New perspectives on the development of extrahepatic portosystemic shunts

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STRUCTURED SUMMARY

Objective: To develop a hypothesis for the developmental modality of extrahepatic portosystemic shunts.

Methods: A retrospective review of a series of dogs and cats managed for congenital portosystemic shunts. Using these data a hypothesis for the role of preferential venous blood flow in the development of common extrahepatic PSSs was postulated. In addition, an online literature search was used to retrieve peer-reviewed data describing the detailed anatomy of shunts in dogs and cats. A systematic review of these data was used as a preliminary test of the hypothesis.

Results: In total 50 dogs and 10 cats met the inclusion criteria revealing five common and distinct shunt types. In the dog, these were spleno-caval, left gastro-phrenic, left gastro-azygos and those involving the right gastric vein. The online search confirmed that these were responsible for 94% of extrahepatic shunts described in this species. In the cat, the four shunt types observed were spleno-caval, left gastro-phrenic, left gastro-caval and left gastro-azygos. Excluding the left gastro-azygos, which from the online search was not described in the cat, the spleno-caval, left gastro-phrenic and left gastro-caval were responsible for 92% of extrahepatic shunts in this species. These data were used to develop, propose and provisionally test a hypothesis for the development of extrahepatic portosystemic shunts.

Clinical Significance: We hypothesise that it is the presence of preferential blood flow that influences the subsequent formation of one of a number of defined and consistent congenital extrahepatic portosystemic shunts in dogs and cats.

KEYWORDS - soft tissue-cardiovascular-portosystemic shunt

INTRODUCTION

Recently, the morphology of common extrahepatic portosystemic shunts (EHPPSs) have been independently described in detail using a combination of computed tomography angiography (CTA), intra-operative mesenteric portovenography (IOMP) and gross anatomical findings (White & Parry 2013, 2015, 2016a). Although these common shunts types were found to involve a number of vessels such as the caudal vena cava and the azygos, right gastric, left phrenic and splenic veins, all three studies concluded that it was, in fact, the left gastric vein that represented the anomalous vessel (shunt) that communicated with the systemic vein (White & Parry 2013, 2015, 2016a). In addition, the morphology of each shunt type described appeared to result consistently from two main factors; an abnormal communication between the left gastric vein and a systemic vein, and the subsequent development of preferential blood flow through an essentially normal portal venous system. It is well recognized that the portal vein in adult humans is without venous valves in its larger channels (Douglass *et al.* 1950, Gabella 1995, Burroughs 2011). Such a valveless portal venous system would allow for potential blood flow in either hepatopetal (normal blood flow towards the liver) or hepatofugal (abnormal blood flow away from the liver) directions and the actual direction of blood flow would be governed solely by the venous pressure gradient between the splanchnic and hepatic capillary networks (White and Parry 2015).

The purpose of this study was to explore the role of preferential flow in the formation of EHPSSs in more detail and, in addition, to develop a hypothesis for the mode of development of the more common extrahepatic PSSs in dogs and cats.

MATERIALS AND METHODS

This retrospective study reviewed dogs and cats seen by the authors between 2009 and 2015 for the investigation and management of congenital PSS. The main inclusion criterion was that all cases must have a congenital EHPSS, have undergone preoperative CTA, recorded IOMP and direct gross observations at the time of surgery.

CTA was performed using a 16 slice multidetector unit (Brightspeed, General Electric Medical Systems, Milwaukee) as described previously (White & Parry 2013, 2015). Studies were assessed in their native format, using multiplanar reconstruction and using surface shaded volume rendering. Vascular maps were obtained and post processing was limited to removal of arterial vessels and unnecessary portions of the caudal vena cava (CVC) from the maps. All CTA studies were reviewed by the authors and special emphasis was placed on assessment for the presence or absence of venous valves within the left gastric vein and its tributaries. In addition, a number of normal CTA studies in dogs and cats were reviewed for the purposes of cross-reference.

IOMP was carried out during surgery by using a mobile image intensification unit to obtain ventrodorsal images of the cranial abdomen (White *et al.* 2003, White & Parry 2015). Images were obtained before the manipulation of the shunt and during the temporary full ligation of the shunting vessel. Angiograms were recorded digitally and were reviewed by the authors.

Data on the type of portosystemic shunt were collected and reviewed. On the basis of the combined data of CTA, IOMP and the normal anatomy of the portal venous system, a hypothesis for the role of preferential venous blood flow in the development of these common and consistent EHPSSs was postulated. An online literature search using PubMed Central® was used to retrieve any peer-reviewed published data providing an anatomical description of an EHPSS in either the dog and the cat which was more detailed than that of just *porto-caval*, *porto-phrenic* or *porto-azygos*. A systematic review of this data was used to test the hypothesis.

RESULTS

In total, 50 dogs and 10 cats met the inclusion criteria. Of these 50 dogs, 23 (46%) were found to have a left gastric vein shunt entering the left phrenic vein (left gastro-phrenic shunt), 13 (26%) had a shunt involving the right gastric vein (type Ai, Aii, Aiii or type B shunt), 9 (18%) had a shunt involving the splenic and left gastric veins entering the caudal vena cava at the level of the epiploic foramen (spleno-caval shunt) and 5 (10%) had a left gastric vein entering the azygos vein (left gastro-azygos shunt).

Of the 10 cats, 6 (60%) were found to have a left gastric vein shunt entering the left phrenic vein (left gastro-phrenic shunt), 2 (20%) had a shunt involving the splenic and left gastric veins entering the caudal vena cava at the level of the epiploic foramen (spleno-caval shunt), 1 (10%) had a left gastric vein entering the azygos vein (left gastro-azygos shunt) and 1 (10%) had a left gastric vein entering the post-hepatic CVC (left gastro-caval).

In both the dog and cat, results confirmed that in these four common EHPSS types the veins involved in the shunting of blood were essentially normal portal tributaries within the portal system. In all cases, regardless of the shunt type, the abnormal communication (shunt) between the portal system and the systemic venous system was via the left gastric vein. Results of preoperative CTA, recorded IOMP and direct gross observations at the time of surgery indicated that blood flow through many of the vessels making up the shunt was in an abnormal hepatofugal direction. Preoperative CTA and intraoperative gross examination of these vessels showed no evidence of venous valves within the left gastric vein and its tributaries; there was a complete lack of any nodular dilatations, a finding associated with the presence of a vein valve within the peripheral venous system.

Hypothesis

Using these findings, we postulate a potential role for the presence of portal venous valves and preferential venous blood flow in the development of common EHPSSs:

- The presence of portal vein valves within a portal tributary vein would dictate the direction of blood flow within that tributary vessel
- The presence of portal vein valves would induce predominantly hepatopetal blood flow within the associated portal tributary vessel.

- The absence of portal vein valves would allow both hepatopetal and hepatofugal blood flow within the associated portal tributary vessel.
- The distribution of portal vein valves within the portal tributary veins would therefore dictate which vessels were capable of showing predominantly hepatopetal blood flow or those which could show both hepatopetal and hepatofugal blood flow.
- The presence of a communication between a branch of the left gastric vein and a systemic vein (CVC, azygos or left phrenic vein) would allow for an abnormal venous blood flow due to a change in the venous pressure gradient within the portal system.
- If the combination of an aberrant communication between a branch of the left gastric vein and a systemic vein, and a lack of venous valves in this vessel and its tributaries, were present in the same individual then there would be the potential for an abnormal venous pressure gradient leading to the development of hepatofugal flow towards the abnormal communication (shunt).
- This new, preferential blood flow (including an increased, abnormal volume) would lead to the distension/dilatation of the ‘shunting’ vessels.
- The presence and distribution of venous valves would determine in which of the tributary portal vessels this abnormal ‘preferential’ blood flow would develop.
- Since this preferential flow was predominantly through an essentially normal vasculature, the distribution of venous valves and the predictable sites of communication (shunt) between the left gastric vein and a systemic vein would result in the development of a defined number of specific types of congenital PSS.

Online systematic literature review

The online literature search using PubMed Central® found nine publications which provided a detailed description EHPSS anatomy in the dog and the cat beyond that of simply *porto-caval*, *porto-phrenic* or *porto-azygos* (Seguin *et al.* 1999, Szatmári *et al.* 2004a, Nelson & Nelson 2011, White & Parry 2013, Kraun *et al.* 2014, Fukushima *et al.* 2014, White & Parry 2015, 2016a, 2016b). In total, these publications described 520 EHPSSs. Of the 50 dogs and 10 cats which met the inclusion criteria of the initial part of this current study, 41 dogs and 7 cats were also included in the online literature search from previously published studies by the authors (White & Parry 2013, 2015, 2016a).

Eleven of the shunts found from the literature search were described as either porto-caval (n = 5) or porto-azygos (n = 6) and were, therefore, excluded from further analysis. Of the remaining 509 shunts, 470 were described in the dog and 39 in the cat. Of the 470 described in the dog, the following shunt types were defined; 160 spleno-caval, 105 left gastro-phrenic, 100 shunts involving the right gastric vein and CVC, 75 left gastro-azygos, 10 left gastro-caval, 10 left colic vein, 6 right gastro-phrenic, 3 right gastro-azygos (type Aiv) and 1 complex spleno-phrenic and azygos. Only a single publication classified shunts involving the right gastric vein and the CVC (so-called right gastro-caval shunts) into their more detailed further subdivisions of type Ai (n = 4), Aii (n = 12) and Aiii (n = 4) and type B (n = 2) (White & Parry 2015). Rather than exclude these shunts (n = 78) due to the weakness of their classification, it was considered appropriate to include them because, in total, they represented a significant number of the extrahepatic shunts described. In the dog, therefore, four distinct shunts were responsible for 94% of the shunt types described; spleno-caval (34%), left gastro-phrenic (22%), shunts involving the right gastric vein and CVC (21%) and left gastro-azygos (16%). Similarly, of the 39 described in the cat, the following shunt types were defined; 19 left gastro-phrenic, 9 left gastro-caval, 8 spleno-caval, and 3 left colic vein. In the cat, therefore, three distinct shunts accounted for 92% of the shunt types described; left gastro-phrenic (49%), left gastro-caval (23%) and spleno-caval (20%).

Postulated role of preferential flow in the development of the four most commonly reported extrahepatic shunt types

The following diagrams show our postulated role of preferential venous flow within the portal system in the development of the four most commonly reported extrahepatic shunts types defined from both the current study and the online literature search (Seguin *et al.* 1999, Szatmári *et al.* 2004, Nelson & Nelson 2011, White & Parry 2013, Kraun *et al.* 2014, Fukushima *et al.* 2014, White & Parry 2015, 2016a,). Figure 1 shows a diagram of a normal portal vasculature with normal hepatopetal portal blood flow for cross-reference.

The left gastro-phrenic shunt (Figures 2A-E)

Figure 2A shows the communication (shunt) between the left gastric vein and the left phrenic vein. Figure 2B shows the affect that such a shunt has on the portal blood flow by creating preferential hepatofugal blood flow within a number of the portal tributary vessels. Figure 2C shows the affect that this preferential blood flow has on the distension/dilatation of the ‘shunting’ vessels. Figure 2D shows the resultant classic left gastro-phrenic shunt type produced by such preferential blood flow. Figure 2E shows an example IOMP of a left gastro-phrenic EHPSS in a six-month-old female Irish Setter. This IOMP also shows the presence of concurrent hepatic portal arborisation.

Shunts involving the right gastric vein and CVC – types Ai, Aii, Aiii and B (Figures 3A-E)

The development of the type Aii shunt is used as an exemplar. Figure 3A shows the communication (shunt) between the left gastric vein and the pre-hepatic CVC. Figures 3B-D show the affect that such a shunt and a certain configuration of portal venous valves has on the creation of preferential hepatofugal blood flow, the distension/dilatation of the 'shunting' vessels and the resultant development of the type Aii shunt involving the right gastric vein. Figure 3E shows an example IOMP of this type of shunt in a 13-month-old female Shetland sheepdog.

The spleno-caval shunt (Figures 4A-E)

Figure 4A shows the communication (shunt) between the left gastric vein and the pre-hepatic CVC (it should be noted that this is the same site of communication as described for shunt involving the right gastric vein). Figures 4B-D show the affect that such a shunt and an alternative configuration of venous valves has on the creation of preferential hepatofugal blood flow, the distension/dilatation of the 'shunting' vessels and the resultant development of the classic spleno-caval shunt. Figure 4E shows an example IOMP of a spleno-caval EHPSS in an 11-month-old male Cairn terrier.

The left gastro-azygos shunt (Figures 5A-D)

Figure 5A shows the communication (shunt) between the left gastric vein and the azygos vein. Figures 5B-C show the affect that such a shunt has on the creation of preferential hepatofugal blood flow, the distension/dilatation of the 'shunting' vessels and the resultant development of the classic left gastro-azygos shunt. Figure 5D shows an example IOMP of a left gastro-azygos

EHPSS in a one-year-two-month-old entire male crossbred. This IOMP also shows the presence of concurrent hepatic portal arborisation.

DISCUSSION

Our proposed hypothesis for the role of preferential portal blood flow in the development of congenital EHPSSs is dependent on a number of suppositions. These, along with their supportive evidence, are as follows.

1) The presence and variable distribution of venous valves within the portal system of the dog and the cat.

Standard and classic references for dog and cat anatomy either fail to describe (Schummer *et al.* 1981, Dyce *et al.* 2010), or so poorly describe (Getty 1975, Bezuidenhout 2013), the presence of valves in the portal system that most investigators assume that this system is valveless. In fact, this is not the case and the occurrence and distribution of valves within the portal system of the adult dog has been described previously using corrosion casting, gross observations and histology (Dawson *et al.* 1988). This study demonstrated the presence of bicuspid valves in almost every tributary vessel draining a splenic segment although the splenic vein itself demonstrated a complete lack of valves in all specimens examined (Dawson *et al.* 1988). The study, unfortunately, did not describe the presence or distribution of valves within either the left or right gastric veins. Regardless, the study concluded that valves within the portal system were relatively common, being most abundantly found in veins closest the organ they drained and at the confluence of two or more veins. The study also concluded that the actual distribution of valves was highly inconsistent between individuals (Dawson *et al.* 1988). In adult humans, it is concluded that the portal vein and its tributaries have no valves, although in the foetus, and for a short postnatal period, valves are demonstrable in the tributaries, usually atrophying but occasionally persisting in a degenerate form (Okudaira 1991, Gabella 1995). There appear to be no studies available regarding the presence of valves within the portal system of the puppy or the cat (both adult or kitten). In respect of the mode of development of EHPSSs, it would be interesting to know if portal venous valves existed in the puppy or kitten and, if they did, whether the structures persisted into adult life or whether they were age-dependent, atrophying in a similar fashion to that of man. Furthermore, if venous valves do exist in puppies and kittens, are there differences in their presence and distribution in individuals with or without congenital EHPSSs. Further studies are required to investigate these issues and what relationship they might have to the development of congenital EHPSSs in dogs and cats.

2) The possibility of hepatofugal blood flow within valveless portions of the portal tributary vessels in the dog and the cat.

Hepatofugal portal blood flow is well recognized in both the dog and the cat and is commonly demonstrated in individuals suffering from arterioportal fistulae, portal hypertension and congenital EHPSSs (Lamb 1996, Wachsberg *et al.* 2002, Szatmári *et al.* 2004b, Szatmári *et al.* 2004c, Szatmári & Rothuizen 2006). Despite a significant number of reports describing hepatofugal portal blood flow, there appear to be no studies discussing a relationship between such a blood flow and the presence or absence of portal venous valves. Presumably, this is because imaging of vessels showing hepatofugal blood flow consistently fails to demonstrate the presence of venous valves within such affected veins.

3) The anatomy of the portal vasculature in dogs and cats with congenital EHPSSs is essentially normal apart from the anomalous connection (shunt) between the portal venous system and the systemic venous system.

A number of recent studies involving the use of CTA to accurately characterize the anatomy of the portal vasculature have concluded that in the four most common EHPSS types seen the veins involved in the portosystemic shunting were essentially normal vessels within the portal venous system (Nelson & Nelson 2011, White & Parry 2013, Fukushima *et al.* 2014, White & Parry 2015, 2016a). The shunt was represented by a connection between a portion of one of these normal portal vessels and an adjacent systemic vein (White & Parry 2013, 2015, 2016a). For example, a number of consistent and defined shunt types involving the right gastric vein have been described; type Ai, Aii, Aiii, Aiv and type B (Nelson & Nelson 2011, White & Parry 2015). In each case, the basic normal portal vasculature is present and, in three types (Ai, Aii and Aiii), the site of connection (shunt) between this portal vasculature and systemic vasculature is the same. As such, it might be expected that these shunts should have the same morphology. This is clearly not the case and we hypothesise that it might be the presence (or absence) and the position of any portal tributary venous valves that dictates the formation of preferential blood flow leading to the development of a relatively small number of consistent and reproducible shunt types involving blood flow through the right gastric vein (White & Parry 2015).

4) In the most commonly observed congenital EHPSSs, the formation of the abnormal communication (shunt) between the portal circulation and the systemic circulation involves only the left gastric vein.

Recent studies using CTA, IOMP and gross findings at the time of surgery have also concluded that in the four most common EHPSS types seen the abnormal communication (shunt) between the portal system and the systemic venous system was through the left gastric vein (White & Parry 2013, 2015, 2016a). This conclusion is also supported by the portosystemic shunt morphology data published by Nelson and Nelson (2011) and Fukushima *et al.* (2014).

5) The abnormal communication between the portal vessel (left gastric vein) and the systemic venous system only occurs between vessels that are adjacent embryologically.

The embryological development of extrahepatic portosystemic shunts remains poorly described in the veterinary literature (Noden & de Lahunta 1985, Payne *et al.* 1990, Hunt *et al.* 1998). The portal vein, of which the left gastric vein is part, develops from the vitelline system. The abdominal CVC, although ultimately a single continuous vessel, develops in five segments (pre-renal, renal, prehepatic, hepatic and posthepatic) from initially discontinuous portions of the supracardinal, subcardinal and vitelline veins (Marks 1969, Hunt *et al.* 1998). The prehepatic CVC (subcardinal system) is programmed to anastomose with the hepatic CVC (vitelline system). An inappropriate anastomosis between the prehepatic CVC and the portal vein (left gastric vein) is considered unsurprising because of the predisposition of the prehepatic CVC to anastomose with veins of the vitelline system (Payne *et al.* 1990, Hunt *et al.* 1998). Embryologically, the mechanism for development of a shunt between the portal vein and the azygos vein (supracardinal system) remains less clear; the supracardinal and vitelline systems are not programmed to anastomose during the development of the embryo (Marks 1969). Similarly, there is no clear embryologically mechanism for the development of the left gastro-phrenic shunt. Presumably, it would be reasonable to conclude that an inappropriate connection between the left gastric vein and the phrenic or azygos veins was at least in some part related to their anatomical proximity within the embryo.

6) If the hypothesis is correct then there should only be a defined number of discrete congenital EHPSSs that are actually observed in affected dogs and cats.

Reviewing the majority of published literature describing EHPSSs in both dogs and cats confirms the limited classification to either porto-caval or porto-azygos in the majority of reports. Reasons for this lack of detailed description relate predominantly to the method by which the shunt was imaged. Additional recent studies utilizing more robust methods of shunt imaging (for example, CTA and examination of corrosion casts made *post mortem*) have confirmed that the morphology of the majority of congenital EHPSSs fit a defined number of discrete anatomical conformations (Seguin *et al.* 1999, Szatmári *et al.* 2004a, Nelson & Nelson 2011, White & Parry 2013, Kraun *et al.* 2014, Fukushima *et al.* 2014, White & Parry 2015, 2016a, 2016b). In the dog, it appears that four distinct shunts types (spleno-caval, left gastro-phrenic, right gastro-caval and left gastro-azygos) are responsible for 94% of EHPSSs described. Similarly, in the cat, three distinct shunts types (spleno-caval, left gastro-phrenic and left gastro-caval) appear to be responsible for 92% of EHPSSs described.

Although the current study has concentrated on the four most commonly recognized EHPSSs, a further five shunt types (left gastro-caval, left colic vein, right gastro-phrenic, right gastro-azygos and complex spleno-phrenic and azygos) that involved 30 individuals were described specifically in the published literature. Future studies will aim to test our hypothesis on these less common but no less relevant shunt types.

We conclude that in dogs and cats with an abnormal communication (shunt) between the left gastric vein (or one of its tributaries) and a systemic vein, it might be the presence or absence of venous valves that dictates the development of preferential venous blood flow and the subsequent formation of one of a number of specific and defined EHPSSs. Such EHPSSs develop from what is essentially a normal portal vasculature.

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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