

## Portal Hypertension: Pathophysiology, Diagnosis, and Treatment

S. Buob, A.N. Johnston, and C.R.L. Webster

Portal hypertension (PH) is the result of increased vascular resistance in the portal circulation, increased portal venous blood flow, or both. In veterinary medicine, where portal pressure is seldom measured directly, the diagnosis of PH often is inferred from identification of associated complications including multiple acquired portosystemic shunts, ascites, and hepatic encephalopathy. Likewise, treatment of PH primarily is aimed at controlling these complications. The goal of this review is to provide an update on the pathophysiology, diagnosis, and treatment of PH. The review draws from information in the veterinary hepatology literature, reviews, and consensus statements in human hepatology and the literature on experimental models of PH.

**Key words:** Ascites; Cirrhosis; Hepatic disease; Portosystemic shunts.

Portal hypertension (PH) is caused by increased resistance, increased blood flow, or both in the portal circulation. The clinical consequences of PH, which include the development of multiple acquired portosystemic shunts (MAPSS), ascites, hepatic encephalopathy (HE), or some combination of these, cause significant morbidity and mortality.<sup>1–3</sup> Reviews of PH appeared in the veterinary literature in the 1980s, which the interested reader is encouraged to consult.<sup>4–6</sup>

### Anatomy and Physiology of Hepatic Blood Flow

The liver receives approximately 25% of the cardiac output through a dual vascular supply. The portal venous circulation provides 75–80% of the blood supply through a low pressure system.<sup>6–8</sup> The hepatic artery delivers the rest of the blood supply.<sup>9</sup> Blood from the portal vein and hepatic artery enter the hepatic lobule at the portal triad and mix together in the hepatic sinusoids (Fig 1). Because sinusoidal endothelial cells (SEC) have large fenestrae and lack a basement membrane, the sinusoids are considered a “leaky” capillary bed. After passing through the hepatic cords, sinusoidal blood drains into the hepatic central vein and then out of the liver through the hepatic veins, eventually reaching the caudal vena cava for return to the right atrium (Fig 1).

In accordance with Ohm’s law:  $P$  (pressure) =  $Q$  (blood flow)  $\times$   $R$  (resistance), portal vein pressure (PVP) is equal to the product of portal blood flow (PBF) and the resistance to that flow (intrahepatic venous resistance [IHVR]):  $PVP = PBF \times IHVR$ .<sup>4,10–13</sup> The PVP can be measured directly or indirectly. Direct measurement is obtained by catheterization of the portal vein or one of

### Abbreviations:

|       |   |
|-------|---|
| ADH   | antidiuretic hormone                          |
| CPSS  | congenital portosystemic shunts               |
| CT    | contrast-enhanced helical computed tomography |
| FHVP  | free hepatic venous pressure                  |
| HE    | hepatic encephalopathy                        |
| HVPG  | hepatic venous portal pressure gradient       |
| IHVR  | intrahepatic venous resistance                |
| MAPSS | multiple acquired portosystemic shunts        |
| NCPH  | noncirrhotic portal hypertension              |
| NO    | nitric oxide                                  |
| NOS   | nitric oxide synthase                         |
| PBF   | portal blood flow                             |
| PH    | portal hypertension                           |
| PHPV  | primary hypoplasia of the portal vein         |
| PVP   | portal vein pressure                          |
| SEC   | sinusoidal endothelial cell                   |
| WHVP  | wedged hepatic venous pressure                |

its tributaries and insertion of a manometer (cmH<sub>2</sub>O) or pressure transducer (mmHg). A considerable body of data exists on the direct measurement of PVP in dogs and cats in both the experimental literature and in reports on surgical attenuation of congenital portosystemic shunts (CPSS).<sup>4,5,14–42</sup> In experimental studies in healthy, anesthetized dogs, PVP averages  $8.24 \pm 0.72$  mmHg (multiply by 1.36 to convert to cmH<sub>2</sub>O), with a mean of  $5.98 \pm 1.99$  mmHg in clinical reports. In experimental studies in anesthetized cats, PVP is  $8.9 \pm 0.35$  mmHg with a mean of  $7.38 \pm 2.7$  mmHg in the literature on portosystemic shunts. The variability in normal PVP reflects the effects of different anesthetic protocols as well as lack of standardization of the baseline zero value, which can be set at the right atrium, liver hilus, or vena cava.

In humans, indirect measurement of PVP is obtained by angiographic balloon catheterization.<sup>43</sup> A balloon-tipped catheter is inserted into the jugular or femoral vein and advanced with fluoroscopic guidance into the hepatic vein where measurement of the free hepatic vein pressure (FHVP) is taken (Fig 1). This measurement approximates pressure in the caudal vena cava. The balloon is inflated to occlude the hepatic vein, and the wedged hepatic vein pressure (WHVP) is measured. The WHVP is equivalent to sinusoidal pressure, which approximates PVP. A slight pressure gradient exists between the sinusoids (WHVP) and the caudal vena cava and hepatic vein

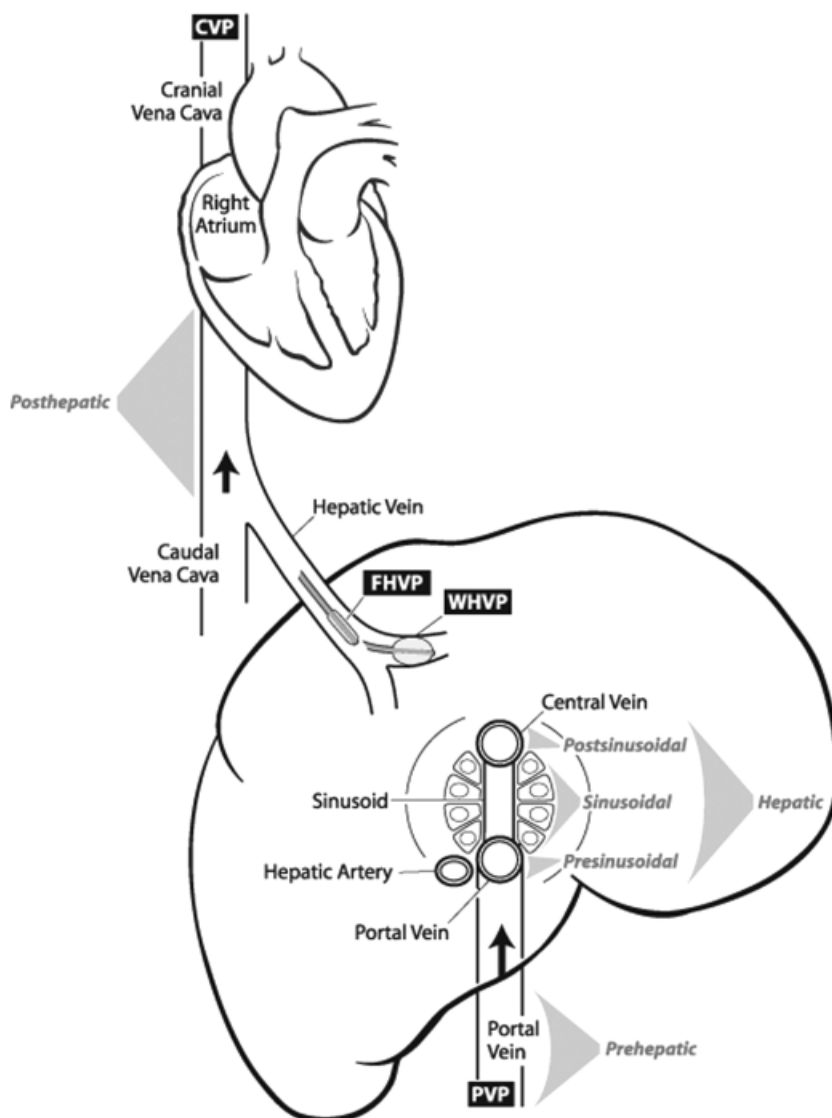
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**Fig 1.** Schematic representation of the anatomic classification of portal hypertension (PH). Portal hypertension can be because of prehepatic, intrahepatic (presinusoidal, sinusoidal or postsinusoidal) and posthepatic causes. Indirect evaluation of portal venous pressure (PVP) can be obtained by catheterization of the caudal vena cava and advancement of the catheter into the hepatic veins. This permits measurement of the free hepatic vein pressure (FHVP), which reflects caudal vena cava pressure. Measurement of the wedged hepatic vein pressure (WHVP) is accomplished by occluding the hepatic vein by inflation of the catheter balloon. WHVP is a measure of sinusoidal pressure which in the normal state is slightly lower (about 1 mmHg) than PVP. The hepatic venous pressure gradient (HVPG) is calculated as the difference between the WHVP and FHVP. This gradient is increased with intrahepatic sinusoidal and postsinusoidal PH, but not with prehepatic and presinusoidal intrahepatic PH (where both WHVP and FHVP are usually normal) or with posthepatic PH (where WHVP, FHVP and central venous pressure, CVP, are elevated).

(FHVP). This difference (WHVP–FHVP), the so-called hepatic venous pressure gradient (HVPG), provides the driving force for hepatopedal blood flow.<sup>10–13,43</sup>

Normal values for HVPG in humans are between 1 and 5 mmHg. Limited data in the dog and cat suggest that normal HVPG values are similar to those reported in humans.<sup>16,43,44</sup> The normal FHVP and WHVP reported in a series of 11 normal dogs was  $1.9 \pm 1.0$  and  $5.6 \pm 1.2$  mmHg, respectively, resulting in a HVPG of  $3.7 \pm 1.4$  mmHg.<sup>16</sup> In a limited number of cats, FHVP and WHVP were reported as  $1.5 \pm 0.7$  and  $6.9 \pm 1.7$  mmHg, respectively, with a calculated HVPG of 5.4 mmHg.<sup>16</sup> In

humans, increases ( $> 12$  mmHg) in HVPG directly correlate with the clinical consequences of PH in cirrhotic patients.<sup>10–13,43</sup> In addition, the success of treatment for PH is defined either by a  $> 20\%$  decrease in HVPG or reduction to  $< 12$  mmHg.<sup>10–13,43</sup>

Indirect measurement of PVP also can be obtained by catheterization of the splenic pulp. Normal splenic pulp values in veterinary patients appear to be 0.5–1.5 mmHg greater than those obtained by direct measurement.<sup>16</sup>

As direct or indirect measurement of PVP seldom is performed in veterinary medicine, the presence of PH most often is inferred by detection of late-stage clinical

consequences (eg, ascites, MAPSS, HE) on physical examination or imaging studies or by assessment of portal vein hemodynamics with Doppler ultrasound.<sup>45</sup>

In the normal liver, PVP is remarkably stable despite changes in PBF.<sup>10-13</sup> A large sinusoidal reserve and adaptive responses in the intrahepatic vasculature contribute to a compliant vascular bed that can increase its volume considerably to accommodate additional PBF without changes in pressure. Increased PBF stimulates SEC's to release nitric oxide (NO), which dilates intrahepatic vessels to accommodate a larger blood volume.<sup>10-13</sup>

Several factors cause minor fluctuations in the PVP. Lower PVP occurs during anesthesia, inspiration, fasting, and exercise. Transient increases develop postprandially, during expiration, by increases in intra-abdominal pressure (such as during barking or defecation), after blood volume expansion and after the injection of angiographic agents.<sup>4,15,46</sup>

### Classification of PH

PH is classified based on anatomical location as prehepatic, intrahepatic, or posthepatic (Table 1).<sup>4,10-13</sup> Prehepatic PH is because of increased resistance in the extrahepatic portal vein and is associated with mural or intraluminal obstruction (eg, congenital atresia or fibrosis, thrombosis, neoplasia) or extraluminal compression.<sup>4,5,8,47-52</sup> Hepatic arteriovenous fistulas cause prehepatic PH as arterial blood floods the portal venous system.<sup>8,53-55</sup> These fistulas usually are congenital, but may develop secondary to surgery, trauma, or neoplastic vascular erosion. Prehepatic PH also may occur as a complication of CPSS attenuation.<sup>7</sup>

Intrahepatic PH is because of increased resistance in the microscopic portal vein tributaries, sinusoids, or small hepatic veins. Intrahepatic PH is further classified by histological criteria into presinusoidal, sinusoidal, and postsinusoidal PH (Table 1, Fig 1). Presinusoidal PH occurs because of increased resistance in the terminal

intrahepatic portal vein tributaries.<sup>48,51,56-63</sup> In humans, the most common cause is noncirrhotic portal hypertension (NCPH) (also called hepatoportal sclerosis and idiopathic portal hypertension).<sup>56</sup> Similar clinical syndromes called NCPH, primary hypoplasia of the portal vein (PHPV), idiopathic hepatic fibrosis, and hepatoportal fibrosis have been reported in dogs.<sup>57-64</sup> Fibropolycystic liver disorders, such as congenital hepatic fibrosis and Caroli's disease, also can cause presinusoidal PH in dogs and cats.<sup>64-68</sup> These developmental disorders because of the persistence of embryonic duct structures are referred to as ductal plate malformations. They lead to varying degrees of bile duct pathology and portal fibrosis. When the latter is severe, PH can occur. A rare cause of prehepatic PH occurs in dogs with trematode infestations (*Schistosoma japonicum* and *Heterobilharzia americana*).<sup>8,69</sup> Increased resistance to flow is because of granulomatous inflammation in the portal veins triggered by trematode eggs.

Sinusoidal intrahepatic PH most often is the result of fibrotic hepatopathies.<sup>70,71</sup> In these disorders, SEC's lose their fenestrae and acquire a collagenous basement membrane (capillarization of the sinusoids) increasing IHVR. In addition, lobular fibrosis and the presence of regenerative nodules contribute to the obliteration and distortion of the sinusoids further increasing IHVR. Although not typical, canine nodular hyperplasia, a common idiopathic lesion in old dogs, also may distort the sinusoids leading to PH.<sup>58,72,73</sup>

Postsinusoidal intrahepatic PH is associated with veno-occlusive disease (also called sinusoidal obstruction syndrome). Veno-occlusive disease is caused by damage to the sinusoidal endothelium and hepatocytes in the centrilobular region, resulting in obliteration of the small terminal hepatic veins and central veins by fibrosis. It has been associated with toxins, graft-versus-host disease and chemotherapy agents in humans, and been reported as an idiopathic condition in veterinary patients.<sup>74-78</sup>

**Table 1.** Classification of portal hypertension.

| Prehepatic (Portal Vein)       | Intrahepatic (Liver)  | Posthepatic (Heart, CVC, Hepatic Veins)  |
|--------------------------------|---|--|
| Congenital portal vein atresia | Presinusoidal   | Right heart failure  |
| Intraluminal obstruction       | Primary hypoplasia portal vein (noncirrhotic portal hypertension) | Congestive   |
| Thrombus                       | Chronic cholangitis   | Pericardial tamponade  |
| Neoplasia                      | Hepatic arteriovenous fistula                                     | Constrictive pericarditis  |
| Stenosis                       | Schistosomiasis   | Intracardiac neoplasia   |
| Extraluminal obstruction       | Nodular hyperplasia   | Congenital cor triatriatum CVC/hepatic vein obstruction (Budd-Chiari syndrome) |
| Neoplasia                      | Ductal plate abnormalities (Caroli's disease)                     | Intraluminal   |
| Lymph node                     | Sinusoidal  | Thrombosis   |
| Granuloma                      | Cirrhosis/chronic hepatitis                                       | Vena cava syndrome   |
| Abscess                        | Chronic cholangiohepatitis  | Neoplasia  |
|                                | Ductal plate abnormalities (Congenital hepatic fibrosis)          | Extraluminal   |
|                                | Lobular dissecting hepatitis                                      | Neoplasia  |
|                                | Postsinusoidal  | Kinking of CVC   |
|                                | Veno-occlusive disease (Sinusoidal obstruction syndrome)          |  |

CVC, caudal vena cava.

Posthepatic PH is associated with obstruction of the larger hepatic veins, the posthepatic caudal vena cava, or right atrium. Obstruction at the right atrium because of right heart failure, pericardial disease, or pulmonary hypertension is a common reason for posthepatic PH in small animals.<sup>79–81</sup> When obstruction occurs in the hepatic venous outflow in the caudal vena cava or larger extrahepatic hepatic veins, it is known as Budd-Chiari syndrome.<sup>74</sup> Budd-Chiari syndrome most often is because of intraluminal (tumor, thrombosis, congenital fibrous webs) or extraluminal (tumor) compression.<sup>44,82–89</sup>

Classification of the site of PH has clinical relevance because the level of obstruction often dictates the clinical presentation (ie, whether MAPSS, ascites, or HE develops), diagnostic evaluation (increases in liver enzyme activities, protein content of ascitic fluid, type of diagnostic imaging), and treatment (Table 2). The impact of PH classification on these variables is discussed next.

### Pathophysiology of PH

PH secondary to prehepatic or posthepatic obstructive, stenotic, or constrictive vascular lesions develops primarily because of increased resistance to flow in the vessels in accordance with Ohm's law. The pathophysiologic mechanisms controlling the development of intrahepatic sinusoidal PH are less intuitive and, despite extensive investigation, not fully understood. An important factor is mechanical obstruction secondary to architectural changes in the liver. These changes include fibrosis, capillarization of the sinusoids, presence of microthrombi in the intrahepatic vasculature, and regenerative nodule formation.<sup>10–13</sup> In addition to mechanical obstruction, dynamic changes in sinusoidal tone contribute to increased IHVR (Fig 2).<sup>10–12</sup> The SECs normally produce vasoactive substances that regulate sinusoidal resistance. These include vasodilatory substances such as NO, carbon monoxide, and prostaglandin E<sub>2</sub>, and vasoconstrictors such as endothelin-1, angiotensin II, leukotrienes, and norepinephrine. In the diseased liver, overproduction of inflammatory mediators and the resultant oxidative stress cause SEC dysfunction, which leads to overproduction and enhanced sensitivity to vasoconstrictors and underproduction of vasodilators. The net result is impaired sinusoidal relaxation.

Vascular NO, the most important vasodilator in the liver, is synthesized in reactions catalyzed by 1 of 2 isoforms of nitric oxide synthase (NOS): endothelial NOS, which stimulates endothelial cell production of NO in response to physical stimuli such as shear stress, and inducible NOS, which is induced by proinflammatory cytokines.<sup>10,11,90</sup> The intrahepatic NO deficiency seen with PH is due primarily to decreased activation of endothelial NOS.<sup>10–13,90,91</sup>

Activation of hepatic stellate cells, which in the unstimulated state are quiescent lipid-storing cells surrounding the sinusoids, also contributes to increased IHVR. During injury, stellate cells differentiate into contractile, fibrogenic myofibroblasts, which produce large amounts of extracellular matrix and secrete inflammatory cytokines and vasoconstrictive substances such as endothelin-1. These vasoconstrictors act in an autocrine

fashion to stimulate stellate cell contraction, which reduces the diameter of the sinusoidal space and increases IHVR.<sup>11,12,90</sup>

Unlike the vasoconstriction seen in the intrahepatic vasculature during PH, the splanchnic vasculature undergoes progressive vasodilatation because of an excess of vasodilatory substances, particularly NO.<sup>11,90,91</sup> The mechanisms responsible for the overproduction of NO include increased vascular shear stress and intestinal absorption of lipopolysaccharide. Increased shear stress activates endothelial NOS. Increased intestinal absorption of lipopolysaccharide secondary to the changes in intestinal permeability that accompany PH stimulates the release of inflammatory cytokines such as tumor necrosis factor- $\alpha$  from the macrophages, which enhances the activity of inducible NOS.<sup>90–92</sup> Other substances that contribute to peripheral vasodilatation include hydrogen sulfide, carbon monoxide, prostaglandins, and endocannabinoids.<sup>11,90</sup> The combined action of all these vasodilatory compounds mediates progressive and sustained vasodilatation of the splanchnic circulation leading to higher PBF, which maintains and aggravates the development of PH (Fig 2).

Recent studies suggest that angiogenesis also contributes to the establishment and maintenance of PH.<sup>11,92</sup> The development of fibrotic septa and capillarization of the hepatic sinusoids results in relative hepatic hypoxia stimulating the release of angiogenic factors from hepatic stellate cells and SEC. These factors, particularly vascular endothelial growth factor and platelet-derived growth factor, stimulate angiogenesis fueling higher PBF and worsening PH.

### Consequences of PH

#### Ascites

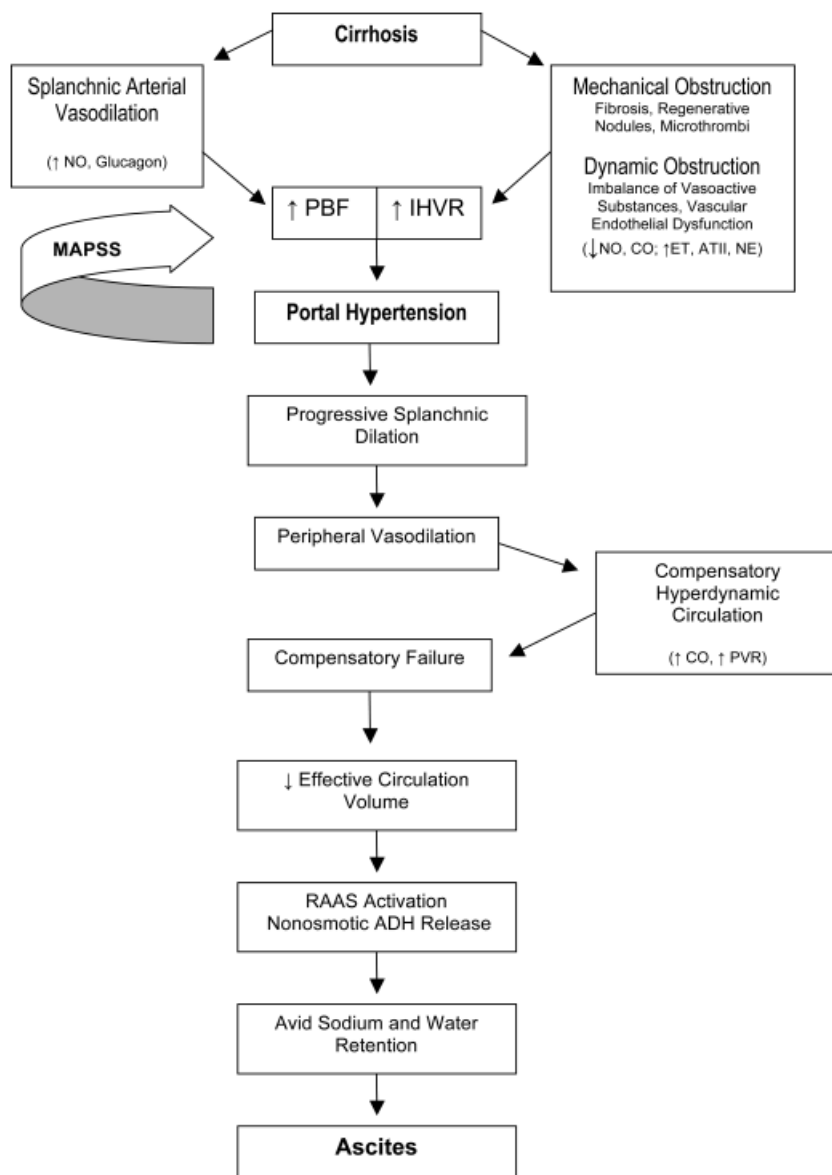
Ascites occurs as a consequence of imbalances in Starling's law so that the forces keeping fluid in the vascular space are less than the forces moving fluid out of the vascular space.<sup>12,13,93,94</sup> In PH, increased PVP drives fluid into the interstitial space. When the capacity of the regional lymphatics is overwhelmed, ascites develops. The development of ascites is perpetuated by the splanchnic vasodilatation that accompanies PH. This vasodilatation results in pooling of blood in the abdomen, which leads to a decrease in effective systemic blood volume (Fig 2). Initially, increased cardiac output is compensatory, establishing the hyperdynamic circulation of hepatic disease marked by high cardiac output and low systemic vascular resistance.<sup>90–94</sup> As liver disease progresses, vasodilators that escape hepatic degradation accumulate in the systemic circulation and systemic arteriolar vasodilatation worsens (Fig 2). Eventually, inotropic and chronotropic compensation fails, and systemic hypotension ensues. This results in activation of the endogenous vasopressor system, including the renin-angiotensin-aldosterone system, sympathetic neurons, and the non-osmotic release of antidiuretic hormone (ADH). Resultant volume expansion further increases hydrostatic pressure in the portal vasculature causing increased lymph

**Table 2.** Clinical assessment of common syndromes associated with portal hypertension.

| Classification   | Physical Exam  | Laboratory Values  | MAPSS | Liver Biopsy: Histopathology   |
|--|--|--|-------|--|
| Prehepatic<br>(PVP- $\uparrow$ , FHVP-N, WHVP-N, HVPG-N)<br>PV atresia   | Young with ascites, HE   | LE: N to mild $\uparrow$<br>Ascites: pure transudate   | ++    | Chronic hypoperfusion  |
| PV obstruction   | Acute onset, abdominal pain, ascites                               |  | $\pm$ | Normal or abnormal with concurrent hepatic disorder  |
| Intrahepatic<br><i>Presinusoidal</i><br>(PVP- $\uparrow$ , FHVP-N, WHVP-N, HVPG-N)<br>Hepatic arteriovenous fistula  | Young with ascites, HE, bruit                                      | LE: N to mild $\uparrow$<br>Ascites: low-protein transudate  | $\pm$ | Chronic hypoperfusion  |
| Primary hypoplasia of the portal vein/<br>noncirrhotic portal hypertension   | Young adult with ascites, GI signs, HE,<br>$\pm$ icterus           | LE: moderate $\uparrow$<br>Coagulopathy<br>$\pm$ $\uparrow$ bilirubin<br>Ascites: low-protein transudate                               | $\pm$ | Chronic hypoperfusion $\pm$ $\uparrow$ periportal fibrosis; no inflammation or nodular hyperplasia   |
| Ductal plate abnormalities<br>(Caroli's syndrome)  | Young with ascites, GI signs, PU/PD                                | LE: moderate $\uparrow$<br>Ascites: low-protein transudate<br>$\pm$ renal cysts  | $\pm$ | Numerous irregular bile ducts localized along the edge of limiting plate; portal fibrosis, no inflammation, or regenerative nodules                              |
| <i>Sinusoidal</i><br>(PVP- $\uparrow$ , FHVP-N, WHVP- $\uparrow$ , HVPG- $\uparrow$ )<br>Inflammatory/fibrotic   | Ascites, HE, GI signs, PU/PD $\pm$ icterus,<br>Breed predilections |  | ++    | Inflammation/necrosis/apoptosis, fibrosis, $\pm$ regenerative nodules  |
| Lobular dissecting hepatitis   | Young to middle age dog, ascites<br>HE, GI signs<br>$\pm$ icteric  | LE: mild to marked $\uparrow$<br>$\pm$ $\uparrow$ serum bilirubin<br>Coagulopathy<br>Ascites: pure or modified transudate <sup>a</sup> | ++    | Parenchymal inflammation, infiltration of lobular reticulin and collagen fibers  |
| Ductal plate abnormalities<br>(congenital hepatic fibrosis)  | Young with ascites, HE, GI signs                                   |  | +     | As in Caroli's above, but extensive panlobular fibrosis, mild degree of portal vasculature hypoplasia and arteriolar proliferation<br>$\pm$ renal cysts/fibrosis |
| <i>Postsinusoidal</i><br>(PVP- $\uparrow$ , FHVP- $\uparrow$ , WHVP- $\uparrow$ , $\pm$ HVPG- $\uparrow$ )<br>Veno-occlusive disease (sinusoidal obstruction syndrome) | Ascites, HE, GI signs,   | LE: N to mild $\uparrow$<br>Ascites: high protein modified transudate  | ++    | $\pm$ Centrilobular fibrosis, intra/extraluminal HV compression, $\pm$ thrombosis, $\pm$ dilated centrilobular lymphatics/vasculature                            |
| Posthepatic<br>(PVP- $\uparrow$ , FHVP- $\uparrow$ , WHVP- $\uparrow$ )<br>Cardiac (CVP $\uparrow$ HVPG-N)   | Ascites, edema, jugular distension, murmur,<br>arrhythmia          | LE: N to mild $\uparrow$<br>Ascites: high protein modified transudate  | -     | Hepatic congestion, dilated centrilobular lymphatics/vasculature   |
| Budd-Chiari (CVC or HV) ( $\pm$ HVPG- $\uparrow$ )   | Ascites  |  | ++    |  |

CrVC, cranial vena cava; CVC, caudal vena cava; CVP, central venous pressure; FHVP, free hepatic venous pressure; GI, gastrointestinal; HE, hepatic encephalopathy; HV, hepatic veins; HVPG, hepatic venous pressure gradient; LE, liver enzymes; N, normal; PVP, portal venous pressure; PU/PD, polyuria/polydipsia; WHVP, wedged hepatic venous pressure; " $\pm$ ", always present; " $+$ ", typically present; " $\pm$ ", variably present; " $-$ ", not present.

<sup>a</sup>Protein content of ascites because of intrahepatic *sinusoidal* PH is dependent on the presence or absence of sinusoidal capillarization.



**Fig 2.** Pathophysiology of intrahepatic sinusoidal portal hypertension and ascites formation in cirrhosis. Increases in the intrahepatic vascular resistance (IHVR) occur because of mechanical (fibrosis in the sinusoids, microthrombi in hepatic veins, and regenerative nodule formation) and dynamic (failure of sinusoidal relaxation) obstructive processes within the liver. At the same time, the splanchnic circulation undergoes progressive vasodilatation, leading to increases in portal blood flow (PBF) that further increase portal vein pressure. Systemic compensation for the splanchnic arterial vasodilation creates a hyperdynamic circulation marked by increased cardiac output (CO) and decreased peripheral vascular resistance (PVR). Progressive splanchnic vasodilatation, however, leads to eventual failure of this circulatory response and development of systemic vasodilatation and hypotension. This decrease in effective circulatory blood volume leads to activation of the renin-angiotensin-aldosterone-sympathetic system (RAAS) and the nonosmotic release of antidiuretic hormone (ADH). This leads to avid renal sodium and water retention creating a volume overload and the development of ascites. ATII, angiotensin II; CO, carbon monoxide; ET, endothelin; NE, norepinephrine; NO, nitric oxide.

formation.<sup>93,94</sup> Concurrent hypoalbuminemia secondary to hepatic synthetic failure lowers vascular colloid osmotic pressure that further aggravates ascites formation.<sup>94</sup> The presence of ascites is a negative prognostic factor in dogs with chronic hepatitis.<sup>1</sup>

#### *Acquired Portosystemic Shunts*

As the HVPG increases above 12 mmHg, MAPSS develop from the opening of embryonic vessels between the

portal vasculature and the cranial and caudal vena cava. Initially, blood flow through MAPSS may lower PVP, but parallel increases in PBF because of splanchnic vasodilatation eventually restore PH. In experimental canine models of PH, MAPSS form over a period of 5–14 weeks.<sup>95,96</sup> Although MAPSS form primarily because of pressure gradients, there also is evidence that angiogenic factors contribute to their formation and maintenance.<sup>92</sup> All forms of PH can be accompanied by MAPSS with the exception being posthepatic PH in which no pressure

gradient exists between the portal and systemic circulation (ie, HVPG is normal, Table 2).

Acquired shunts are classified based on anatomic location. Portal precaval shunts connect the portal vein with the caudal vena cava either directly or by way of the azygous vein, whereas portal postcaval shunts connect the portal vasculature to the cranial vena cava. In humans, a common site for precaval MAPSS is between the portal vein and submucosal esophageal vessels.<sup>97</sup> These shunts, called esophageal varices, are prone to rupture and bleeding and are an important cause of morbidity in humans with PH. Esophageal varices form in the dog and cat, but are rarely of clinical relevance.<sup>98–100</sup> Most MAPSS in small animals are portal postcaval shunts. In dogs, large velar-omental shunts arise from the splenic vein, anastomose with embryonic connections to the left gonadal veins and empty into the left renal vein and ultimately the caudal vena cava.<sup>4,5,8,100</sup> In dogs, smaller portal collateral vessels develop and are classified by their location and drainage patterns as left gastric, gastrophrenic, omental, gallbladder, abdominal wall duodenal, and colic varices.<sup>4,5,100</sup> Cats tend to develop shunts between the left gastric veins and phrenicoabdominal veins and from the left colic vein to the left gonadal vein.<sup>4,5,8</sup>

### **HE**

HE is a syndrome of neurocognitive impairment that clinically is manifested as a range of signs from subtle behavioral deficits to stupor and coma.<sup>101–103</sup> The pathogenesis is multifactorial, and associated with toxins derived from the gastrointestinal tract that bypass hepatic metabolism. Ammonia derived primarily from the action of colonic bacterial on the breakdown products of ingested protein is one of the most important toxins. Ammonia, which normally is transported to the liver via the portal circulation where it is metabolized in the urea cycle, directly enters the systemic circulation through MAPSS. The excess blood ammonia penetrates the blood brain barrier and causes neuronal dysfunction by incompletely understood mechanisms. Current evidence supports a central role of ammonia-induced astrocyte dysfunction.<sup>101–103</sup> Astrocytes, which are the only cells in the brain that express glutamine synthetase, detoxify brain ammonia with this enzyme to catalyze the conversion of glutamate to glutamine. The intracytoplasmic accumulation of osmotically active glutamine results in low-grade astrocyte swelling and subsequent induction of signaling pathways that lead to the formation of reactive oxygen species. This results in astrocyte dysfunction and altered neurotransmission.<sup>103</sup>

### **Hyponatremia**

The same forces that promote ascites formation can lead to development of dilutional (hypervolemic) hyponatremia.<sup>93,104</sup> Nonosmotic release of ADH, in response to decreased effective blood volume secondary to peripheral vasodilatation, acts on water channels in the renal tubules to promote water retention. This action eventually leads to a deficit in free water excretion and results in

hyponatremia. In human patients with cirrhosis, the development of hyponatremia is a marker of late stage disease and a negative prognostic indicator.<sup>93,104</sup>

### **Hepatorenal Syndrome**

Another consequence of the hyperdynamic circulatory derangements associated with PH is hepatorenal syndrome. This syndrome, a form of reversible renal failure, occurs as a consequence of profound renal vasoconstriction secondary to the release of angiotensin, norepinephrine, and ADH in response to splanchnic vasodilatation.<sup>105,106</sup> Although hepatorenal syndrome can be induced in experimental canine models,<sup>107,108</sup> it has not been reported clinically in veterinary patients. In humans, the syndrome is always accompanied by a state of refractory ascites and end-stage liver failure.<sup>11–13,105,106</sup>

### **Hepatopulmonary Syndrome, Portopulmonary Syndrome, and Hepatic Hydrothorax**

Hepatopulmonary syndrome, portopulmonary hypertension, and hepatic hydrothorax are pulmonary complications of PH in humans that have not been reported in veterinary medicine.<sup>109–112</sup> Hepatopulmonary syndrome occurs because of microvascular pulmonary arterial dilatation (most likely because of NO overproduction in the lung) leading to ventilation-perfusion mismatch.<sup>109–111</sup> Portopulmonary hypertension is likely mediated by humoral substances that enter the systemic circulation through MAPSS.<sup>110,112</sup> Initially, these substances cause vasoconstriction, but subsequent thrombosis leads to vessel obliteration. Hepatic hydrothorax is the presence of pleural effusion in patients with hepatobiliary disease. It likely arises because of direct passage of ascites from the abdomen to the thorax through undetectable diaphragmatic rents.<sup>111</sup>

### **Spontaneous Bacterial Peritonitis**

Spontaneous bacterial peritonitis is infection of ascitic fluid without a detectable nidus.<sup>113,114</sup> It occurs in 8–30% of hospitalized cirrhotic human patients with ascites, with an associated mortality of 20–40% if untreated.<sup>113</sup> Many patients are asymptomatic, but clinical signs can include abdominal pain, fever, and diarrhea. A neutrophil count  $>250$  cells/mm<sup>3</sup> in the ascitic fluid is diagnostic, regardless of whether or not organisms are visible cytologically. The pathophysiology of spontaneous bacterial peritonitis is incompletely understood but 4 key components are involved: (1) the presence of small intestinal bacterial overgrowth, (2) increased intestinal permeability, (3) intestinal bacterial translocation, and (4) immunosuppression. Spontaneous bacterial peritonitis occurs in dogs and cats,<sup>115,116</sup> but has not been reported in the setting of PH.

### **Hypersplenism**

Splenomegaly is a rare finding in PH in dogs and cats,<sup>117</sup> but is common in humans with PH and can lead

to hypersplenism.<sup>10–13</sup> Hypersplenism is associated with pooling of blood in the spleen, destruction of blood cells by the enlarged spleen, or both. The clinical consequence is pancytopenia. This syndrome has not been described in dogs or cats with PH, perhaps because of anatomic differences that prevent splenic congestion in these species.<sup>117</sup>

### Portal Hypertensive Gastropathy

In humans, gastric mucosal lesions associated with portal hypertensive gastropathy are present in 51–98% of patients with PH.<sup>118</sup> Histologically, this gastropathy is defined by mucosal and submucosal vascular ectasia in the absence of inflammation. Similar lesions can be found in the small and large bowel. Many factors including alterations in splanchnic blood flow, humoral factors, and local dysregulation of vascular tone have been implicated in the pathophysiology. In humans, portal hypertensive gastropathy increases the risk for acute and chronic gastrointestinal bleeding.<sup>118</sup>

Although the characteristic histologic lesion associated with portal hypertensive gastropathy has not been reported in veterinary patients, dogs and cats with hepatic disease are at increased risk for gastrointestinal ulceration.<sup>59,119,120</sup> In humans with PH, impairment of gastric mucosal defense occurs and is associated with thrombosis of mesenteric vessels because of circulatory stasis, alterations in gastrointestinal motility, bacterial overgrowth because of lack of intestinal bile acids, and mucosal edema because of increases in gastrointestinal mucosal permeability. Overproduction of vasoconstrictors such as endothelin-1, increased generation of free oxygen radicals, or both also have been implicated in the pathophysiology.

## Diagnostic Evaluation of PH

### Clinical Pathology

**CBC.** Microcytosis is seen in dogs with MAPSS. It is not associated with iron deficiency, but rather with a currently unknown defect in mobilization of iron stores.<sup>121,122</sup> Mild thrombocytopenia, anemia, or both maybe seen in some dogs with PH.<sup>59,123,124</sup>

**Serum Liver Enzyme Activity.** The magnitude of increases in serum liver enzyme activities is dependent on

the underlying disorder causing PH. Typically, moderate to marked liver enzyme activity increases are associated with intrahepatic PH secondary to inflammatory or fibrotic hepatobiliary disorders. Disorders associated with posthepatic PH typically result in mild to moderate increases in serum enzyme activity, particularly the aminotransferases, because of hepatic necrosis or ischemia from congestion. Serum liver enzyme activities usually are normal or only mildly increased in prehepatic PH.

**Liver Function Tests.** Abnormal liver function tests can be used to infer the presence of PH. Blood ammonia or total serum bile acid concentrations can be increased in the presence of MAPSS or functional hepatic failure.<sup>125</sup> Based on evidence in the literature on CPSS, postprandial total serum bile acid concentrations may be the most sensitive test for detection of MAPSS.<sup>126</sup> Blood ammonia concentration, however, is more specific for MAPSS, reflecting the fact that total serum bile acid concentrations are more likely to be increased in cholestatic disorders.<sup>125,127</sup> Ammonia is the only HE toxin that can be measured clinically, and documentation of hyperammonemia suggests the presence of HE (Table 3). Other clinicopathological indicators of hepatic dysfunction such as hyperbilirubinemia and decreases in serum albumin, urea nitrogen, and cholesterol concentrations may be seen in dogs or cats with intrahepatic sinusoidal PH (Table 2).

**Coagulation Parameters.** Because the liver is responsible for the synthesis, activation, and clearance of both anti- and procoagulant factors, patients with hepatobiliary disease are in a precariously balanced state of coagulation.<sup>128</sup> Spontaneous bleeding or thrombosis is rare, but when other predisposing factors such as infection, renal failure, endotoxemia, anesthesia, or drugs (eg, corticosteroids or nonsteroidal anti-inflammatory drugs) are present, they can tip the balance in favor of bleeding or thrombosis.<sup>128</sup> In the literature available on the coagulation status of dogs with PH, the presence of prolonged bleeding times (prothrombin time and activated partial thromboplastin time) seems to parallel the extent of functional hepatic failure,<sup>48,123,124,129</sup> and 2 studies in dogs have shown a relationship between prolongation of these parameters and survival.<sup>124,129</sup> Other coagulation abnormalities that accompany hepatic disorders in dogs associated with PH are decreased serum concentrations of fibrinogen, antithrombin, and protein C.<sup>123,126</sup> In cats

**Table 3.** Clinical features of portal hypertension in dogs and cats.

| Parameter  | Change with Portal Hypertension   |
|--|---|
| Measurement of portal vein pressure <sup>a</sup> | Dog: > 11 mmHg<br>Cat: > 12 mmHg  |
| Ultrasound                                       | Detection of MAPSS<br>Decreased velocity of portal vein blood flow<br>Hepatofugal flow in portal vein<br>Portal vein/aortic <0.65 in the absence of single CPSS                             |
| Detection of complications                       | Ascites: Nonneoplastic, noninflammatory pure or modified transudate<br>HE: Neurologic signs compatible with diffuse cerebral disease ± increased blood ammonia<br>Gastrointestinal bleeding |

CPSS, congenital portosystemic shunt; HE, hepatic encephalopathy; MAPSS, multiple acquired portosystemic shunts.

<sup>a</sup>Values in anesthetized dogs and cats.



(with their predilection to cholestatic biliary disorders), the most common coagulation abnormality reported is vitamin K-dependent prolongation of prothrombin time.<sup>130</sup>

**Ascitic Fluid.** In PH, the ascitic fluid typically is a pure or modified transudate (Table 3). The protein content of the fluid often reflects the anatomic location of PH. Prehepatic and presinusoidal PH increases intestinal lymph formation. Because the intestinal lymphatic system has a large absorptive capacity and tight capillary beds, the ascitic fluid has a low protein concentration (<2.5 g/dL). Posthepatic, postsinusoidal, and sinusoidal intrahepatic PH increase hepatic lymph formation, resulting in loss of a high protein fluid (>2.5 g/dL) through the leaky sinusoidal endothelium. However, because sinusoidal intrahepatic PH most often is accompanied by capillarization of the sinusoids and hepatic synthetic failure, the accumulating fluid typically has a low protein content.

### Diagnostic Imaging

**Radiography.** The presence of ascites can be inferred on survey abdominal radiographs by loss of abdominal detail. Radiographic microhepatica or hepatomegaly may help confirm the presence of a hepatic disorder. Changes in thoracic radiographs, including cardiomegaly, prominent pulmonary vasculature, or compression or dilatation of the caudal vena cava, may indicate a posthepatic intrathoracic cause of PH.

**Ultrasonography.** Ultrasound examination of the abdomen is essential in the diagnostic appraisal of PH. Several findings can indicate the presence of PH (Table 2).<sup>131–136</sup> First, ultrasonography can demonstrate the presence of even small amounts of ascites and aid in the acquisition of a diagnostic sample to determine if its composition is compatible with PH. Second, ultrasonography can identify the presence of MAPSS. Typically, MAPSS appear as a plexus of small, tortuous splenic to renal vessels in the left dorsal perirenal area.<sup>8,117,131,132</sup> Large left splenogonadal shunts can be identified in some patients.<sup>100,117</sup> MAPSS commonly run caudally from the site of origin and tend to disappear into the intestine. Multiple shunts can be differentiated from single congenital shunts by their greater number (>2), and smaller size (<0.4 cm).<sup>131</sup> Postprandial increases in PBF may facilitate detection of MAPSS. Additional ultrasonographic findings suggestive of PH include an enlarged portal vein, decreased PBF velocity (<10 cm/s) hepatofugal flow, a dilated left gonadal vein, and a portal-vein-to-aorta ratio (PV/Ao)  $\leq$  0.65 (Table 3).<sup>100,117,131–135</sup> In humans, ultrasonographic findings of increased PBF, decreased PBF velocity and increased congestive index (cross-sectional area of the PV/mean PV velocity) have 95% sensitivity and specificity for the identification of PH.<sup>45,136</sup>

Ultrasonographic evaluation of the hepatic parenchyma and biliary tract may help to anatomically localize the cause of PH. The liver may appear large and hypoechoic with congestion because of posthepatic PH or small with focal or diffuse parenchymal lesions in chronic hepatic disease leading to intrahepatic PH. Vascular anomalies such as intrahepatic hepatic arterio-

venous fistulas and thrombosis in the portal vein can be identified. Evaluation of the biliary tree may show changes such as biliary tract dilatations, cysts, or mineralization that may be consistent with ductal plate abnormalities. Ultrasonographic evaluation of the heart and thorax can identify causes of posthepatic PH such as right heart failure, pericardial effusion, pulmonary hypertension, or intra- or extraluminal obstruction of the caudal vena cava.

**Scintigraphy.** Rectal or transplenic scintigraphy can confirm the presence of portosystemic hepatic bypass.<sup>137,138</sup> Neither method, however, reliably defines the location of portosystemic bypass or differentiates between a single CPSS and MAPSS. Transplenic scintigraphy may enable visualization of a distinct plexus of multiple anomalous vessels in some, but not all patients.<sup>132</sup>

**Angiography.** Angiography is most useful for evaluating hepatic arteriovenous fistula and obstructive vascular causes of PH, which typically are pre- or posthepatic.<sup>45,86,138,139</sup>

**Contrast-Enhanced Helical Computed Tomography (CT).** Standard protocols for CT developed to evaluate the portal vasculature for CPSS in dogs, can be applied to the investigation of the portal vasculature in PH.<sup>100,140–142</sup> The use of CT permits the identification of MAPSS, obstructive venous lesions, and hepatic arteriovenous fistula as well as determination of hemodynamic changes such as hepatofugal blood flow.<sup>142</sup> A recent study provided a detailed description of patterns of MAPSS in veterinary patients with naturally occurring PH.<sup>100</sup>

**Contrast-Enhanced Magnetic Resonance Angiography (MRA).** MRA permits both accurate depiction of portal vascular anatomy and measurement of portal hemodynamics.<sup>143–146</sup> Anatomical image quality is superior to CT for vascular assessment, but additional studies are needed to validate the method for use in disorders associated with PH.

### Liver Histopathology

Histopathology is crucial in the evaluation of intrahepatic PH because it can differentiate among congenital, inflammatory, fibrotic, and vascular disorders. In inflammatory disorders, the distribution and type of infiltrating cells can be determined and the extent of both fibrosis and inflammation evaluated.<sup>8,124,147</sup> Ductal plate abnormalities can be identified by typical patterns of bile duct proliferation and fibrosis. Diseases associated with chronic portal hypoperfusion of the liver such as hepatic arteriovenous fistula, NCPH, or portal vein obstruction, atresia or stenosis cause a stereotypical histological pattern in the liver that includes loss or diminution of the portal vasculature, arteriolar hyperplasia and tortuosity, hypertrophy of parenchymal hepatic arterioles, and hepatocellular atrophy.<sup>8</sup> Biopsy changes with posthepatic syndromes such as veno-occlusive disease, Budd-Chiari syndrome, and cardiac failure can be subtle and difficult to differentiate. Changes occur predominantly in centrilobular or perivenular areas and include congestion within the space of Disse and centrilobular hepatocyte degeneration. With chronicity, fibrosis may appear in

the sinusoids and centrilobular area eventually bridging between central veins.<sup>74</sup> In prehepatic PH, histologic abnormalities may be absent unless the obstruction is longstanding in which case some degree of centrilobular hepatocyte degeneration can occur.

### Clinical Differentiation of Pre-, Post-, and Intrahepatic PH (Table 2)

Prehepatic causes of PH involve portal vein obstruction and hepatic arteriovenous fistula. Because some causes such as portal vein atresia and hepatic arteriovenous fistula are congenital lesions, the typical clinical presentation is a young animal with ascites and signs of HE.<sup>48–53</sup> With portal vein obstruction, animals may present with abdominal pain and acute onset of ascites. Portal vein thrombosis often occurs in the presence of predisposing conditions such as chronic hepatitis, cirrhosis, pancreatitis, peritonitis, abdominal neoplasia, or endogenous or exogenous excess of corticosteroids.<sup>47,148–151</sup> With prehepatic PH, serum liver enzyme activities typically are normal to mildly increased unless an underlying hepatopathy is present. Low protein ascites may be present. The diagnosis is made with ultrasound examination, CT, or contrast-enhanced MRA.

Posthepatic causes of PH involve the heart, cranial vena cava, and hepatic veins. Clinically, jugular venous distension, increased central venous pressure, cardiac murmur, high protein ascites, and hepatomegaly may be present.<sup>79–81</sup> Hepatic congestion and subsequent ischemia cause mild to moderate increases in serum transaminase activities. Thoracic and abdominal ultrasonography or contrast angiography is needed for diagnosis.

Reports of presinusoidal intrahepatic PH, although not confirmed by manometry, have been described in dogs.<sup>48,51,57,59–63</sup> In these reports, the syndrome has been called NCPH, hepatoportal scleral fibrosis, idiopathic hepatic fibrosis, and PHPV. The latter term is recommended by the World Small Animal Veterinary Association liver study group.<sup>8</sup> It is unclear, however, if the lesion in all cases is primary hypoplasia of the intrahepatic portal vasculature or a consequence of a primary congenital or acquired disorder in hepatic perfusion. The pathogenesis of NCPH/PHPV in veterinary patients is unknown, but in humans NCPH is a vasculopathy involving the small and medium branches of the portal vein associated with exposure to toxins absorbed from the gastrointestinal tract (eg, lipopolysaccharide), autoimmune disorders, prothrombotic states, drugs or toxins (eg, methotrexate, arsenic, vinyl chloride), and hypervitaminosis A.<sup>59,152</sup>

Typically, dogs with NCPH/PHPV are young (<2 years of age), with ascites, HE, and gastrointestinal signs. Rottweilers, Cocker Spaniels, and Doberman Pinschers may be predisposed.<sup>51,57–59,62,63</sup> Dogs have moderate to severe increases in liver enzyme activities, mild to moderate hyperbilirubinemia, increased total serum bile acids and blood ammonia concentrations, hypoalbuminemia, and a low protein ascitic fluid. Imaging studies show microhepatica with MAPSS. It may be impossible to differentiate this disorder from intrahepatic sinusoidal PH caused by inflammatory or fibrotic disease on the

basis of clinical presentation, biochemical testing, and imaging findings. Instead, hepatic biopsy is necessary. In NCPH/PHPV, the liver has lesions associated with chronic hypoperfusion with varying degrees of periportal or centrilobular fibrosis. Noteworthy is the absence of inflammation and regenerative nodules. Supportive treatment has resulted in extended long-term survival in some dogs. Dogs with this syndrome appear to be predisposed to gastric ulceration.<sup>48,59,63</sup>

Postsinusoidal intrahepatic PH is caused by diseases affecting the small sublobular hepatic veins and central veins. It can occur as an idiopathic lesion in young, primarily large breed, dogs. German Shepherds appear to be overrepresented in these reports.<sup>61,63,78,145</sup> Clinically and biochemically, they can be difficult to differentiate from dogs with NCPH/PHPV. Histopathologically, the liver has moderate to marked noninflammatory perivenular fibrosis, but not the classic signs of hypoperfusion seen with NCPH/PHPV. There are reports of extended survival in some of these dogs with symptomatic management. Whether some affected dogs represent overlap with NCPH/PHPV requires additional study.

Sinusoidal PH most often is associated with fibrosis in the sinusoids and accompanies chronic hepatitis or cirrhosis. Several breed-specific hepatopathies marked by copper- and noncopper-associated chronic hepatitis are known to progress to cirrhosis with development of PH.<sup>8,70,71</sup> These diseases are seen in the Bedlington Terrier, West Highland White Terrier, Dalmatian, Doberman Pinscher, Cocker Spaniel, and Labrador Retriever.<sup>71</sup> Another inflammatory disorder that culminates in PH in dogs is lobular dissecting hepatitis, a disorder reported primarily in young large breed dogs.<sup>153–155</sup> Histologically, it is marked by a mixed inflammatory infiltrate in the sinusoids and hepatic parenchyma with rare involvement of portal areas. The lobular parenchyma is infiltrated by fine reticulin and collagen fibers. Regenerative nodules may be present but are not a prominent feature. The cause is unknown and response to supportive treatment is poor with most dogs dying within a few weeks of diagnosis.

Fibropolycystic hepatobiliary disease (ductal plate abnormalities) can cause either sinusoidal or presinusoidal PH. When the ductal plate abnormality is associated with small bile ducts (eg, congenital hepatic fibrosis), diffuse fibrosis and sinusoidal PH occur.<sup>64,68</sup> Ductal abnormalities in larger bile ducts (Caroli's disease) may be associated primarily with portal fibrosis and result in presinusoidal PH.<sup>65,156</sup> Histologically, the fibropolycystic diseases are characterized by the presence of numerous irregular bile duct profiles localized along the edge of the limiting plate with extensive, portal fibrosis. Inflammation and regenerative nodules are absent. In congenital hepatic fibrosis, dogs may have some degree of hypoplastic portal vasculature on biopsy with mild arteriolar proliferation. Thus, it may be difficult to differentiate congenital hepatic fibrosis from NCPH/PHPV, but the latter lacks profound changes in the bile ducts.<sup>64</sup> Dogs with Caroli's disease typically have imaging abnormalities of the larger bile ducts, including

dilatation and associated calcification, and have many concurrent renal cysts on ultrasound examination.<sup>65,156</sup>

PH and ascites formation occurs in cats with posthepatic PH (eg, right heart failure, Budd-Chiari syndrome), intrahepatic disease (eg, HAV, chronic hepatitis, congenital hepatic fibrosis), or prehepatic PH (eg, portal vein thrombus, postattenuation of CPSS).<sup>42,55,68,84,150,157–159</sup> PH, however, is not as common in cats with inflammatory biliary disease.<sup>160,161</sup> This may be related to the fact that feline cholangitis initially is marked by periductal fibrosis, but only in later stages does fibrosis progress to the hepatic architectural distortion or perisinusoidal fibrosis typically associated with development of PH in other species.<sup>161</sup> Alternatively, cats may succumb to complications of hepatic failure before an advanced stage marked by ascites develops.<sup>159,162–165</sup>

## Treatment of PH

### Correct Etiologic Factors

Treatment of PH ideally is based on correction of the underlying disease. This often is possible for PH associated with right-sided heart failure (after- and preload reduction), pre- or posthepatic thrombotic or obstructive vascular lesions (placement of stents,<sup>86</sup> surgical embolectomy, use of thrombolytics, and anticoagulants), or HAV (liver lobectomy, ligation of the nutrient artery, fluoroscopically guided glue embolization of the fistula).<sup>7,53</sup> Although specific therapies to directly lower PH accompanying intrahepatic PH are used in humans, their use has not been explored in veterinary patients. Thus, treatment is centered on management of complications and control of factors that potentiate PH. Potentiating factors that may exacerbate PH are fluid overload, excessive sodium intake and increased intra-abdominal pressure. Thus, judicious use of low sodium fluids, rest, fasting, dietary sodium restriction, and sedation is indicated.

### Manage Complications

**Ascites.** Mobilization of ascites requires establishment of natriuresis. Sodium restriction is the initial therapeutic step. A diet that delivers <0.05 g/100 kcal of sodium is initiated. Diuretics are added if there is no response to sodium restriction. The diuretic of choice is the aldosterone antagonist, spironolactone, which acts in the renal collecting ducts to increase sodium excretion and conserve potassium. Spironolactone works slowly to mobilize fluid, and in humans, a response may take up to 14 days.<sup>94,102,166</sup> The initial dosage is 1–2 mg/kg/d, which may be increased gradually over 3–5 day cycles. Low dose furosemide (0.5–1 mg/kg/d) facilitates establishment of natriuresis. Daily weight and abdominal girth assessments should be performed and hematocrit as well as serum creatinine and electrolyte concentrations monitored. A safe rate of diuresis extrapolated from human medicine is 0.5% of body weight daily.<sup>166</sup> Diuretic dosage is tapered to the lowest effective dosage with maintenance on spironolactone alone. Diuretics should be discontinued or re-evaluated when hypo-

natremia, hypokalemia, azotemia, or worsening signs of HE occur.<sup>8,166</sup>

Abdominal paracentesis may be necessary initially or intermittently if tense ascites is present. Benefits include improvements in renal blood flow, splanchnic venous return, and respirations. Typically, 20–50% of the ascitic volume may be removed without incident, but circulatory collapse or decreased renal function can occur when removing large fluid volumes.<sup>94,166</sup> In humans, treatment pre- or postparacentesis with human albumin or colloids IV is used when total volume paracentesis is performed to prevent alterations in renal function.<sup>94,166</sup>

Refractory ascites may necessitate greater dietary sodium restriction, total volume paracentesis, or the use of experimental therapies. Intravenous infusion of human or canine albumin to enhance intravascular colloid concentration may be attempted in acutely decompensating patients.<sup>166</sup> In humans, transjugular intrahepatic portosystemic shunts are created.<sup>166</sup> This technically challenging procedure lowers PVP by creating a direct intrahepatic pathway between the hepatic and portal veins. This procedure has not been used in veterinary patients, but surgical vena cava banding to attenuate MAPSS in dogs with experimentally induced hepatic failure has been reported.<sup>26</sup> In this study, long-term survival and quality of life were similar in banded dogs and those treated medically, and thus the procedure was not recommended.

**Hyponatremia.** Aquaretics (tolvaptan and lixivaptan) bind to V2 receptors in the renal collecting ducts and antagonize the action of ADH, effectively blocking reabsorption of water.<sup>104</sup> They are used in humans for the acute management of hyponatremia in a hospital setting. They have not been evaluated in veterinary patients.

**HE.** Modulation of intestinal production and absorption of toxins is the mainstay of HE treatment.<sup>102,167</sup> Enteral administration of nonabsorbable disaccharides (eg, lactulose and lactitol) acidifies the colonic lumen, leading to conversion of  $\text{NH}_3$  to  $\text{NH}_4^+$ , which is membrane impermeable. Lactulose also provides a cathartic effect and limits intestinal bacterial ammonia production. Adverse effects of treatment include diarrhea, flatulence, and abdominal cramps. The initial dosage is 0.25–0.5 mL/kg PO q12h–q8h, but the dosage should be adjusted to achieve 2–3 soft stools per day. Lactulose enemas after a warm cleansing enema may be used as an emergency treatment for patients with severe HE. Lactitol (0.5–0.75 g/kg PO q12h) or lactulose powder<sup>a</sup> may be better tolerated or more easily administered in some patients.

Antibiotics frequently are used in combination with lactulose for a synergistic effect in treating HE.<sup>168</sup> Antibiotics work in the gut to limit urease-producing bacteria. The antibiotics most commonly used are metronidazole and neomycin.<sup>102</sup> Neomycin's adverse effects include nephrotoxicity and ototoxicity, whereas metronidazole may cause neurotoxicity. In human medicine, there is a shift toward the use of rifaximin, an oral rifamycin-based antibiotic, because of its superior safety profile.<sup>168</sup> The use of rifaximin has not been described in veterinary medicine, but safety profiles have been completed in dogs.<sup>169</sup>

Dietary protein restriction decreases colonic ammonia production, but in order to avoid protein calorie malnutrition, it should not be first-line treatment to control HE. Protein tolerance should first be increased with lactulose and antibiotic therapy, and protein restriction initiated if these interventions do not control HE. The protein source used is crucial. Dairy and soy protein along with higher amounts of vegetable fiber are best tolerated.<sup>170,171</sup>

Correction of factors that might precipitate HE such as metabolic alkalosis, infection, increased protein load (eg, gastrointestinal bleeding, diet), azotemia, constipation, and concurrent administration of sedatives or analgesics should be addressed.

**Gastropathy.** Gastrointestinal ulceration accompanying hepatobiliary disease can be treated by gastric acid reduction with H<sub>2</sub> receptor antagonists or proton pump inhibitors and use of gastric mucosal cytoprotective agents such as sucralfate. Hepatotoxicity because of H<sub>2</sub> receptor antagonists occurs as a rare idiosyncratic drug reaction in humans, but has not been reported in veterinary patients.<sup>172</sup>

### Target Vasoactive Regulatory Pathways (Table 4)

#### Induce Splanchnic Vasoconstriction (Reverse Splanchnic Vasodilatation)

**β Blockers.** Oral treatment with nonselective β blockers such as propranolol and nadolol is used in humans to lower PVP on a chronic basis.<sup>97</sup> They reduce PVP by way of both β<sub>1</sub> and β<sub>2</sub> blockade, which decreases cardiac output and mediates splanchnic vasoconstriction, respectively. However, 3 experimental studies and 1 clinical study in dogs have failed to document any reduction in PVP with propranolol even at doses high enough to elicit systemic hypotension.<sup>173–175</sup> Carvedilol, another nonselective β blocker, also lowers PVP in humans. It is 2–3

times more potent than propranolol as a β-receptor antagonist.<sup>176</sup> It also has mild α-1 adrenergic activity, which decreases IHVR resulting in a further reduction in PVP, but also may be associated with systemic vasodilatation and hypotension. Carvedilol has antioxidant activity, which may benefit patients with inflammatory or fibrotic disease.<sup>176</sup> Its use has not been reported in veterinary patients with PH.

**Somatostatin and Analogues.** Somatostatin can decrease PVP in humans without leading to systemic hypotension.<sup>97</sup> Somatostatin inhibits the release of splanchnic vasodilators such as glucagon and has a direct splanchnic vasoconstrictor effect. Somatostatin analogues such as octreotide are used parenterally to acutely lower PVP during active variceal bleeding in humans. Octreotide has been used in dogs to treat glucagonomas and insulinomas, but its use for PH has not been reported.<sup>177–178</sup>

**Vasopressin and Analogues.** Vasopressin acting at V<sub>1</sub> receptors is a potent splanchnic vasoconstrictor.<sup>97</sup> Terlipressin, a synthetic ADH analog, often is used alone or in combination with a somatostatin analogue to acutely lower PVP in humans with variceal bleeding.<sup>97</sup> Adverse effects include systemic hypertension, arrhythmias, and myocardial and intestinal ischemia. In 1 experimental study, vasopressin was able to decrease gastric mucosal ischemia in dogs with PH.<sup>174</sup> Potential applications of combinations of ADH and somatostatin analogue therapy in veterinary medicine include PH associated with acute increases in PVP such as might occur after PVT or as a complication of CPSS ligation.

#### Induce Sinusoidal Vasodilatation (Decrease IHVR)

**Drugs that Increase the Availability of NO.** Nitrovasodilators (which increase intrahepatic NO) decrease

**Table 4.** Potential therapeutic agents to modulate portal hypertension.

| Therapeutic Goal                | Agent  | Mechanism of Action                         | Clinical Use (Humans)   | Limitations/Advantages   |
|---------------------------------|--|---|---|--|
| Splanchnic vasoconstriction     | Propranolol<br>Nadolol<br>Carvedilol             | Nonselective β-adrenergic antagonists       | Chronic maintenance to ↓ PVP  | Propranolol not effective in dogs<br>Carvedilol also an α <sub>1</sub> agonist |
|                                 | Octreotide                                       | Somatostatin analogue                       | Acute ↓ PVP   | Parenteral only  |
|                                 | Terlipressin                                     | Vasopressin analogue                        | Acute ↓ PVP   | Parenteral only  |
| Sinusoidal vasodilation (↓IHVR) | Isosorbid 5- mononitrate<br>Isosorbid –dinitrate | Deliver NO to intrahepatic vasculature      | Use in combination with β blockers for chronic maintenance to ↓ PVP | Worsens splanchnic vasodilation<br>Symptomatic systemic hypotension            |
|                                 | Lovastatin<br>Atrovastatin                       | ↑ endothelial NOS                           | Preclinical to ↓ PH additive effect with β blockers                 | Cholesterol lowering<br>Corrects endothelial cell dysfunction                  |
|                                 | Losartan   | Angiotensin II receptor antagonist          | Preclinical to ↓ PH and portopulmonary hypertension                 | Antifibrotic   |
|                                 | Bosentan   | Nonselective endothelin receptor antagonist | Portopulmonary hypertension   | Antifibrotic   |
|                                 | ↓Splanchnic neovascularization                   | Sorafenib                                   | Tyrosine kinase inhibitor   | Preclinical to ↓ PH and portopulmonary hypertension                            |

IHVR, intrahepatic venous resistance; NO, nitric oxide; NOS, nitric oxide synthase; PVP, portal vein pressure; PH, portal hypertension.

IHVR, but often at the expense of potentiating splanchnic vasodilatation and systemic hypotension.<sup>97</sup> Thus, these compounds are not used as sole treatment for PH. Chronic oral treatment with isosorbide 5-mononitrate, however, is frequently used in combination with nonselective  $\beta$  blockade as first-line treatment to treat PH in humans.<sup>97,179,180</sup> Although pharmacokinetic data are available for the oral administration of isosorbide 5-mononitrate in dogs, its use in PH has not been described.<sup>171</sup>

The statins, best known for their cholesterol lowering effects, also decrease IHVR without any adverse effects on systemic hemodynamics.<sup>181–183</sup> They work in part by selectively increasing NO production in the liver through enhancement of endothelial NOS activity. The use of statins to control PH has not been investigated in veterinary patients, although these drugs have been used to lower cholesterol and treat inflammatory skin disease.<sup>184,185</sup> An important concern with the use of statins is the potential for inducing idiosyncratic hepatotoxicity. A number of studies in humans, however, have shown that the safety profile of statins in patients with liver disease is no different than that observed in the general population.<sup>186</sup>

**Renin-Angiotensin System Blockade.** Activation of the renin-angiotensin-aldosterone system system occurs with PH and contributes to excessive vascular tone in the liver. ACE inhibitors decrease HVP in humans, but often cause systemic hypotension.<sup>187</sup> Losartan, an angiotensin II receptor antagonist, decreases PVP without causing systemic hypotension.<sup>187</sup> Losartan also corrects splanchnic and pulmonary vascular endothelial dysfunction by preventing upregulation of endothelial NOS and decreasing reactive oxidative stress. Chronic administration can decrease PVP in some, but not all, studies.<sup>187</sup> Losartan also inhibits hepatic stellate cell activation and can attenuate hepatic fibrosis in experimental rodent models making it particularly attractive for the treatment of PH associated with chronic fibrotic hepatopathies. Losartan has been used experimentally in dogs, but not to treat PH.<sup>188,189</sup>

**Blockade of Endothelin-1.** Bosentan, an oral endothelin-1 receptor antagonist, decreased PVP in preclinical studies of PH and is considered a first-line treatment in managing portopulmonary hypertension.<sup>109–111</sup> In addition, nonselective endothelin-1 antagonists have antifibrotic effects.<sup>190</sup>

**Inhibition of Angiogenesis.** The tyrosine kinase inhibitors such as sorafenib and imatinib block growth factor pathways crucial to angiogenesis. In experimental models of PH in rodents, sorafenib decreases splanchnic neovascularization, markedly attenuates the hyperdynamic splanchnic and systemic circulation, and decreases in the formation of MAPSS.<sup>191,192</sup> The successful use of imatinib to treat portopulmonary hypertension in cirrhotic patients also has been reported.<sup>193</sup> Although tyrosine kinase inhibitors are used in veterinary oncology, their use in PH has not been described.<sup>194</sup>

## Conclusion

Definitive diagnosis and treatment of PH in dogs and cats is challenging. Diagnosis often is delayed because it

must be inferred by late-stage clinical signs such as accompanying ascites or HE, or by the identification of MAPSS by imaging techniques. The treatment of veterinary patients with PH is primarily directed at controlling complications such as ascites, HE, and gastric ulceration. In cases, in which these clinical syndromes are refractory to treatment, pharmacologic intervention to lower PVP may be indicated. Challenges in veterinary medicine are to further define the use of imaging techniques to enable early detection of PH and to conduct clinical trials of pharmacologic interventions that lower PVP in dogs and cats in order to assess their effect on survival and quality of life in patients with PH.

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## Footnote

<sup>a</sup> Kristalose (lactulose), Cumberland Pharmaceuticals Inc, Nashville, TN

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