Association of computed tomographic angiography findings on the outcome in dogs receiving partial ligation of an intrahepatic congenital portosystemic shunt, a retrospective study of 24 cases (2008-2016).

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Objective - To verify whether CTA-findings exceed abdominal US in diagnosing an IH CPSS and to determine whether CTA findings have predictive value on the outcome in dogs that receive ligation surgery for IH CPSS.
Design - Retrospective case study.
Animals - 24 dogs, each with a single IH CPSS, in which CTA-images were made before partial or complete ligation surgery between 2008 and 2016.
Procedures - Medical records were reviewed preoperatively and postoperatively (at 1 month and at 3 months after surgery) for patient description, clinical symptoms, laboratory findings, diagnostic imaging, surgery reports and recovery. Univariate and multivariate analyses were used to discover any significant correlations between information derived from CTA-imaging and surgical outcome.
Results - Based on the amount and the accuracy of the information obtained from CTA compared to abdominal US, CTA-imaging exceeds abdominal US in diagnosing an IH CPSS. A correlation was found between the presence of CTA-images and possible closure. No predictive value on surgical outcome can be assigned to CTA-imaging. Less residual blood flow through the shunting vessel results in a lower classification of HE symptoms. A larger shunt diameter may predict portal branching and location (subtype) appears to be correlated with a superficial course of the shunt.
Conclusions and clinical relevance - Data suggests that CTA-imaging does not help predict surgical outcome of IH CPSS attenuation. Future studying with a larger group of patients in a prospective design is advised.

Introduction

The liver is the biggest internal organ in the body and it is responsible for various metabolic processes. In a healthy individual the liver receives oxygenated blood from the hepatic artery (25-40% of the total blood supply) and deoxygenated blood from the portal vein (60-75% of the total blood supply).(1, 2) The blood in the portal vein originates from the spleen, pancreas, intra-abdominal digestive organs, caudal thoracic esophagus and the majority of the rectum.(2, 3) The major tributaries of the portal vein are the left gastric, gastroduodenal, splenic and cranial and caudal mesenteric veins.(3) In dogs the portal vein divides into left and right branches.(3) The liver parenchyma is divided into hexagonal lobules. Located on the edge of these lobules are the portal triads consisting of branches of the portal vein, hepatic artery and the bile ducts. The blood flows from the portal triads past the hepatocytes through the sinusoids towards the central veins, which form the hepatic veins that enter the caudal caval vein. Numerous metabolic processes take place in the hepatocytes, such as the metabolism of bilirubin, bile acids, the carbohydrate-, fat-, xenobiotics- and protein metabolism and several steps of the immune response.(1, 4) Therefore, it is of great importance that the liver can execute these processes adequately.

The liver function can be compromised by many different diseases, including conditions in which an abnormal portal circulation causes a partial or complete bypass of the liver parenchyma.(2) This is the case in animals with a congenital portosystemic shunt (CPSS), which is one of the most common vascular abnormalities in dogs.(2, 3, 5) There are 2 types of CPSS: extrahepatic (EH) and intrahepatic (IH), both resulting in identical clinical signs.(6) Extrahepatic shunts are most common in small dog breeds, while intrahepatic shunts often occur in larger dog breeds.(2, 3, 6, 7) An EH CPSS originates from an abnormal communication between the cardinal and vitelline venous systems, which causes vascular anomalies in which the extrahepatic portal system is connected with the caudal vena cava, left phrenic or (hemi)azygos vein.(5, 6) An IH CPSS often results from the persistence of a fetal vessel.

During the embryonic development of an individual, the hepatic circulation is bypassed physiologically by a structure that is known as the ductus venosus. It connects the left umbilical vein with the right vitelline vein, or the portal vein with the caudal cava vein.(1, 7, 8) This duct usually closes within 2-9 days postpartum to establish a normal hepatic circulation.(2, 7) When the duct does not close after birth, a patent ductus venosus or a left-divisional IH CPSS remains. Although the etiology is not quite clear yet, there is substantial evidence that the anomalies are hereditary.(8)

A gene called WEE1 is responsible for cell viability under hypoxic conditions. Oxygen tension is known to play an essential role in the postnatal closure of a comparable structure, the ductus arteriosus.(9) The ductus arteriosus constricts immediately after birth, when blood oxygen tension is rising. The physiological resemblance between the ductus venosus and the ductus arteriosus makes it likely that oxygen may have a comparable role in the postnatal closure of these 2 anatomical structures.(6) An increased expression of WEE1 in the liver parenchyma, which is found in dogs with an IH CPSS, might cause a protective response against the altered oxygen tension, while this tension might be essential for normal closure.(6) The IH CPSS are divided into 3 categories, depending on the position of the shunt: left, central or right-divisional shunts (figure 1-3).(3, 5) Shunt position can be defined in a number of ways. In this study, an intrahepatic shunting vessel is called left-sided when the majority of the vessel lies within the left part of the liver, right-sided when the majority lies within the right part of the liver and central when it is mostly in the middle. The majority of shunts is left-divisional and are called a patent ductus venosus. A right-divisional shunt is called a patent right ductus venosus, a persistent right omphalomesenteric vein or a hepatic sinusoid malformation.(2) Thus the central and right-divisional shunts probably have a different, still unidentified etiology.

Figure 1: Left-sided IH CPSS

Figure 2: central IH CPSS

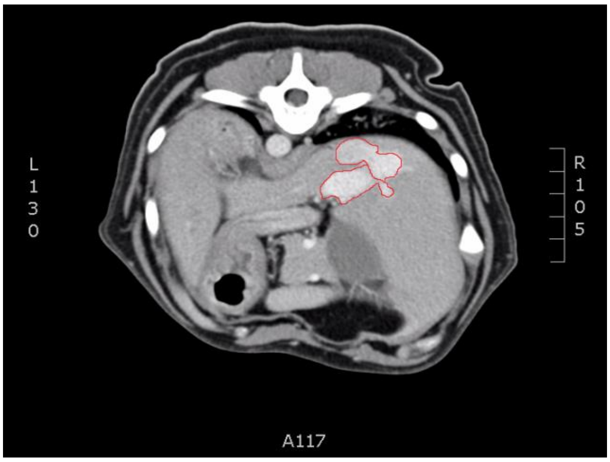

Figure 3: Right-sided IH CPSS

What are the symptoms of an IH CPSS?

Congenital portosystemic shunts cause atrophy of the liver and hepatic dysfunction, which can lead to several clinical symptoms. These symptoms are generally related to the central nervous, gastrointestinal or urinary systems and are not very specific.(3, 6) Ammonia, aromatic amino acids, absorbed bacteria and endotoxins are not metabolized by the liver and increased concentrations enter the systemic and also the cerebral circulation, being potentially toxic. This can give rise to a spectrum of neuropsychiatric abnormalities, defined as hepatic encephalopathy (HE).(10) A gene called CCBL1 has a significantly lower expression in CPSS dogs compared with control dogs. It encodes for an enzyme that metabolizes cysteine conjugates of halogenated alkenes and alkanes, leading to the formation of reactive metabolites that can lead to nephro- and neurotoxicity. This enzyme is probably secondarily involved in CPSS in dogs and may play a role in the pathophysiology of HE.(6) Most of the clinical signs are related to HE and include: ataxia, behavioral changes, unresponsiveness, pacing, wandering, circling, head pressing, blindness, seizures and coma.(3) Urinary tract signs can be pollakiuria, stranguria, haematuria, dysuria, urethral obstruction and urolithiasis, and are primarily related to the formation of ammonium biurate crystals. These crystals also develop due to the elevated blood ammonia levels.(3) Gastrointestinal signs can include vomiting, diarrhea, anorexia and ptyalism and may be a result of maldigestion and malabsorption or hepatic dysfunction. Decreased hepatic function leads to a decrease in bile production, which contributes to the maldigestion.(3) Dogs with an IH CPSS may be retarded in growth, polydipsic and polyuric, and also cryptorchidism has been reported.(3)

How to diagnose an IH CPSS?

Signalment, history, clinical signs and laboratory findings can already provide a presumptive diagnosis of IH CPSS.(11) Changes present on routine blood analysis are often mild and non-specific. Haematological changes may include a mild non-regenerative, microcytic, normochromic anaemia and erythrocyte conformational changes. A leukocytosis is variably present and altered serum biochemistries may be found as well. These can include decreased concentrations of albumin, total protein, urea nitrogen, cholesterol and glucose, which arise due to decreased hepatic synthesis. Mildly increased activity of alanine transaminase, aspartate transaminase and alkaline phosphatase may also be detected.(3) These mild and non-specific changes are why alternative tests on liver function are necessary for a diagnosis. Diagnostic tests include fasted serum or plasma bile-acid and ammonia concentrations and an ammonia tolerance test or a bile acid stimulation test.

The role of diagnostic imaging in dogs with signs compatible with portosystemic shunting is to provide a definitive diagnosis. It is helpful to determine if a shunt is present, what its morphology is and to assess the effects of surgical treatment. This is possible with portography, abdominal ultrasonography, scintigraphy, magnetic resonance angiography (MRA) and computed tomographic angiography (CTA).(3, 12) Some of these techniques can present useful information about the internal organs as well. Such as size of liver and kidneys or presence of urolithiasis, which are indicative of CPSS. So which of these techniques proves to be the most helpful?

Intraoperative mesenteric portography was performed frequently to diagnose CPSS historically.(13) It is a very sensitive method that is quite easy to interpret and which findings may be predictive of outcome after attenuation.(11) Vessel opacification increases significantly after partial or complete CPSS attenuation, which assesses changes in blood flow.(14) The sensitivity range is 85-100%, depending on animal positioning.(15) The vessel opacification correlates with the degree of pre-operative encephalopathy and post-operative clinical improvement.(13) However, influence of dog positioning, exposure to radiation of dog and staff and the invasiveness of this technique (laparotomy is required) form insuperable impediments.(13, 15) Transvenous retrograde portography is less invasive since laparotomy is not necessary, but anesthesia is still required.(16) Both techniques provide the possibility to measure portal pressures before and after occlusion and facilitate intraoperative identification of the shunt.(13, 16) These aspects are only constructive when surgery follows immediately. More advanced and less-invasive techniques have led to a decreased use of portography.(11)

Abdominal ultrasonography has become quite popular, because it is quick, non-invasive and does not require anesthesia or ionizing radiation.(11) It has a sensitivity range from 80-95% and a specificity range from 67-100%.(13, 17) Using a Doppler, these numbers even increase to 95% and 98% respectively and abnormal blood flow can be assessed.(13) Evaluation of the entire abdomen is possible. Nonetheless, operator experience is very influential.

Scintigraphy can be performed trans-splenic (TSPS) or per rectum (PRPS) and can provide information about the amount of blood that flows through the shunting vessel. Scintigraphy is fast and minimally invasive, but the anatomical detail is poor and the use of radioactive substances and anesthesia is required.(11, 18) PRPS has a sensitivity of 88% and a specificity of 67%, while TSPS scores 100% on both parameters.(13, 19) In TSPS less radioactivity is needed, the scanning procedure is shorter and the obtained images possibly render more information about shunt conformation.(18) Although, complications such as splenic hemorrhage are more likely to occur in TSPS.(13, 19)

MRA is a non-invasive technique that can accommodate three-dimensional imaging of the shunt and other internal organs in good detail, but it is time consuming, expensive and general anesthesia is needed.(11, 12) The sensitivity and specificity rates are 79% and 100% respectively.(13, 20)

CTA is the preferred diagnostic modality for evaluation of the portal vasculature in human medicine and has recently been reported to have superior accuracy compared with abdominal ultrasound in dogs with CPSS.(21, 22) It has a sensitivity of 96% and a specificity of 89%.(13) It is performed rapidly, allows excellent three-dimensional evaluation of the major portal vessels and other internal organs, is noninvasive and provides great anatomical localization. This facilitates surgical planning.(21, 23) The downside is that animals have to be anesthetized for the CTA-scan and images have to be made with careful timing because the contrast fluids have to be in the right area. Based on the advantages, disadvantages and sensitivity/specificity numbers CTA is now the gold standard for differentiation of CPSS and provides detailed anatomical information.

What complications are to be expected during and after attenuation?

A few main complications are to be expected when closing an IH CPSS, whether it is done completely, partially or gradually. The first and most obvious of them all is portal hypertension. The diversion of a large volume of blood through the hypoplastic hepatic portal circulation precipitates an increase in portal pressure. The occurrence is more likely when the shunt is closed too much, too fast and the portal vasculature is poorly developed. This can give rise to an increased pressure in the vasculature of every portal organ (spleen, pancreas, intestines) and in time lead to distributive shock symptoms. These include cyanosis of the portal organs, an increase in the heart rate, an increase in the respiratory rate, a decrease in the arterial blood pressure, a decrease in the blood carbon dioxide concentration, a weak pulse, pale mucous membranes, cold extremities and death (in acute/severe portal hypertension) or ascites (in more chronic/mild portal hypertension). The dog should be monitored carefully during and after surgery to detect any form of hypertension early on. The second complication which should be taken in account is the occurrence of bleedings. The risk of internal bleedings during or after surgery is realistic. Many dogs died after successful surgery because of it.(24) Dissecting the shunting vessel can cause trauma to the liver parenchyma, surrounding blood vessels or the IH CPSS itself. This can be life-threatening on its own, but an additional coagulopathy could complicate this even further. The liver normally produces clotting factors, but in dogs with an IH CPSS the liver does not function adequately and the plasma concentration of a number of clotting factors can be dangerously low.(25) Clotting times (APTT, PT) should be measured before surgery and plasma transfusion should be administered if clotting factors appear to be low to minimize the risk of internal bleeding.

The third, well recognized but uncommon complication is the occurrence of the post-ligation seizure syndrome (PLS). It is more common in dogs with EH CPSS than it is in IH CPSS and it is generally not associated with biochemical evidence of metabolic encephalopathies.(26) Dogs who suffer from this syndrome show ataxia, generalized motor seizures, behavioral changes, vocalization, status epilepticus, nystagmus, disorientation or muscle tremors unrelated to hyperammonaemia, hypoxia or hypoglycemia.(26, 27) Suggesting that a different mechanism accounts for neurological dysfunction in some cases postoperatively. The neurological symptoms can be controlled by the intravenous administration of phenobarbitone or propofol.(27) However, initial management is difficult and PLS has a high mortality rate. Survivors can show persistent neurological dysfunction.(26) The etiology of this complication is still quite unclear, but brain pathologies have been described in dogs that have died or have been euthanized during postoperative seizures.(26) These pathologies are consistent with ischemia/hypoxia, hypoglycemia or prolonged seizure activity and include neuronal necrosis with variable glial responses in the cerebral cortex.(26)

What are the therapeutical options?

Attenuating an IH CPSS can be an unnerving process, considering all the possible complications that might occur. Yet, it beats the alternative of not treating the dog at all. The HE and hepatic dysfunction worsen and the dog can enter a coma and die. A conservative, medical therapy is available, but is only palliative.(5) It is indicated when a dog presents with hepatic encephalopathy, when stabilization or short-term management is required prior to more definitive surgical treatment, or when surgery is not possible due to the location or type of the vascular anomaly.(3) The treatment aims to reduce the systemic absorption of products that can contribute to the HE. Short-term management includes the withholding of protein-rich food, lactulose, antibiotics administration and fluid therapy.(3) Lactulose prevents ammonia absorption from the gastro-intestinal tract. It is a synthetic, non-absorbable disaccharide that is hydrolyzed by colonic bacteria to lactic acid and acetic acid. This lowers the colonic pH and serves to ionize neutral ammonia, blocking the absorption. Oral antibiotics in combination with metronidazole can be administrated to change the bacterial flora in the gastro-intestinal tract and subsequently decrease the amount of produced ammonia.(3, 28) Long-term management consists of a high quality diet that is easily digestible and moderately restricted in protein.(2) Protein reduction serves to limit the offending substrate (certain amino acids and ammonia). However, it is difficult to find balance between the nutritional needs of the already hypoproteinemic animal and the amount of necessary protein restriction.(28) Often dogs are placed on a very low protein diet initially, which is then gradually increased to higher levels.(28) A higher carbohydrate and moderate fat concentration of the diet should provide for an adequate caloric intake to prevent the body from breaking down its own proteins to generate energy.(28) Lactulose and antibiotics can also be used in a long-term conservative therapy, but antibiotics are not favorable due to the side effects and possible antibiotic resistance. These conservative treatments can reduce the intensity of the symptoms, but do not improve hepatic function. Permanent recovery from portosystemic shunting and liver function improvement can only be achieved by surgical attenuation of the shunt. After shunt attenuation, hepatotropic factors cause the liver to expand, allowing the portal pressure to decline and improve the portal blood flow to the liver. Blood flow through a partially occluded shunt may further decrease over time and cause the shunt to close functionally. But surgical shunt attenuation is not without risks. Dogs with a compromised liver function have a higher anesthesia risk and the amount of narrowing that is needed for complete recovery from shunting is difficult to determine.

Immediate complete ligation of the shunt is often not possible due to an acute increase in portal pressure that is too much for the hepatic portal circulation to cope with. To assure an acceptable increase in portal pressure the shunt is usually closed partially or gradually if complete closure is not possible.(10) A partial closure of the shunt can be obtained by partial ligation. Partial ligation of intrahepatic shunts often results in residual portosystemic flow, does not always lead to complete remission of clinical signs and requires careful intra-operative assessment of hemodynamic parameters to determine the point of optimal or maximal closure.(5) A second surgery may be necessary. However, the ligation technique is less expensive and does not require as much dissection as the other open surgical methods known to partially close the shunt.

Gradual closure of the shunt can be obtained by "ameroid ring constrictor placement" or "cellophane banding". An ameroid ring constrictor is a slotted stainless-steel or plastic ring surrounding an inner compressed casein band with a casein key mechanism, which allows the constrictor to be placed around a vessel. Ameroid is a hygroscopic casein derivative that undergoes rapid volumetric expansion that plateaus in 60 days.(29) The inner diameter of the ring narrows due to fluid absorption, which establishes a gradual and complete occlusion of the shunt vessel in 14-35 days.(30) Cellophane banding is a technique in which a cellophane band is fitted around the shunt vessel, without occlusion or partially occluding the blood flow. In the following weeks or months the band gradually attenuates the shunt by inciting an inflammatory reaction and thus fibrosis of the vessel.(31-33) Both procedures are technically more difficult in IH CPSS than in EH CPSS.(5, 34) They require a more extensive and risky dissection around the anomalous vessel compared to partial ligation. In addition, these techniques have been shown to perform unpredictably. Either resulting in premature vascular occlusion or ultimately not achieving complete occlusion.(34)

Hydraulic occluders could provide controlled vascular occlusion via subcutaneous injection and withdrawal of saline. If portal hypertension develops, the occlusion could theoretically simply be reduced. While this attenuation technique sounds useful in theory, it is rather disappointing in practice. The disadvantages are that the device is quite expensive and substantial shunt dissection is required for the large device size. This increases surgery time and the risks of hemorrhages.(34) Another inconvenience of a hydraulic occlude, and also of the ameroid constrictor, is that these devices are relatively heavy, which may cause complete attenuation when the animal stands upright, especially in extrahepatic shunts.

Sadly, not every IH CPSS can be accessed surgically as a result of the shunts position in the liver, the short length or wide diameter and/or the occurrence of life-threatening hemorrhages during shunt dissection. Therefore, a promising endovascular technique using coils is developed for these types of IH CPSS which is called percutaneous transvenous coil embolization (PTCE).(5, 34) This is a gradual closing method in which endovascular coils form a thrombus that progressively attenuates the vessel.(2) A skin incision of 3-5 mm is made to facilitate percutaneous placement of a vascular introducer sheath. Access is performed via the right jugular vein alone, the right jugular vein and percutaneous portal vein access, the left jugular vein or the right jugular vein and right femoral vein. With the help of contrast angiography a catheter with a guidewire is placed into the shunt and the portal vein. A second catheter with guidewire is advanced into the sheath into the caudal vena cava. The second catheter is then removed so a stent delivery system can be advanced over the guidewire and can be deployed in the right location. An auto-expendable mesh stent is placed in the caudal vena cava at the height of the shunt to prevent the coils from migrating (figure 4).(5) The first catheter inflates a balloon in the shunt, to evaluate the maximal attenuation. Another catheter is placed and deploys thrombogenic stainless steel coils into the shunt while measuring portal pressure. Between 1 and 30 coils are placed for a single embolization, but the most common number of placed coils is 4-6.(34) Compared with surgical treatments of IH CPSS, placement of endovascular coils is less invasive and associated with a quicker recovery and shorter hospitalization time.(35) Unfortunately, sometimes a single treatment does not provide enough attenuation of the vessel. Seventeen percent of the dogs require more than 1 treatment.(34) Secondly, this minimally invasive technique is expensive. The costs make it difficult to motivate an owner to embrace endovascular catheter-based shunt occlusion instead of a surgical treatment, although in some dogs this technique would likely be more safe and successful.

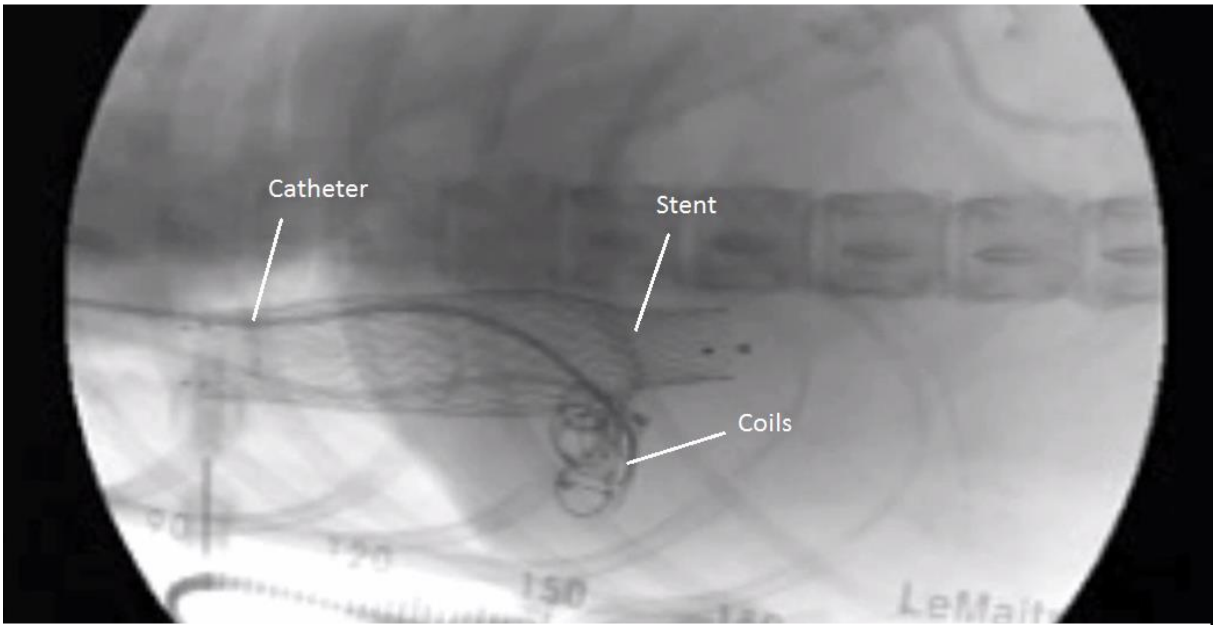

Figure 4: Percutaneous transvenous coil embolization

Aims of this study
The aim of this study is to consider if CTA actually exceeds abdominal ultrasound as a diagnostic imaging method for IH CPSS and to find out whether CTA findings have a predictive value on the possible attenuation of the shunt and clinical, metabolic and anatomical outcome after surgical treatment. If it does, this may provide insight in to which treatment is preferred for each dog and it can facilitate in motivating an owner to decide on endovascular attenuation rather than surgical attenuation in specific cases.

Methods and materials
The medical records registered in VetWare of 54 dogs with a clinical history or laboratory findings suggestive of an IH CPSS examined at the University of Utrecht between 2002 and 2016 were reviewed retrospectively. Dog signalment, clinical symptoms, laboratory findings, abdominal ultrasounds, CTA and surgery reports of each dog were evaluated before, 1 month after and 3 months after surgical treatment. The dog description was composed out of date of birth, breed and gender and is descriptive of the population that has been used for this study.

To compare the usefulness of 2 different types of diagnostic imaging (abdominal ultrasounds and CTA-imaging) all information that can be helpful for a surgeon to decide whether or not to operate was collected from abdominal ultrasound reports and CTA-images/-reports. The data that was collected from abdominal ultrasounds reports included information on whether or not an abdominal ultrasound was performed (no ultrasound=0, ultrasound=1), the location of the shunting vessel (left-sided=0, central=1 or right-sided=2), liver size (extra small=0, small=1, normal=2) and the presence of portal branching (absent=0 or present=1). The data that was collected from the dogs' CTA-images included whether or not CTA was performed (absent=0 or present=1), liver size (extra small=0, small=1, normal=2 or when one half was smaller than the other=3), shunt location (left-sided=0, central=1 or right-sided=2), the average diameter of the shunting vessel (8-10 mm=0, 10-12 mm=1, 12-14 mm=2, 14-16 mm=3, 16-18 mm=4 or >18 mm=5), the estimated length of the shunting vessel (70-120 mm=0, 120-170 mm=1, 170-220 mm=2 or 220-270 mm=3), if portal branching was visible (not-visible=0 or visible=1), if hepatic branches were visible (not-visible=0 or visible=1), if the shunting vessel reached liver surface (no-surface=0 or surface=1) and if the surfacing occurred proximal or distal to portal branching (proximal=0, distal=1). CTA images before 2015 were made using the Philips Secura and CTA images from and after 2015 were made using a Siemens 64 slice CT scanner. The average diameter of the shunting vessel was obtained by measuring the width of the shunting vessel every 5 CTA layers and subsequently calculating the average, starting at the insertion of the gastroduodenal vein in the portal vein and finishing at the insertion of the portal vein in the vena cava. The estimated length of the shunting vessel was obtained by measuring the dexter-sinister two-dimensional distance of the shunting vessel (measured from the vessel center) and adding this value to the caudal-cranial two-dimensional distance (number of CTA-frames multiplied by the frame intervals) as shown in figure 5. Both these measurements were performed using AGFA Impax radiology software.

Figure 5: Example of IH CPSS length measuring

Surgery reports were made by the surgeon immediately after surgical treatment. Degree of closure was obtained from these surgery reports. In every IH CPSS in this study maximal ligation was attempted using 2-0 ligature of a non-absorbable material (multifilament Nylon or monofilament Prolene). Surgical closure was dichotomized as not attenuated=0 or attenuated=1. The data collected from the surgery reports also included the dogs' age at the time of surgery, shunt location, diameter of the shunting vessel and the occurrence of intraoperative complications.

To be able to evaluate the effects of surgical intervention within these dogs, the results were described as a clinical outcome, a metabolic outcome and an anatomical outcome. The clinical outcome was scored using the dogs' symptoms of hepatic encephalopathy after surgery, classified with a clinical grading system for HE designed by J. Rothuizen (table 1).(36) Clinical outcome was defined as normal=1 in dogs with grade 0, and abnormal=0 in dogs with grade 1-4.

0 - No clinical symptoms **1** - Sopor, behavioral changes, polyuria **2** - Ataxia, disorientation, compulsory movements, apparent blindness, hypersalivation **3** - Stupor, severe hypersalivation, incidental seizures **4** - Coma

Table 1: Clinical grading system for HE designed by J. Rothuizen et al.

The metabolic outcome was composed out of ammonia concentration in µmol/L (where concentrations below 45 µmol/L were considered normal=1 and concentrations above 45 µmol/L were considered abnormal=0) and when fasted ammonia concentrations were mildly increased, results from ammonia tolerance testing in µmol/L (negative testing=1 and positive testing=0).(37) Other laboratory findings were described as well, which included fasted plasma bile acids in µmol/L (concentrations of <10 µmol/L were considered normal=1 and concentrations above 10 µmol/L were considered abnormal=0), total protein level in g/L (concentrations between 55-72 g/L were considered normal=1 and concentrations below 55 and above 72 g/L were considered abnormal=0) and albumin concentration in g/L (concentrations between 26-37 g/L were considered normal=1 and concentrations below 26 or above 37 were considered abnormal=0). Metabolic outcome was defined as normal=1 (both ammonia concentration and tolerance testing) or abnormal=0 (abnormal ammonia concentration and/or abnormal tolerance testing).

The anatomical outcome was composed out of residual blood flow through a shunting vessel, determined by abdominal ultrasound. The abdominal ultrasound reports were reviewed and any indication of remaining blood flow, whether this originated from the original congenital shunting vessel or a new acquired shunting vessel, was recorded. The anatomical outcome was defined as either normal (shunting absent=1) or abnormal (shunting present=0).

Postoperative complications within 3 months after surgery were recorded and labelled as shunt-related or not shunt related.

A commercial software program (SPSS 24.0) was used for the statistical analysis of the collected data. Univariate correlations between surgical closure, clinical, metabolic and anatomical outcome and CTA findings which included: shunt location, liver size, diameter of the shunting vessel, length of the shunting vessel, visibility of portal branches, visibility of hepatic vein branches, the shunting vessel reaching liver surface and where it reaches liver surface (proximal or distal to any portal branching) were checked with Pearson Chi Square tests or Fisher's Exact tests and Pearson correlation coefficients. Finally, a multivariate analysis of the CTA variables was performed using logistic regression to predict closure and outcome.

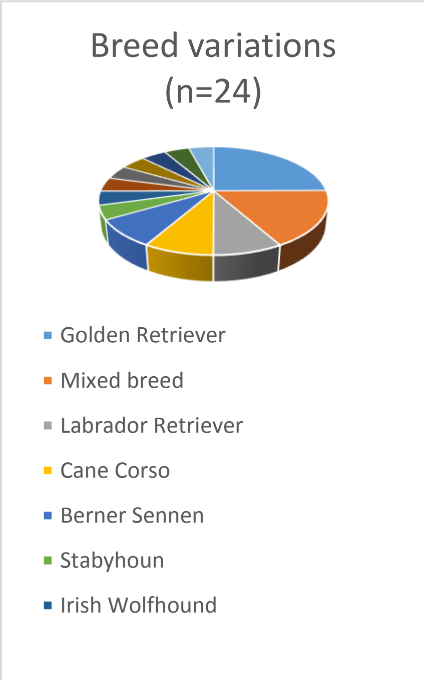

Figure 6: Breed variations

Results

Out of 54 known cases that had surgery of an IH CPSS between 2002 and 2016, only 24 dogs were included in the study, due to the fact that no CTA images were made of any dogs before December 2007. These 24 dogs all had pre-operative CTA and all of them underwent surgical attenuation of the shunting vessel. Ten dogs were females and 14 were males. Seventy-nine percent of the group consisted out of large breed dogs (meaning breeds with an average weight of >20 kg n=19). The most common breed was the Golden Retriever (25%, figure 6). Fourteen dogs attended the control visit 1 month after surgery and only 7 dogs attended the control visit 3 months after surgery. Ten dogs did not attend any of the control visits.

Before surgical intervention

The average age at surgical intervention was 11 months. Ninety-six percent of the dogs showed clinical symptoms of hepatic encephalopathy although some demonstrated more severe symptoms than others. Most dogs were categorized as grade 1 (46%) or 2 (37,5%) using the grading system developed by J. Rothuizen (figure 7).(36) These dogs had already received a conservative treatment at the time these symptoms were reviewed.

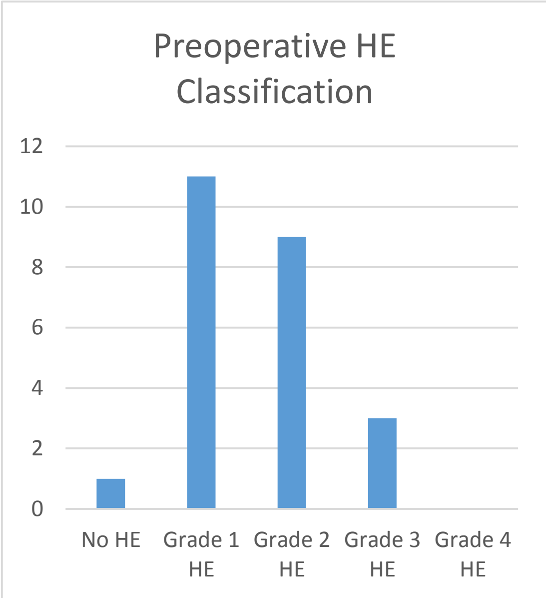

Figure 7: Preoperative HE classification

None of the dogs had normal bile acids or ammonia levels, all of them were elevated. Ammonia tolerance testing was performed preoperatively in only 2 dogs and both of them were abnormal. Plasma albumin levels were low (<26 g/L) in 92% of cases. Quite similar to total protein levels. These were low (<55 g/L) in 88% of the dogs before treatment. In 18 dogs (75%) of the dogs a preoperative abdominal ultrasound was made.

Reviewing abdominal ultrasound reports from 18 dogs and CTA images from 24 dogs, the following information could be retrieved:

Shunt location could only be determined in 13 dogs by abdominal ultrasound. The reports revealed that 62% of the shunts were left-sided, 38% were right-sided and none of the shunts were central. Liver size was documented in all 18 dogs. Eighty-three percent of the livers were perceived as being too small, 17% were of normal size and none of the livers were enlarged. The presence of portal branches was mentioned in only 2 dogs, existent in both dogs (figure 8).

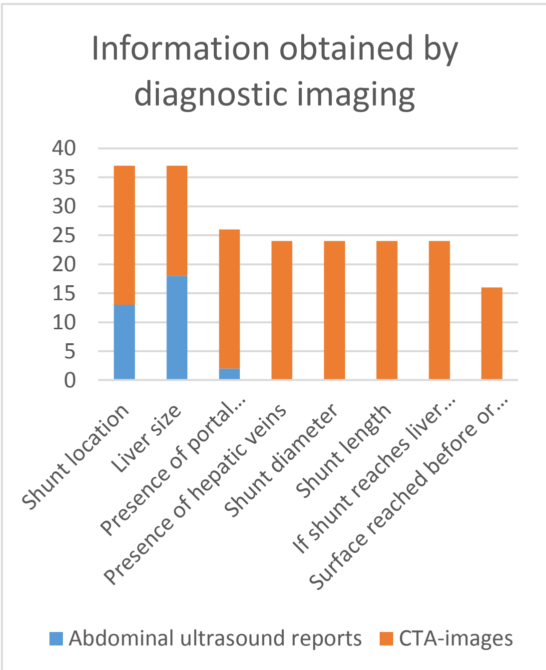

Figure 8: Information obtained by diagnostic imaging

CTA-images also provided information on shunt location. The location could be determined in all 24 dogs, 75% was left-sided, 16% was right-sided and 8% was central. Liver size was documented in 19 of 24 dogs, being too small in 79% of the dogs and normal in the rest of them. The presence of portal branching could be assessed in all of the dogs. Twenty-nine percent had no visible portal branching, while the other 71% did have clear portal branching. Every one of the 24 dogs showed evident hepatic veins. Shunt diameter and length could also be measured in every dog. The diameter was 8-10 mm in 17%, 10-12 mm in 25%, 12-14 mm in 33%, 14-16 mm in 21% and 16-18 mm in 4% of the dogs. The average shunt diameter was 12 mm. Assessing shunt length, 29% of the shunts were 70-120 mm, 38% were 120-170 mm, 16.5% were 170-220 mm and 16.5% were 220-270 mm. The average shunt length was 158 mm. Eighty-eight percent of the shunts (21 dogs) reached liver surface. In 57% of them the shunting vessel surfaced distally from any portal branches (12 dogs), 14% (3 dogs) surfaced proximally from any portal branches, 5% (1 dog) surfaced both before and after portal branching and 24% (5 dogs) reach liver surface but had no visible portal branching (figure 8).

Intraoperative information

Shunt location was mentioned in the surgery reports in 23 of the 24 dogs. Seventy-four percent of the shunts were perceived as being left-sided, 17% was right-sided and 9% was central. Shunt diameter was estimated in 18 dogs before attenuation and also known by intraoperative measuring in 18 dogs after attenuation, however 1 dog was only estimated before attenuation and in another dog shunt diameter was only measured intraoperative after attenuation. The average shunt diameter before attenuation was 11 mm. The IH CPSS was surgically attenuated in 17 dogs. Complete ligation was possible in only 1 dog. After attenuation, the average diameter of these 18 dogs was 4 mm. The attenuation percentage was calculated for 17 dogs, because the diameter of 1 dog was not estimated preoperatively. The average attenuation was 65%.

Three dogs had an attenuation of 0%, due to intraoperative complications that inhibited further surgery. Intraoperative complications occurred in 8 of the 24 dogs. These include bleedings (n=6), a decrease in arterial pressure (n=1) or inaccessibility of the shunting vessel (n=2). One dog suffered from both a decrease in arterial pressure and inaccessibility of the shunting vessel.

Outcome 1 month after surgical intervention

Three dogs died within 30 days after surgical treatment because of reasons that were assumed to be shunt-related. All 3 dogs were euthanized. Two dogs could not be surgically ligated because the shunting vessel was unapproachable. They did not respond well to conservative treatment so the decision was made to euthanize them. The third dog presumably suffered from cerebral necrosis. Other postoperative complications include aspiration pneumonia (n=1) and exudation of excessive wound fluid (n=1). HE gradation was mentioned in 11 dogs 1 month after surgery. Two dogs categorized as grade 2, two dogs as grade 1, and most of them categorized as grade 0 (7 dogs). Most of the dogs HE symptoms decreased, but in 5 dogs HE classification remained the same. Bile acids were measured in 10 dogs 1 month after surgery and all of them were elevated. Ammonia levels were measured in 11 dogs and were within normal limits (20-45 µmol/L) in 3 of them. The 7 other dogs' ammonia levels were elevated. Ammonia tolerance testing was then performed in 5 of these 11 dogs, four of them were abnormal. Total protein levels were measured in only 5 dogs and were within normal limits (55-72 g/L) in 3 dogs, the other 2 dogs had total protein levels close to normal (41 and 52 g/L) but were still aberrant. Plasma albumin levels were measured in 10 dogs and were within normal limits (26-37 g/L) in only 2 dogs. The other dogs' plasma albumin levels were low.

No CTA-images were made 1 month after surgery.

Abdominal ultrasound reports from the dogs 1 month after surgery were available in 12 of the 21 dogs. Liver size was small in 7 and normal in 4 dogs. While liver size was documented differently in 1 of the dogs compared to the preoperative ultrasound report, the other 3 dogs' liver size remarks remained the same. One dog was said to have a small liver preoperatively, but was classified as being normal in the postoperative abdominal ultrasound report. Portal branching was mentioned in 3 reports and 6 of 12 dogs had residual shunting flow.

Outcome 3 months after surgical intervention
Unfortunately, 1 dog suffered from cardiac failure (not related to the IH CPSS) and the decision was made to euthanize her. Other complications included melena (n=1) and anemia (n=1). Ten dogs returned to the clinic for a checkup 3 months after surgical intervention. Seven of them attended the 1 month check-up and for the other 3 dogs this visit was the only check-up moment.

Eight dogs' HE gradation were documented. One dog demonstrated grade 2 HE, 1 dog grade 1 HE but the other 6 dogs no longer showed any symptoms of hepatic encephalopathy. Bile acids were measured in 9 dogs. They were normal (<10 µmol/L) in 1 dog, elevated (>10 µmol/L) in the rest of them. Ammonia levels were low (<24 µmol/L) in 3 dogs and high (>45 µmol/L) in the other 6. Ammonia tolerance testing was performed in 2 dogs, one being normal and the other being abnormal. Total protein levels were measured in 6 dogs, being normal (55-72 g/L) in 3 and low (<55 g/L) in 3. Plasma albumin levels were also measured in 6 dogs, also normal (26-37 g/L) in 3 and low (<26 g/L) in 3.

Three dogs of the remaining 20 dogs underwent postoperative CTA-imaging. All 3 dogs had partial ligation of the shunting vessel. Liver size was small in 1 dog and was not mentioned in the other 2. In 1 dog shunt location was the same as in the preoperative scans, but in the other 2 the shunting vessel appeared to be located differently than in the preoperative scan. One of these shunts was left-sided preoperatively and central postoperative, the other was central preoperatively and left-sided postoperative. Narrowest shunt diameter was measured for all 3, being 7.9 mm, 7.4 mm and 8.1 mm. The differences in measurements made before, during and after surgery are shown in table 2.

Shunt diameter	Dog 900878	Dog 903618	Dog 1003615
Preoperative CTA (average)	15.9 mm	13.1 mm	12.5 mm
Intraoperative before attenuation	15 mm	12 mm	6 mm
Intraoperative after attenuation	5 mm	2 mm	2.25 mm
Postoperative CTA (at narrowest point)	7.9 mm	7.4 mm	8.1 mm

Table 2: IH CPSS diameter measurements

Shunt length could not be measured in any of the postoperative CTA images. All 3 dogs still had visible portal branching and visible hepatic veins.

Abdominal ultrasound reports were present for 3 dogs. Two of these dogs also had postoperative CTA images. All 3 dogs had a normal sized liver and the shunting vessels remained to show slight residual flow.

Statistical analysis
There appears to be a significant correlation between the presence of CTA-images and possible closure (attenuation) (Fisher's exact test, P=0.046). None of the other CTA variables proved to be significantly associated with clinical, metabolic or anatomical outcome or with shunt attenuation.

There seem to be a few significant correlations using univariate analysis between the CTA-variables and therapy outcomes themselves. There was a significant correlation between the anatomical and clinical outcomes (P=0.042, correlation coefficient=0.437). Another significant correlation was seen between the location of the IH CPSS and whether the shunting vessel reaches the liver surface (P=0.002, correlation coefficient=0.612). And finally, a significant correlation was found between the diameter of the shunting vessel and the presence of portal branching (P=0.013, correlation coefficient=0.497).

No model could be constructed to predict closure or outcome.

Discussion

The aim of this study was to find out whether CTA-imaging actually exceeds abdominal ultrasounds in diagnosing an IH CPSS. According to this study CTA is the preferred diagnostic imaging method, due to the fact that it provides more information about the shunting vessel. The difference in the amount of information that could be retrieved from abdominal ultrasounds and CTA-imaging was substantial. Abdominal ultrasounds appear to only provide data on shunt location, liver size and the presence of portal branching. This is much less than the results of CTA-imaging, which additionally provides information on presence and location of hepatic veins, shunt diameter, shunt length and if/where the shunting vessel reaches liver surface. Furthermore, the information provided by CTA-imaging proves to be more specific, and thus more valuable. Shunt location can be determined using different definitions. There does not seem to be a gold standard just yet, according to recent literature.(3, 5, 38) A dog has to lie on its back for any of these 3 methods to inspect the shunting vessel (abdominal ultrasound, CTA-imaging and during surgery). Abdominal ultrasounds and CTA-images were thus compared with intraoperative shunt location determination. Abdominal ultrasounds revealed a 62%-38%-0% left-right-central distribution respectively. CTA-images gave a 75%-17%-8% distribution. When comparing this to the intraoperative numbers (74%-17%-9%), CTA-imaging appears more accurate in predicting the IH CPSS location. However, when comparing the preoperative and postoperative CTA-images, an inconsistency was found in shunt location. Two of the 3 dogs' shunts appeared to be in another location after surgery. Could this also be the cause of tissue manipulation by the surgeon? Or is this inconsistency caused by location determination by different radiologists, using different definitions? Retrospective evaluation with one of the radiologists at the clinic already revealed that no clear definition of shunt location is being used to describe the IH CPSS. The other 2 variables that were documented using abdominal ultrasound (liver size and portal branching) were probably also reported more accurately by CTA-imaging. Liver size was evaluated in 18 dogs with abdominal ultrasound and in 19 dogs with CTA-imaging. Portal branching was mentioned in only 2 dogs using abdominal ultrasounds, but was mentioned in 19 dogs using CTA-imaging. However, the accuracy of either method could not be compared with intraoperative information, because these variables were not mentioned in most surgery reports. Shunt diameter before attenuation was measured in CTA-images as well as in vivo during surgery. Preoperative the average diameter measured in CTA was 12.2 mm. The average diameter measured during surgery was 11.5 mm before attenuation. It is to be expected that the shunt diameter deviates from normal during surgery, because of tissue manipulation by the surgeon which can influence the diameter of the shunt (constriction). This information leans toward a more trustworthy measurement in CTA-imaging, although further study is necessary for confirmation. Shunt diameter after attenuation was mentioned for 18 dogs during surgery, but the postoperative minimal diameter was only measured in 3 dogs using CTA-imaging. Table 2 shows dramatic aberrance in these postoperative measurements. However, measurements taken from the narrowest point on CTA-images are not necessarily measurements of the site of ligation. These findings suggest that knowledge of the intraoperative, post-ligation shunt diameter is more reliable than postoperative CTA-imaging measurements, assuming that the ligature remains intact.

Another aim of this study was to see if CTA-findings have any predictive value on attenuation and outcome: statistical analysis confirmed that the correlation between the presence of CTA-images and shunt closure is significant, but perhaps this is not relevant. This finding indicates that the success of attenuating the shunting vessel is more probable when the surgeon has access to CTA-images. The additional information derived from CTA could provide a better idea of what is to be expected during surgery. Dogs that are presumably difficult to operate can be denied, which causes selection of dogs prior to surgery and the success rate to increase. However, there are other aspects that can influence the amount of closure. Aspects such as a transition from an experienced surgeon to a less experienced surgeon that operated the dog, transition from a protocol without CTA or CTA in only difficult cases to a routine CTA in all cases, changes in the used materials or the type of anesthesia that were not taken in account in this study. This makes it difficult to state that the presence of CTA-images has a positive effect on attenuation of the IH CPSS. Besides, the correlation between these 2 variables is low. A larger study group or reviewing the cases prospectively might give a better representation of the relation between preoperative CTA-imaging and closure of the shunting vessel.

Unfortunately, more than half of the dogs that were initially included in this study were excluded from the statistical analysis due to the fact that there were no CTA-images made of the abdomen, leaving only 24 dogs in the study. The documentation of all the dogs' symptoms, laboratory findings and surgical outcomes was not consistent. Not every dog underwent the same laboratory testing and not every dog had a 1 and/or 3 month control visit. Which is comprehensible in a retrospective study. Besides, some of the owners were travelling from afar. When their dog made a satisfactory recovery, the urgency to commit to further testing decreases. A prospective study design, asking the owners to participate in the follow-up visits and execute these moments by protocol, would provide more reliable results. Furthermore, 4 dogs did not survive until the control visit due to different reasons, which were not all shunt-related. One dog died from cardiac failure. In a population this small, only cautious conclusions can be made.

The findings on symptoms of hepatic encephalopathy imply that surgical attenuation of the shunting vessel decreases signs of hepatic encephalopathy in the majority of dogs. The findings on bile acid concentrations make it is safe to state that bile acid levels rarely normalize within 3 months after surgical attenuation. This observation is confirmed by Bristow et. all, who studied serum bile acid (SBA) concentrations in 51 dogs after complete EH CPSS ligation. They found that even at their long-term follow-ups (mean ±SD, 158 ±832.7 months), SBA concentrations remained above the laboratory reference range in 64.7% pre- and 86.3% post-prandial.(39) According to this study, ammonia levels seem to normalize more quickly than bile acid levels. Also, surgical attenuation seems to have a positive effect on plasma albumin levels, reflecting an improvement of the hepatic function. Comparable with the changes in total protein levels. Running through all the laboratory results and the HE classifications before, 1 month and 3 months after surgical attenuation, it is interesting to find that there is a delay in metabolic improvement. Hardly any changes are visible in a dogs' blood 1 month after surgery. While the HE symptoms seem to decline right away. This indicates that the best method to evaluate success after surgical attenuation is by clinical symptoms of hepatic encephalopathy. Less blood flow through the shunting vessel causes a redistribution and thus more perfusion of the liver parenchyma. This might normalize blood ammonia levels, reducing HE symptoms and improve hepatic function, followed by increased albumin and total protein levels because these parameters are less specific for portosystemic shunting.

Location of the shunting vessel seems to be significantly correlated to whether the shunting vessel reaches liver surface. Left-sided shunts have better odds of reaching liver surface than central- or right-sided shunts. This also indicates that left-sided shunts are easier to access during surgery, increasing the chance of a successful attenuation. However, CPSS location or CPSS surface do not seem to have significant correlations with closure or anatomical outcome. So somehow, other factors may also be important to predict closure or anatomical outcome, or the numbers in this study were too small to confirm this assumption.

In like manner, the diameter of the shunting vessel seems to be significantly correlated with the presence of portal branching. Portal branches are more likely to be present or visible in the CTA images in shunting vessels that have a wide diameter. A possible explanation is that dogs with larger shunts, which are more difficult to dissect, more often also have clear portal branches to the other liver lobes, which is favorable. Another reason might be that in these dogs a better portal flow of contrast medium during the CTA provides a better filling and visualization of the shunt and the portal branches, while in dogs with less portal flow the shunt appears to be narrower and the portal branches are more often not clearly visualized. The question remains how reliable CTA is to exclude the presence of portal branches, as long as the shunt is not temporarily closed such as in intraoperative portography.

In this 24-dog test group there were 10 females and 14 males. Most of the dogs (79%) were large breeds, which matches the expectation.(2, 3, 6, 7) An IH CPSS mostly presents itself in young dogs, because the median age at surgical intervention was 11 months. The large spread in age (50.5 months) is caused by 2 dogs that were notably older than the other 22 dogs (28 and 54 months old).

Conclusion

Based on the amount and the accuracy of information that can be obtained by abdominal ultrasound and CTA-imaging, this study validates the supremacy of computed tomographic angiography in diagnosing and treating an IH CPSS. Information on the IH CPSS derived from CTA-imaging does not seem to have any influence on closure, clinical, metabolic or anatomical outcome, according to this study, but there seemed to be a correlation between the presence of a preoperative CTA-scan and closure. No predictive value on surgical outcome can be assigned to CTA-imaging. Other variables did seem to be significantly correlated to one another. When residual blood flow through the shunting vessel is low, less symptoms of hepatic encephalopathy are present. Also, a wider average diameter of the IH CPSS provides a better prospect at the presence of portal branching. And finally, a left-sided IH CPSS is more likely to reach liver surface than a central- or right-sided IH CPSS. Nonetheless, the small number of dogs and the inconsistency in follow-ups support a recommendation for extended research on this subject. Future studies should consider reviewing a larger number of dogs in a prospective manner to prevent the scarcity on available information.

Acknowledgements

I would like to thank dr. A. Kummeling, my project tutor, for guiding the writing process and providing me with a chance to fully dive in the world of portosystemic shunting (theoretically, but also practically). The infinite patience and willingness to review and comment on my work is something I am truly grateful for. I would also like to thank drs. L.W.L. van Bruggen for her assistance on the assessment of the abdominal ultrasounds and CTA-images. A last thank you note goes out to dr. R.P. Favier and dr. V. Szatmári for serving as back-up project tutors.

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