuated shunts (continued shunting, persistent anomalous vessels) had hepatic arterial fractions and shunt fractions in the same range as dogs with completely attenuated shunts. This may indicate that the residual shunting was not significant physiologically; however, this needs to be correlated with other measures of clinical outcome.

All dogs had short-term amelioration of clinical signs; however, the relationship between liver volume and liver function has yet to be clarified. The relationship between biochemical markers of hepatic function, liver volume, liver perfusion, and clinical outcome measures such as the need for dietary modification and medical management, and incidence of abnormalities such as hepatic encephalopathy, polyuria and polydipsia, urinary calculi, and clinically significant hypoproteinemia would be worthy of further investigation.

Our observations are of clinical relevance because they show that measurement of liver volume either before or after surgery can document hepatic response to CPS attenuation. A small liver volume preoperatively does not preclude significant growth, and liver volume in the normal range indicates that less growth will occur. CT angiography, hepatic arterial perfusion, increase in portal vein diameter, and shunt fraction document the response of the liver and vasculature to surgical attenuation and can provide indications of device failure or development of acquired shunts.

DISCLOSURE

The authors report no financial or other conflicts related to this report.

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