Liver regeneration in dogs after CPSS surgery

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Abstract

Background: The purpose of this study was to investigate macroscopic liver regeneration after congenital portosystemic shunt (CPSS) surgery and determine a possible connection with clinical outcome. We also wanted to compare MRI and CT as technique for liver volumetry.
Methods: MRI and/or CT scans were made before and on day 8, 1 month and 2 months after surgery. Liver surface areas were measured and liver volumes were calculated using the images.
Results: Liver growth was the strongest in the period between day 0 and day 8, with decreasing growth afterwards. No significant difference was found in growth rate for dogs who had completely recovered and dogs that had not. Measurements made on MRI images and on CT images correlated well (R^2=0.94), but a significant difference was found (P=0.0094). On average, volumes estimated from MRI scans were 7.5% larger than volumes estimated from CT scans.
Conclusion: We have not been able to find a difference in post-operative liver growth between dogs that recovered completely and dogs that still showed subclinical persistent shunting. In addition, our data suggested that using CT scans for volume estimation is more accurate than using MRI scans.

Key words: Computed tomography; hepatic size; magnetic resonance imaging; portosystemic shunt; volumetry

Introduction

Congenital portosystemic shunt (CPSS) is a common anomaly among dogs and usually causes problems at a young age. The vessel shunts the blood away from the liver, which results in an abnormal ammonia metabolism and hepatic malfunction due to liver atrophy. This can lead to neurological signs and other symptoms. The main therapy of choice for dogs with a CPSS is partial or full closure of the shunt during surgery[1,2].

Unfortunately not all patients recover completely in the long term from the surgery, and these animals usually retain an abnormal ammonia metabolism. Researchers have not been able to find good prognostic factors to identify these at-risk patients[3,4].

It is thought that the ability of the liver to regenerate after surgery is a key factor in long term recovery of the patient. This ability seems independent of the surgical technique that is used to close the shunt (suture ligation, ameroid constrictor or cellophane banding), or the degree of closure[4].

Liver volume has been determined by several different techniques, including radiographs, magnetic resonance imaging (MRI), computed tomography (CT), ultrasonography and scintigraphy[5-10]. Studies showed that liver volume estimation with CT is the most reliable method[11,12].

So far, only in one study CT imaging has been used to determine liver volume in dogs with CPSS[13]. In this research, Stieger et al. compared liver volumes of dogs with CPSS with liver volumes of healthy normal dogs. They also looked at the preoperative en postoperative liver volumes in three affected dogs. Aside from the work that Stieger et al. have done, there has been no research into macroscopic liver regeneration in dogs after CPSS surgery. More insight into the process of liver regeneration in these dogs could contribute to a better estimation of prognosis for dogs with CPSS.

In our study CT and MRI scans were made in ten dogs with CPSS on four consecutive occasions. By determining liver volumes and analyzing the data, we aim to gain a better understanding of the growth rate of the liver after surgery and possibly identify a prognostic factor for long term recovery. Another goal is to gain more insight into the difference between using MRI or CT images to determine liver volumes.

Material and methods

Patients

Ten dogs with single extrahepatic CPSS were entered into our study. The dogs had been referred for surgical attenuation of the shunt. Owners agreed to participate with fully informed consent.
The dogs were suspected to have portosystemic shunting by measurements of abnormal high 12-hour fasting ammonia and bile acids concentrations or an abnormal rectal ammonia tolerance test[14]. Ultrasound was used to confirm that portosystemic shunting was caused by a single extrahepatic shunt. During surgery, visual confirmation of the shunt was obtained.

All dogs were operated on by the same surgeon (FJvS). Premedication consisted of an intramuscular injection of methadone (0.5 mg/kg) and atropine (0.03 mg/kg) and prophylactic antibiotics (amoxicillin/clavulanic acid 20 mg/kg IV). Anesthesia was induced 30 minutes later with propofol (1-5 mg/kg IV) and maintained with isoflurane in oxygen. The dogs received lactated Ringer's solution (10 mL/kg/h IV) during surgery, and sufentanil or fentanyl for sufficient analgesia (1 µg/kg/h IV). Intermittent positive-pressure ventilation was used to support respiration. During the operation the patient was monitored by using electrocardiography, pulse oximetry, respirometry, capnography and measuring peripheral arterial pressure, central venous pressure, body temperature, and plasma glucose concentration. Shunts were surgically attenuated using nonabsorbable material (*Ethibond*^{tm} *excel 2-0*, Ethicon INC., New Jersey), according to the technique reported by Wolschrijn et al[15].

Analgesia was continued post-operatively with methadone and carprofen or tramadol. At the intensive care unit, the patient was monitored until recovery was sufficient to dismiss the dog, usually at 2 days after operation.

All dogs were put on a low-protein diet during the course of our research study, starting approximately two months before surgery and continuing until at least two months after.

Long term recovery was monitored in our clinic 8 days, 1 month and 2 months after surgery. The decrease in portosystemic shunting was evaluated by ultrasound examinations of the flow through the shunt, by determining 12-hour fasting bile acids concentrations in the blood and measuring plasma ammonia or applying a rectal ammonia tolerance test. Clinical recovery was monitored by the owners and reported during these check-ups. Body weight was determined at every visit. A dog was defined 'completely recovered' when at two months after surgery there were no clinical signs of shunting, no abnormal high concentrations of ammonia and bile acids in the blood, and no abnormal rectal ammonia test.

Except for the presence of a single extrahepatic CPSS and consent of the owners, no other criteria were used for the selection of dogs to be used in this study.

Scans

MRI and/or CT scans were made on four occasions, namely pre-operatively (day 0) and 8 days, 1 month and 2 months after surgery.

MRI scans were obtained using a Magnetom Open Viva® scanner (0.2 Tesla, Siemens). The images used for the measurements were T1 weighted (repetition time 560 ms, echo time 15.0ms). The abdominal scan usually ranged from the xiphoid to the right kidney. Slice thickness was 5 millimeters.

CT scans were made with a CT Secura® scanner (Philips). Slice thickness was set at 3mm and the images were reconstructed to a thickness of 2mm. Scans were made of the entire abdomen.

The dogs were anesthetized during the procedure with propofol after premedication with methadone and atropine. Ventilation and heart rate were monitored continuously. Several seconds of apnea were achieved by hyperventilating or disabling intermittent positive-pressure ventilation, in order to obtain accurate abdominal scans.

Measurements

To determine liver volumes, the liver was outlined on each individual slice by hand, which resulted in a calculation of the surface area. The total surface area of the liver on each slide was multiplied with the slice thickness to calculate the volume. While outlining the liver, careful consideration was made to exclude the vena cava and gallbladder.

The MRI images were viewed with Numaris version VB33G software (Siemens) and areas were calculated using the same software. The window settings for viewing were window width 1892 and window center 891. All images were outlined by hand with these window settings. Surface area was expressed in square centimeters.

CT images were viewed and area calculations were made with EasyVision 5.1 software (Philips). The same window settings were used for all of the images, namely a window width of 150 Hounsfield units (1000 scale) with a level of 40. Outlines were made by hand after which the program calculated the size of the area. Surface area was expressed in square millimeters.

Measurements were randomly done twice, on all series of CT and MRI scans by one person.

Statistical analysis

The statistical tests were executed using the software SPSS Statistics 16.0® (SPSS Inc. HQ, Chicago, Ill.).

Kolmogorov-Smirnov tests were performed to determine if data were normally distributed. To determine if there was a significant difference between the first time measuring and the second time, paired T-tests were performed. The correlation coefficients (R^2) between both data sets were also determined.

For further analysis of the data, averages of both measurements were used for each series. Data from MRI and CT scans of the same dog at the same time were compared using a paired T-test and again the R^2 was determined.

To compare liver volumes and growth of all the dogs, the CT measurements were used. For dogs 1 and 2, who only had MRI scans, values were adjusted to fit the rest of the data.

Liver volumes and growth were also corrected for body weight (BW). Using paired T-tests, we determined if there was significant growth in different time intervals. We compared the uncorrected data with the data corrected for BW.

Finally, we used paired T-tests to compare the volumetric data of dogs that recovered completely with that of dogs that did not, and to compare the data of dogs with fully closed shunts with that of dogs whose shunts were closed to the smallest diameter possible during surgery.

Results

The majority of dogs in this study were female (7/10). Ages at time of surgery ranged from 5 months to 40 months, with a mean of 15.9 months. The dogs were all of small breeds, which is typical for extrahepatic portosystemic shunts[1].

Although four consecutive volumetric scans of each dog were planned, one scan unfortunately was not made (dog 7). In addition, 4 scans were lost due to technical errors. This meant that for dog 5 only three scans, and for dogs 6 and 7 only two scans were available for volumetric measurements (*Table 1)*.

Table 1.

Dog #	**Breed**	**Sex**	**Age at time of surgery**	**MRI**	**CT**
1	Jack Russell	Female	10 months	4 series	-
2	Cairn Terrier	Male	5 months	4 series	-
3	WHW Terrier	Female	15 months	4 series	4 series
4	Cairn Terrier	Female	12 months	4 series	4 series
5	Shih Tzu	Female	7 months	3 series*	3 series*
6	Mixed	Male	14 months	-	2 series**
7	Mixed	Female (n)	39 months	-	2 series***
8	Welsh Terrier	Female (n)	40 months	-	4 series
9	Yorkshire Terrier	Female	6 months	-	4 series
10	Cairn Terrier	Male (n)	11 months	-	4 series

N = these dogs had been neutered before surgery

* Due to technical difficulties, the series made 8 days post-operatively was lost.

** Due to technical difficulties, the series made 29 days post-operatively was lost.

*** Due to technical difficulties, the series made 8 days and 64 days post-operatively were lost.

The results of the volumetric measurements were normally distributed. There was no significant difference between both MRI measurements (P= 0.181), but the first measurements of the CT series were slightly higher than the second measurements (mean difference of 1.6%, P= 0.040). This difference was not considered to be relevant. The correlation between the first and second measurements was high; R^2 was 0.99 for both CT and MRI (*Figures 1 and 2*).

Figure 1. Volumes (cm^3) measured on CT scans

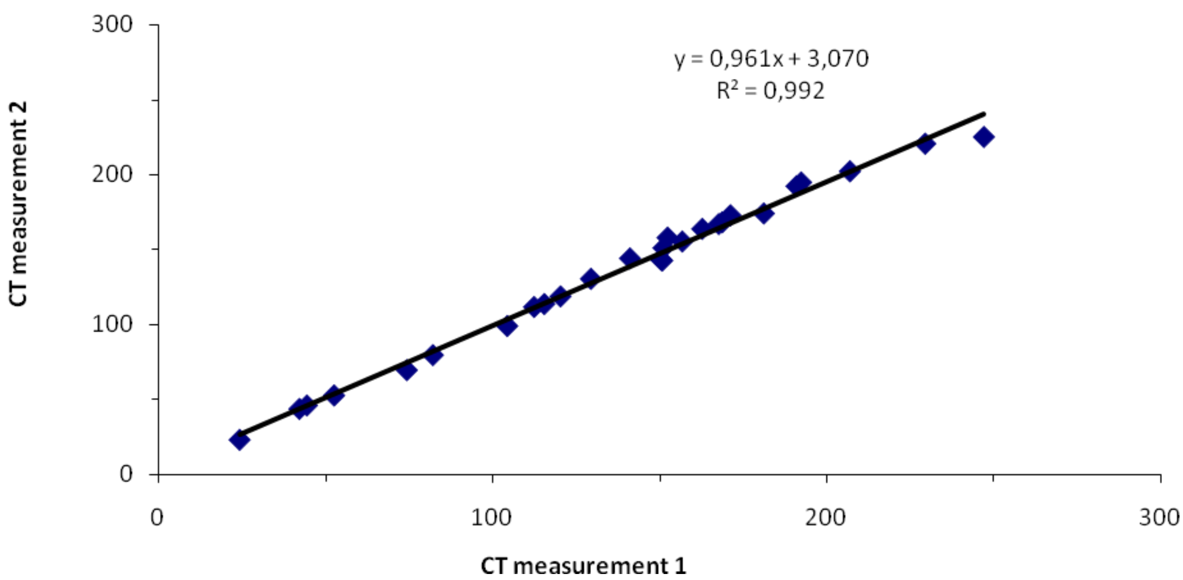
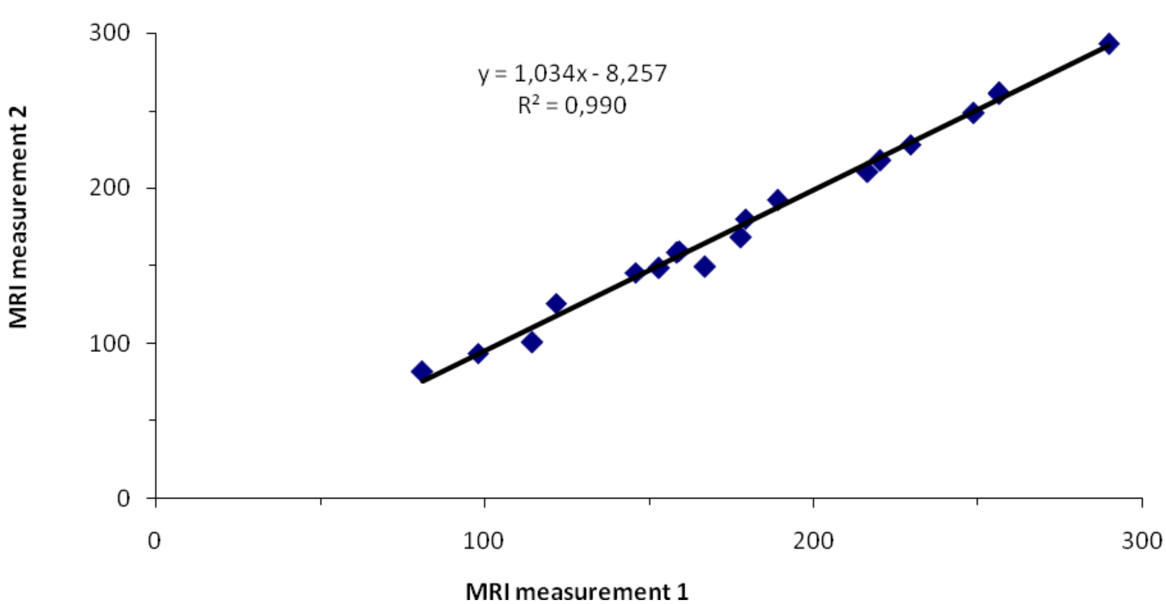
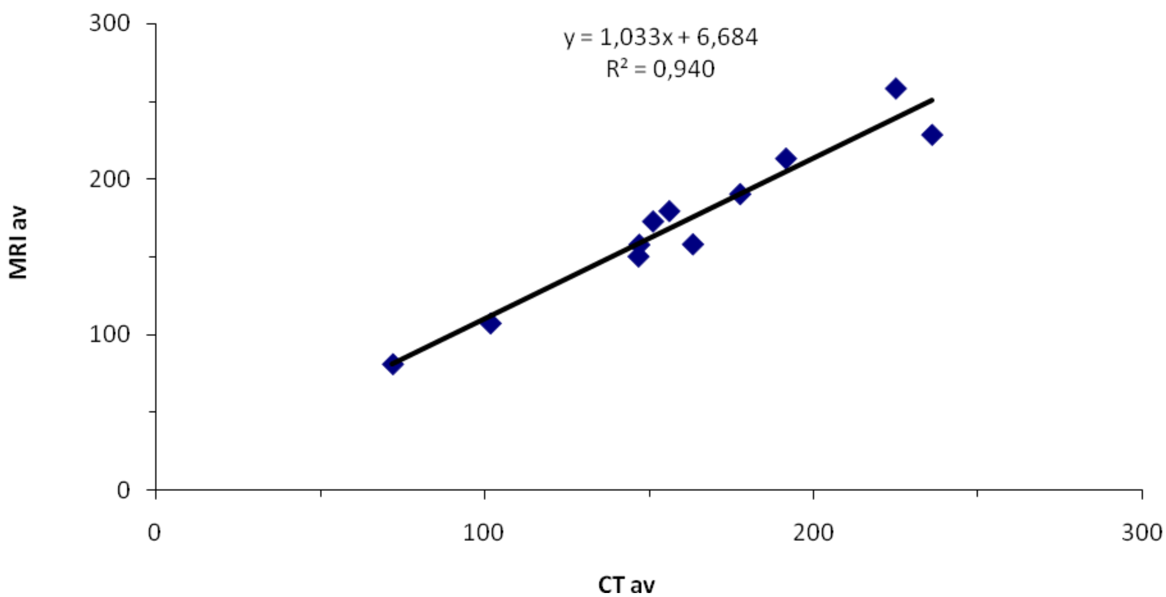


Figure 2. Volumes (cm^3) measured on MRI scans



The measurements made on MRI scans were also compared with measurements made on CT scans of the same dog at the same time. These values also correlated well (R^2 = 0.94, *Figure 3*), but there was a significant difference (P= 0.0094). On average, measurements made on MRI scans showed 7.5% larger volumes than measurements on CT scans.

Figure 3. Volumes (cm^3) from CT and MRI scans



For further analysis of liver volumes and growth, the values derived from CT measurements were used. In the dogs with no CT scans performed (dog 1 and 2), the volume data from the MRI scans were corrected to fit the rest of the data. The liver volumes and growth (in % of the volume on day 0) are shown in Table 2. The strongest growth occurred in the period between day 0 and day 8, with a decreasing growth afterwards.

Table 2.

	Age day 0	Volume day 0	8 days postoperative Volume	Growth	1 month postoperative Volume	Growth	2 months postoperat. Volume	Growth
	months	cm^3	cm^3	%	cm^3	%	cm^3	%
Dog 1	10	88.6	114.4	129	147.4	166	134.9	152
Dog 2	5	202.5	239.4	118	229.8	113	269.3	133
Dog 3	15	101.7	156.1	153	177.6	175	151.1	148
Dog 4	12	146.7	191.6	130	236.0	161	225.0	153
Dog 5	7	72.0			146.9	204	163.2	227
Dog 6	14	114.6	130.0	113	142.6	124	167.3	146
Dog 7	39	80.9					112.1	138
Dog 8	40	155.2			168.4	108		
Dog 9	6	23.8	43.0	181	45.3	190	52.7*	221*
Dog 10	11	119.5	172.0	144	193.5	162	204.5	171
Average	**15.9**	**110.6**	**149.5**	**138**	**165.3**	**156**	**164.5**	**166**

Values for Dog 1 and Dog 2 are corrected from MRI values to CT values.
*These values are from 3 months post operatively, instead of 2 months.
Growth: in % compared to V0

Body weight (BW), liver volume and growth per kilogram BW are shown in Table 3 and 4.

Table 3. Body weight (BW) in kilograms (kg)

BW on:	Day 0	Day 8 p.o.	1 month p.o.	2 months p.o.
Dog 1	5.2	4.3*	5.0	5.0
Dog 2	6.2	6.7	7.0	7.9
Dog 3	6.2	5.9	6.5	6.5
Dog 4	8.0	7.7	8.4	8.7
Dog 5	4.0	4.2	4.7	4.9
Dog 6	5.0	4.8	5.0	5.1
Dog 7	4.7	4.4	4.5	4.8
Dog 8	8.0	7.9	8.0	8.1
Dog 9	1.2	1.2	1.4	1.5
Dog 10	6.5	6.5	7.0	7.1

*Strong weight loss compared to day 0, may be due to recent spell of diarrhea and vomiting.
p.o. = postoperatively

Table 4. Liver growth corrected for body weight

	Volume day 0	8 days postoperative		1 month postoperative		2 months postoperative	
		Volume	Growth	Volume	Growth	Volume	Growth
	cm^3/kg	cm^3/kg	%	cm^3/kg	%	cm^3/kg	%
Dog 1	17.0	26.6	156	29.5	173	27.0	158
Dog 2	32.7	35.7	109	32.8	100	34.1	104
Dog 3	16.4	26.4	161	27.3	166	23.2	142
Dog 4	18.3	24.9	136	28.1	153	25.8	141
Dog 5	18.0			31.2	174	33.3	185
Dog 6	22.9	27.1	118	28.5	124	32.8	143
Dog 7	17.2					23.3	135
Dog 8	19.4			21.0	108		
Dog 9	19.8	35.9	181	32.3	163	35.1*	177*
Dog 10	18.4	26.5	144	27.6	150	28.8	157
Average	**20.0**	**29.0**	**144**	**28.7**	**146**	**29.3**	**149**

Values for Dog 1 and Dog 2 are corrected from MRI values to CT values.
*These values are from 3 months post operatively, instead of 2 months.
Growth: in % compared to V0

With respect to liver volumes not corrected for body weight, significant growth was seen between day 0 and day 8 (P= 0.001), between day 8 and day 30 (P=0.040), but not between day 30 and day 60 (P= 0.452). Liver growth between day 8 and day 60 was significant as well (P=0.008).

With regard to the liver volumes corrected for body weight, significant growth was seen between day 0 and day 8 (P= 0.002) and between day 0 and day 30 (P= 0.001). There was no significant growth between day 8 and day 30 (P= 0.664), day 30 and day 60 (P= 0.752) or day 8 and 60 (P= 0.633).

Of the ten dogs in our study, two dogs did not recover completely metabolically and retained a low level of persistent shunting (*Table 5*). Owners did see complete clinical recovery in these dogs.

Table 5. Blood results and ultrasound findings

	Test results day 0		**Test results day 8**		**Test results 1 mo.**		**Test results 2 months**		
	NH3/ATT	B.a.	NH3/ATT	B.a.	NH3/ATT	B.a.	NH3/ATT	B.a.	Ultrasound
Dog 1	>286	260	18	17	14-10-10	1	14	0	mild patency
Dog 2	48 (SI 100%)	19	11	1	9-11-9	1	24-32-19	2	no patency
Dog 3	35-281->286	160	10	1	7-47-9	2	7-7-9	3	no patency
Dog 4	67-286-258	175	13-47-25	7	8-23-16	2	16-15-12	1	no patency
Dog 5	>286		14-29-35	38	10-154-66	3	8-34-7	5	unknown
Dog 6	81		7-36-7	7	7-15-7	3	7-54-7	6	unknown
Dog 7	174		7-45-18	4	7-8-12	4	7-16-15	13	no patency
Dog 8	88	190	10-19-17	3	7-25-13	1	<7-7-<7	1	no patency
Dog 9	146		21	8	13	2	18->286-137*	3*	mild patency*
Dog 10	70		94	38	27-175-234	111	51-286-150	59	mild patency

*These values are from 3 months post operatively, instead of 2 months.
NH3/ATT = ammonia concentration or results ammonia tolerance test in µmol/L
B.a. = bile acids concentration in µmol/L

Comparing the volumetric data of the fully recovered dogs with both dogs that did not completely recover, we found no significant differences on day 8 (P= 0.295), on day 30 (P=0.276), or day 60 (P= 0.331).

Neither did we find any significant differences between dogs that had their shunts completely closed (n=2) and dogs whose shunts were partially closed, to the smallest diameter possible (n=8), on day 8 (P=0.189), day 30 (P= 0.479), and day 60 (P= 0.153).

Discussion

Even though a few series of images were lost, sufficient data was collected to provide accurate results. All measurements were done in duplo to improve accuracy. They were made by hand by a research student (D.V.), who had no prior knowledge or experience working with CT or MRI images. This lack of experience and the resulting learning curve, may explain the slightly higher values found with the first CT measurements compared to the second CT measurements (mean difference 1.6%, P=0.040). Why this difference was not found with the MRI measurements, is possibly due to the higher number of frames to be measured and therefore more risk for error with the CT scans.

As suggested by an experienced radiologist, the vena cava and gallbladder were excluded, so as not to overestimate the liver volume. This was consistently done on all frames to prevent extra bias in the interpretation of the images.

When we started our research project, the CT scanner was temporarily unavailable due to renovation of the department of Diagnostic Imaging, so we could only use MRI scans in the first two dogs to determine liver volumes. When the CT scanner was available again, both MRI and CT scans were made in order to compare both techniques for volumetry. Because the total duration of the two scans before surgery meant too much stress for the dogs (causing a prolonged anesthesia time and severe hypothermia in high-risk surgical patients), the volumetric studies were continued with only CT scanning. CT imaging was preferred because this technique was faster and seemed to be more reliable than MRI.

Computed tomography has long been established as a very accurate technique for volumetry; some even call it the non-invasive gold standard[9,11,12]. There are few studies on the accuracy of magnetic resonance imaging as a technique for liver volumetry, but one study did report a high correlation coefficient (0.90) for MRI estimated liver volume and liver volume estimated by the fluid displacement method. However, measurements on both transverse and coronal planes were used to estimate liver volume, which may be more accurate than measurements on a single plane[5]. In our study, we found a correlation coefficient of 0.94 for MRI derived liver volume and CT derived liver volume, but also a significant difference (P=0.0094) with an average over-estimation of liver volume on MRI scans by 7.5%. The cause of this difference between techniques is hard to determine.

Difference in slice thickness (MRI 5mm, CT 3mm reconstructed to 2mm) may play a role, because it can lead to loss of accuracy for the MRI measurements. It is also possible that differences in software may have contributed; the software for MRI scans for example does not allow corrections of the outline after it has been made, which is possible with the CT software. As a result, small deviations from the outline of the liver may have been left uncorrected. However, MRI images were viewed frame by frame, where as CT images were viewed on a screen of 2x2 frames. Outlining the liver on MRI images could therefore be done fairly accurately, so there was no need for readjustment of the outline.

Another possibility for the difference between MRI derived liver volume and CT derived liver volume could be respiratory movement of the abdominal organs during the MRI scans, that did not occur during the CT scans since the dogs were held in apnea for the duration of the CT scan. This could not be done during MRI scans, since the duration is significantly longer and apnea of that duration would be unjustifiable in high-risk patients.

Regarding the contrast between liver tissue and other abdominal organs, MRI and CT images were very comparable with the window settings used. The slight difference in contrast in favor of the MRI did not result in a significant ease of measuring compared to CT images.

In the final analysis of liver volumes and growth, the volumes derived from CT measurements were used since the majority of the data consisted of CT scans and this technique has been established as being very accurate for liver volumetry.

One of our goals was to describe liver volume and growth in dogs with CPSS, since there have been few studies on the subject[10,13] and it is thought that liver regeneration may play a key role in long-term outcome of the patient after attenuation of the shunt[4]. Due to breed and age, the dogs in this study varied in body weight. Liver volume is known to be related to body weight and it is also known that dogs with CPSS often show retarded growth. Therefore liver volume and growth were expressed with and without correction for body weight to asses the influence of these factors.

Looking at tables 2 and 4, something peculiar can been seen. In several dogs liver volumes seem to have decreased two months after surgery compared to volumes measured 1 month postoperative, even though still resulting in growth compared to day 0. A decrease in volume can also been seen between day 8 postoperative and one month. The growth between day 8 and 1 month is significant when using data not corrected for body weight (P=0.040), but it is not when volumes are corrected for body weight (P=0.664). Growth for the period between 1 month and 2 months postoperative is not significant whether corrected for body weight (P=0.752) or not (P=0.452). The seeming decrease in liver volume may be the result of inconsistencies in the positioning of the dogs. Unfortunately, the scanning protocol was not always followed correctly and dogs were placed lying on their abdomen instead of on their back. This resulted sometimes in distorted images which made outlining liver tissue more challenging and it may have influenced liver volume by hepatic blood volume changes. However, the incidence in which this occurred, is not enough to explain for all the apparent decreases in volume.

We found an average increase of liver volume by 49% at 2 months after surgery. Stieger et al.[13] have reported an increase of 62% in liver volume in a single dog with an extrahepatic shunt. Compared to the dogs used in their research, our study group contained younger dogs with higher volume : body weight ratios on day 0. Comparison of results may therefore not be justified.

Recently, Doran et al. reported that dogs that were tolerant to full closure of the shunt during surgery had greater liver volume to body weight ratios than dogs intolerant of occlusion[16]. Our data however does not corroborate this.

Comparing the volumetric results of completely recovered dogs with those of dogs with low levels of persistent shunting, no significant differences were found. Neither did we find any significant differences when comparing volumetric results of dogs with completely closed shunts and of dogs with shunts closed to the smallest diameter possible. The number of cases may be too small to find significant differences. A follow-up study with more dogs or with dogs with less improvement of portosystemic shunting postoperatively may show more conclusive results.

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