Endovascular treatment of a high-flow hepatic arteriovenous malformation with secondary portal hypertension in a dog

J. Brad Case DVM, MS
Sarah E. Boston DVM, DVS:
Erin P. Porter DVM
Beau B. Toskich MD

From the Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL 32610 (Case, Boston, Porter); and the Division of Vascular and Interventional Radiology, Department of Radiology, College of Medicine, University of Florida, Gainesville, FL 32610 (Toskich).

Address correspondence to Dr. Case (caseb@ufl.edu).

CASE DESCRIPTION
A 17-month-old neutered female Labrador Retriever with a 3- to 4-month history of abdominal distention was referred for evaluation and treatment.

CLINICAL FINDINGS
Evaluation of a peritoneal fluid specimen collected by the referring veterinarian indicated a pure transudate. At admission, transabdominal ultrasonography revealed microhepatica, dilation of the intrahepatic and mesenteric vasculature, portal effusion, and multiple aberrant blood vessels. A large, high-flow hepatic arteriovenous malformation (HAVM) with secondary portal hypertension, portal effusion, multiple acquired portosystemic shunts, and microhepatica was evident on CT angiography.

TREATMENT AND OUTCOME
Transfemoral hepatic arteriography and staged coil and glue (n-butyl cyanoacrylate) embolization of the complex arteriovenous malformation nidus and central main left hepatic artery resulted in ablation of the lesion, restoration of arterial blood flow to the contralateral hepatic lobes, and resolution of the peritoneal effusion. The dog remained without clinical signs of hepatic disease until it was euthanized 5 months after treatment for an unrelated condition.

CLINICAL RELEVANCE
Successful endovascular management of a HAVM was accomplished by means of coil and glue embolization in the patient of this report. Dogs with comparable HAVMs may benefit from similar minimally invasive treatment. (J Am Vet Med Assoc 2017;251:824–828)
the thorax, abdomen, and pelvis were acquired during the arterial, venous, and delayed phases. Peak contrast enhancement in regions of interest was evaluated with bolus tracking software.\(^5\) Subsequently, 2-D coronal and sagittal multiplanar reformations, and a 3-D reconstruction of the portal system were generated.\(^6\) Review of images showed contrast enhancement of the portal vasculature during the arterial phase, attenuation of the right branch of the hepatic artery, advanced ectasia of the left branch of the hepatic artery supplying a high-flow left HAVM with both a large fistula and complex intraparenchymal nidus, and large splenorenal and portosystemic varices. Poor hepatic venous opacification was evident, including on delayed-phase images, suggesting peripheral attenuation of intrahepatic portal vasculature. Additional findings included a diminutive right branch of the hepatic artery (2.4-mm diameter), moderate splenomegaly, and a large volume peritoneal effusion. The diagnosis of a left intrahepatic HAVM with secondary portal hypertension, peritoneal effusion, multiple acquired portosystemic shunts, and microhepatica was confirmed. The dog recovered from anesthesia without apparent complications. Treatment options discussed with the owners included left partial liver lobectomy and endovascular embolization of the HAVM. The owners elected embolization and returned the dog for treatment 2 weeks later.

On readmission, the dog was prepared for the procedure. Hydromorphone was administered for sedation, and general anesthesia was induced with propofol (1.5 mg/kg [0.7 mg/lb] IV). An endotracheal tube was then placed, and anesthesia was maintained with delivery of isoflurane in oxygen. Heart rate, direct blood pressure, arterial oxygen saturation (by means of pulse oximetry), respiratory rate, and temperature were monitored throughout. The caudal portion of the abdomen and both inguinal regions were prepared for surgery. Prior to transportation of the patient to the endovascular suite, peritoneocentesis was performed with removal of 2 L of peritoneal fluid. This was performed for patient comfort and to improve compliance of the abdomen prior to the procedure.

The patient was then positioned in dorsal recumbency, and the right inguinal region was prepped and draped for sterile femoral arterial access. Ultrasound-guided\(^7\) access to the right common femoral artery was achieved by use of the Seldinger technique with a 4F microintroducer.\(^7,8\) Accurate guidewire location in the right external iliac artery was confirmed with fluoroscopy.\(^8\) Femoral arterial access was then obtained with removal of the 4F dilator (sheath) over an 0.035-inch guidewire, followed by insertion of a 5F X 11-cm-long introducer sheath.\(^1\) External iliac and caudal abdominal femoral arteriography was then performed with manual injection of 3 mL of a 1:1 solution of iohexol\(^6\) and sterile saline (0.9% NaCl) solution to confirm appropriate access. A 5F X 65-cm-long reverse curve angiographic catheter\(^1\) was advanced over a 0.038-inch hydrophilic guidewire, then positioned in the aortic arch; the catheter was then retracted caudally to select the celiac artery. The reverse curve of the angiographic catheter was oriented ventrally when viewing the patient from above. Celiac arteriography was performed and demonstrated predominant opacification of the left hepatic arterial inflow to the HAVM and trace flow to a diminutive right branch of the hepatic artery. The catheter was positioned so that it extended approximately 1 cm into the common hepatic artery and remained in this position for the duration of the procedure.

A 3F X 150-cm-long microcatheter\(^8\) and 0.010-inch X 205-cm-long platinum guidewire\(^1\) were advanced within the 5F angiographic catheter and used to select the left branch of the hepatic artery for diagnostic angiography. This revealed a hybrid HAVM consisting of a large, direct, apparently extrahepatic arteriovenous communication (Cho-Do type I)\(^2\) abutting the caudal left lateral liver lobe and an arteriovenular left hepatic intraparenchymal nidus (Cho-Do type IIIb; Figure 1).\(^2\) Delayed portal venous angiography demonstrated hepatofugal flow via the caudal mesenteric vein to a middle hemorrhoidal (caudal rectal vein) anastomosis. The large diameter and high-velocity blood flow through the HAVM were thought to exceed safe parameters for treatment with glue embolization alone. Therefore, we elected to treat the patient with a commercially available sterile compressed gelatin sponge\(^6\) mixed with sterile saline solution manually injected via the microcatheter in an attempt to attenuate flow through the lesion to facilitate subsequent glue embolization. After 2 injections of 3 mL of the embolic solution with no observable angiographic reduction in flow, the decision was made to deploy multiple 0.018-inch fibered platinum coils\(^8\) into the arteriovenous fistula moiety to further attempt to attenuate blood flow and enable glue embolization of the residual nidus. A total of 21 coils were ad
were subsequently deployed within the fistula and successfully reduced blood flow, as evaluated with fluoroscopy, to an extent that was subjectively assessed as sufficient to safely proceed with glue embolization. Repeated angiography at this time revealed the dominant hepatic artery that supplied the largest portion of the intraparenchymal nidus of the HAVM. This vessel was selected for injection and anatomically confirmed with manual angiography (Figure 1).

The microcatheter was flushed with 5 mL of sterile 5% dextrose solution in water. Three mL of a 3:1 mixture of ethiodized oil\(^5\) and n-butyl cyanoacrylate\(^6\) was administered in a primed (5% dextrose solution in water) polyacrylamide syringe through the microcatheter, forming an approximately 4-cm-long cast of the HAVM nidus that finely and uniformly penetrated the arteriolar and venular segments. The microcatheter was then slowly retracted and placed in a location approximately 3 cm upstream, such that it further centrally occluded the ectatic main left hepatic arterial inflow and would prevent future recanalization. The result was complete embolization of the HAVM and contributing subsegmental hepatic arteries; the absence of blood flow to the lesion with right hepatic arterial redistribution was confirmed on postprocedural hepatic arteriography (Figure 1). Celiac arteriography was then performed, which confirmed the absence of any additional arterial communications with the nidus. The procedure time was 130 minutes.

All catheters were then removed, and the femoral arterial defect was closed routinely by means of arterial ligation after an arterial cut-down procedure. During recovery from anesthesia, a small amount of regurgitation was noted and was removed from the oropharynx with a suction unit. The dog recovered in the critical care unit overnight without further apparent complications. It was bright and alert and eating and drinking well by the next morning. The severe abdominal distension evident on initial physical examination appeared to have resolved within 24 hours of the procedure, although repeated abdominal ultrasonography at that time demonstrated a small volume of residual peritoneal effusion. The dog was discharged 2 days after the procedure with instructions for activity restriction and planned repeated CT angiography at a follow-up examination 6 to 8 weeks later. Treatment with S-adenosylmethionine (14 mg/kg, PO, q 24 h) combined with silibinin-phosphatidylcholine (4 mg/kg [providing 35 mg of silybin A and B], PO, q 24 h)\(^a\) and cephalexin (20 mg/kg [9.1 mg/lb], PO, q 12 h) was prescribed.

The owners reported that the dog appeared well; however, it developed nasal discharge 5 weeks after the procedure. On examination 6 weeks after treatment, it was found to have mucopurulent nasal discharge that was ultimately attributed to nasopharyngeal stenosis. The stenosis was thought to have been the result of nasopharyngeal reflux and regurgitation subsequent to a congenitally short palate. Computed tomography of the head and an endoscopic examination of the upper respiratory tract confirmed the presence of severe (luminal diameter, 4 mm) nasopharyngeal stenosis. The stenosis was treated with endoscopic balloon dilation to a diameter of 10 mm, followed by copious lavage of the nasopharynx with saline solution. A CBC performed at this time revealed a mild stress leukogram, with all other values within reference limits. Serum biochemical analysis, including evaluation of bile acids concentration, revealed a BUN concentration of 8 mg/dL, albumin concentration of 2.9 g/dL, glucose concentration of 87 mg/dL, alanine transaminase activity of 550 U/L, preprandial bile acids concentration of 55.1 \(\mu\)mol/L, and postprandial bile acids concentration of 165.7 \(\mu\)mol/L.

Repeated 4-phase abdominal CT angiography was performed 7 weeks after embolization treatment and demonstrated no perfusion of the HAVM, although, as expected, multiple portosystemic varices remained. Compared with results of initial CT angiography, the right hepatic arterial branch diameter had increased from 2.4 mm to 4.2 mm at its bifurcation from the common hepatic artery (Figure 2). Additionally, a large thrombus was present in the main portal vein.
that extended beyond the porta hepatis into the left, right, and central portal branches, causing complete obstruction of the portal vein. There was subjective enlargement of the right hepatic division and notable atrophy of the left division, compared with the initial CT angiographic images. The peritoneal effusion and splenomegaly had completely resolved. The dog continued to receive S-adenosylmethionine and commenced treatment with amoxicillin-clavulanic acid (14 mg/kg, PO, q 12 h) for 6 weeks.

Subsequent follow-up occurred via several telephone calls with the owner and included discussions regarding further treatment of the upper airway disease with serial balloon dilations and the placement of a covered nasopharyngeal stent. The owners declined these options and the dog was reported to be doing well; however, nasal discharge and stertor persisted 4 months after the balloon dilation procedure. Unfortunately, because of the persistent nasal discharge and the guarded prognosis associated with nasopharyngeal stenosis, the owners elected euthanasia 5 months after treatment of the HAVM. At the time of euthanasia, there were no apparent clinical signs related to the HAVM. A necropsy was not performed.

**Discussion**

Congenital HAVMs are rare in dogs and have been reported to be associated with considerable morbidity and mortality when treated surgically. Additionally, a HAVM, defined as an arterial-to-venous communication proximal to a capillary bed, has been suggested to represent a particularly high risk for surgical resection and is technically challenging to completely embolize. In the patient of the present report, successful treatment of a HAVM was accomplished by means of interventional, staged coil-and-glue embolization, with complete elimination of the main fistula and HAVM nidus.

Hepatic arteriovenous malformations are aberrant connections between the hepatic arteries and portal veins. They can vary in morphology and in the number or type of vascular anastomoses, and the individual variant or type has important implications for treatment and prognosis. The Cho-Do system, which classifies arteriovenous malformations on the basis of nidus morphology, is used in human medicine in an effort to appropriately guide treatment decisions. The dog described in the present report had lesion attributes consistent with both a Cho-Do type 1 HAVM (i.e., direct communication between the left hepatic artery and the portal vein) and a Cho-Do type 3b AVM, with subsegmental left hepatic arteries and arterioles forming aberrant anastomoses with high-output portal veins. Effective treatment in this scenario required either complete surgical extirpation of the left liver division or complete, robust embolization of the main arteriovenous communication and the nidus. We elected to treat the dog of this report with complete embolization; clinical response was dramatic in that the severe ascites almost completely resolved by 24 hours after the procedure. Furthermore, complete embolization was confirmed at the time of procedural completion with angiography, and its robustness was confirmed with repeated CT angiography 7 weeks later.

Most interesting was the compensatory ability of the patient of this report to effectively become dependent on the right branch of the hepatic artery. Indeed, the right branch of the hepatic artery approximately doubled in diameter (2.4 to 4.2 mm) to accommodate the increase in blood flow induced by the change in pressure, with obliteration of vascular steal after occlusive embolization of the left branch of the hepatic artery and the HAVM. Also notable was the presence of a large thrombus completely occluding the portal vein detected on repeated CT angiography 7 weeks after treatment. We suggest that although this would seem to be incompatible with health, the patient of the present report was apparently tolerating this condition well, without any apparent clinical signs during the period of follow-up. This may have been because of long-standing (ie, congenital) portosystemic venous diversion, as evidenced by poorly developed intrahepatic portal branches visible on delayed portography, and the capacity for the right branch of the hepatic artery to accommodate the majority of hepatic blood flow. The multiple acquired extraportal shunt vessels also likely contributed to the lack of clinical signs related to the thrombus in this patient. The most likely etiology of the portal vein thrombus was long-standing hepatofugal blood flow and an underdeveloped portal venous system; the source of this blood flow, the left hepatic artery branch, ceased with embolization of the HAVM. The result was vascular stasis, which likely led to the development of a large but subclinical portal thrombus.

Whereas the dog of this report apparently responded well in the short term (ie, 5 months), we cannot speculate regarding the long-term prognosis, in particular because of the concurrent nasopharyngeal stenosis, which is also an exceptionally difficult condition to treat. In regards to the HAVM, the veterinary literature is limited to a report of 4 dogs that underwent glue embolization alone for treatment of HAVMs, with all patients reported to be alive between 9 and 17 months following treatment. In those 4 dogs, 1 inprocedural complication occurred. Inadvertent glue embolization of the distal portion of the aorta caused temporary cardiac arrest; however, the dog survived with no apparent long-term complications. Owner-perceived outcome for the patients of that report was good or fair in 3 dogs and poor in 1 dog that required surgery after persistent shunting was documented at a follow-up examination. Successful endovascular management of a high-flow HAVM was accomplished with embolization in the patient described in the present report, suggesting that dogs with similar HAVMs may benefit from comparable interventional treatments. However, future study is needed to determine whether such treatment results in improved long-term outcome.
**Footnotes**

a. Denamarin for large dogs (S-adenosylmethionine, 425 mg; silybin-phosphatidylcholine complex, 120 mg; providing 35 mg of silybin A and B), Nutramax Laboratories Inc, Edgewood, Md.


c. Toshiba Aquilion 8 CT Scanner, Toshiba Medical Systems, Tustin, Calif.

d. Omni-paque 350, GE Healthcare, Milwaukwee, Wis.

e. SUREStart, Toshiba Medical Systems, Tustin, Calif.


g. Stiffen Fluent Micro-introducer, Galt Medical Corp, Garland, Tex.

h. Toshiba Medical Systems, Tustin, Calif.


k. Renegade Hi Flo, Boston Scientific, Natick, Mass.

l. Transend, Boston Scientific, Natick, Mass.

m. Gelfoam, Pfizer Inc, New York, NY.


o. Ethiodol, Savage Laboratories, Melville, NY.

p. Verbond, 3M, Saint Paul, Minn.

q. Clavamox, Pfizer, New York, NY.

**References**


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**From this month’s AJVR**

**Pharmacokinetics and oral bioavailability of metformin hydrochloride in healthy mixed-breed dogs**

Charlotte A. Johnston et al

**OBJECTIVE**

To investigate the pharmacokinetics of metformin hydrochloride in healthy dogs after IV and PO bolus administrations and determine the oral dose of metformin that would yield serum concentrations equivalent to those thought to be effective in humans.

**ANIMALS**

7 healthy adult mixed-breed dogs.

**PROCEDURES**

Each dog was given a single dose of metformin IV (mean ± SD dose, 24.77 ± 0.60 mg/kg) or PO (mean dose, 19.14 ± 2.78 mg/kg) with a 1-week washout period between treatments. For each treatment, blood samples were collected before and at intervals up to 72 hours after metformin administration. Seventy-two hours after the crossover study, each dog was administered metformin (mean dose, 13.57 ± 0.55 mg/kg), PO, twice daily for 7 days. Blood samples were taken before treatment initiation on day 0 and immediately before the morning drug administration on days 2, 4, 6, and 7. Serum metformin concentrations were determined by means of a validated flow injection analysis–tandem mass spectrometry method.

**RESULTS**

After IV or oral administration to the 7 dogs, there was high interindividual variability in mean serum metformin concentrations over time. Mean ± SD half-life of metformin following IV administration was 20.4 ± 4.1 hours. The time to maximum serum concentration was 2.5 ± 0.4 hours. Mean systemic clearance and volume of distribution were 24.1 ± 0.55 mL/min/kg and 44.8 ± 23.5 L/kg, respectively. The mean oral bioavailability was 31%.

**CONCLUSIONS AND CLINICAL RELEVANCE**

The study data indicated that the general disposition pattern and bioavailability of metformin in dogs are similar to those reported for cats and humans. *(Am J Vet Res 2017;78:1193–1199)*