

STANDARD ARTICLE

Evaluation of hepatic tumor portal perfusion using mesenteric angiography: A pilot study in 5 dogs

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Background: Mesenteric angiography is a sensitive method for visualizing portal perfusion in the dog.**Objectives:** To evaluate hepatic portal perfusion in dogs with incompletely resectable hepatic tumors using mesenteric angiography.**Animals:** Five client-owned dogs with incompletely resectable hepatic tumors evaluated with mesenteric angiography.**Methods:** Retrospective case series. Electronic medical records at the Animal Medical Center were analyzed to identify dogs that underwent mesenteric portography to determine blood flow to nonresectable hepatic tumors and subsequently determine ideal routes for transarterial embolization, vascular stent placement, or both. The images obtained from mesenteric angiography were analyzed and compared to those obtained from computed tomography angiography.**Results:** Portography was accomplished using direct mesenteric venography in 3 dogs with hepatocellular carcinoma (HCC), cranial mesenteric arteriography in 1 dog with hepatic adenoma or well-differentiated HCC, and via splenic arteriovenous fistula in 1 dog with diffuse hepatic hemangiosarcoma metastases. Mean pixel densities in areas of hepatic tumor growth identified statistically significant decreases in portal blood flow ($P = .02$) compared to normal hepatic parenchyma.**Conclusions and Clinical Importance:** Initial findings indicate that the blood supply to large and metastatic hepatic tumors in dogs may correlate with that in humans, such that the majority of the tumor blood supply arises from the hepatic artery and not the portal vein. Differences in blood supply between normal hepatic parenchyma and hepatic tumors might be exploited by developing selective tumor therapies such as arterial embolization or chemoembolization that largely spare normal liver tissue. Further investigation is warranted.**KEYWORDS**

canine, hemangiosarcoma, hepatocellular adenoma, hepatocellular carcinoma, mesenteric angiography, portal vein

1 | INTRODUCTION

The liver has a generous blood supply that makes it prone to bleeding during surgical manipulation.¹⁻³ For this reason, less invasive measures such as embolization and chemoembolization, which target and

occlude tumor vasculature, have been attempted to treat hepatic tumors not amenable to safe surgical resection.^{4,5} Anatomically, the normal liver receives 70%-80% of its blood supply from the portal vein and approximately 20%-30% from the hepatic artery.⁶ In the human medical literature, many studies have been conducted that illustrate that HCC tumors have a primarily arterial blood supply.⁷⁻¹⁰ This change from dual blood supply to a primarily singular arterial blood supply occurs as the tumor grows in size.¹¹ In an experimental

Abbreviations: CT, computed tomography; HCC, hepatocellular carcinoma; HSA, hemangiosarcoma; ROI, regions of interest; TAE, transarterial embolization; TACE, transarterial chemoembolization.

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study of hepatic murine adenocarcinoma, 2 forms of radioactive material were injected into the liver vasculature: 1 in the hepatic artery and the other in the portal venous system.¹² In that same study, the hepatic artery was shown to contribute 85% of total hepatic tumor blood flow, and as the tumors increased in size, the contribution from the hepatic artery increased to 95%.¹² The portal vein was shown to contribute to only 4% of blood flow to large hepatic tumors.¹² In another study, experimentally induced hepatic tumors in mice and rabbits were shown to infiltrate small branches of both the portal and hepatic veins at the edge of the tumor, causing occlusion; infiltration did not occur in the arterial branches.⁷ This occlusion was believed to be the cause for the primarily arterial blood supply to these hepatic tumors.⁷ In the same study, human livers affected by metastatic carcinomas were evaluated on necropsy and also shown to have a predominant arterial blood supply.⁷ These tumors had comparable tumor infiltration into and occlusion of the portal blood supply, as demonstrated experimentally in mice and rabbits.⁷ Tumor neoangiogenesis also can be attributed to changes in the vasculature of these tumors. As tumors outgrow their blood supply, angiogenic growth factors are released and cause the formation of new capillaries. The increased capillary formation causes an increase in arterial supply to these neoplasms.¹³ It remains unclear if liver tumors in dogs share this transformation in blood supply during growth. If so, arterial directed therapies could be explored in these dogs.

The prevalence of primary hepatic neoplasia in dogs ranges from 0.6% to 0.9%.^{1,14} Hepatocellular carcinoma (HCC) accounts for 50%-70% of all non-hematopoietic neoplasia in the canine liver.^{14,15} Three different forms of canine HCC occur: massive, nodular, and diffuse.^{14,15} The massive form of HCC is the most common (61%), and complete surgical resection is the treatment of choice, carrying a good prognosis.¹⁶ The nodular and diffuse forms of HCC often are not amenable to surgical excision.^{17,18} Unfortunately, chemotherapy and radiation therapy have been unsuccessful at inducing reliable tumor responses.¹⁹ For diffuse tumors and massive tumors not amenable to safe surgical excision, regional therapy provides a possible alternative means of treatment.

Hepatocellular adenomas account for 30% of primary hepatocellular neoplasia in dogs.¹⁵ They are well-differentiated, benign tumors that are often large and appear as single neoplasms within the liver.²⁰ Hepatocellular adenomas are well-encapsulated and compress the surrounding parenchyma; however, they do not invade local parenchyma as do HCCs.²⁰ In general, surgical resection is the treatment of choice and is often curative.²⁰ To our knowledge, targeted treatments other than surgical excision have not been widely explored for hepatic adenomas not amenable to surgical excision.

Hemangiosarcoma (HSA) is a vascular endothelial tumor that accounts for up to 2% of all neoplasia in dogs but accounts for only 4%-6% of primary hepatic tumors.^{8,21-23} Although the most common site for HSA in dogs is the spleen, primary HSA also occurs in the liver.¹⁵ Hepatic metastases may develop from primary splenic HSA as a result of drainage of the spleen by the portal system. The mortality rate of HSA is high in dogs because of metastatic disease that typically is not amenable to complete resection.⁸ Surgery and chemotherapy can prolong the lives affected dogs, but ultimately, the prognosis for this disease is grave.^{8,24} Targeted treatments such as embolization or

chemoembolization have not been instituted widely as treatment for nonresectable hepatic HSA.

Transarterial embolization (TAE) and chemoembolization (TACE) have been investigated for treatment of nonresectable hepatic tumors, especially HCCs in dogs, and are helpful in decreasing the potential for hemorrhage.^{1,4,5} These less invasive measures have been tested in dogs without hepatic tumors and were shown to be well tolerated.²⁵ The dominant arterial blood supply to hepatic tumors in people is well documented in the medical literature, but to our knowledge, no similar reports describing hepatic tumor perfusion in dogs exist.^{7,9,10,26} A dominant arterial blood supply would support further investigation of arterial treatments in dogs. In recent years, measurement of pixel intensity on angiography has proven to be a valuable and objective way of distinguishing differences in tissue composition and perfusion, especially in the field of cardiology, to assess organ blood flow in various disease processes.²⁷ The role of pixel intensity measurements to assess blood flow to hepatic neoplasms has not been established to our knowledge. The purpose of this pilot study was to evaluate the portal perfusion of incompletely resectable hepatic tumors in dogs using mesenteric angiography and to compare perfusion of canine hepatic tumors to normal hepatic parenchyma.

2 | MATERIALS AND METHODS

Electronic medical records from the Animal Medical Center were retrospectively analyzed to identify dogs diagnosed with hepatic tumors that underwent mesenteric angiography between March 2016 and November 2017. Criteria for inclusion were a complete patient medical record, evidence of incompletely resectable hepatic neoplasia, tumor cytology or histopathology, computed tomography angiography (CTA) (with a complete report from a board-certified radiologist), mesenteric angiography images available for review, and client consent for all diagnostic tests to have been performed. Incompletely resectable hepatic neoplasia was defined as multifocal or diffuse hepatic neoplastic disease or a single hepatic tumor sufficiently large or invasive as to make complete surgical resection highly unlikely or associated with considerable risk. Incomplete resectability of the tumors was considered necessary as 1 of the inclusion criteria because the study was meant to determine blood flow to hepatic tumors to plan specific therapeutic interventions such as TAE, vascular stenting, or both for each dog.

Case records were reviewed, and images from mesenteric portograms and CTA were analyzed to help define hepatic tumor perfusion. All dogs had multiphase abdominal CTA performed to determine if the hepatic tumor could be resected surgically. After determination of an incompletely resectable tumor, mesenteric angiography was performed to assess hepatic tumor blood flow, in preparation for treatment with embolization or stenting. Portography was accomplished using direct jejunal mesenteric venography in 3 of the dogs with HCC, cranial mesenteric arteriography in 1 dog with a hepatic adenoma or well-differentiated HCC, and by splenic arteriography through an arteriovenous fistula in 1 dog (that formed secondary to previous splenectomy) with diffuse hepatic HSA metastases. Mean pixel densities of areas of hepatic tumors and 2 other areas of subjectively normal



FIGURE 1 A 10-year-old male castrated Yorkshire Terrier with no history of hepatic disease or hepatic neoplasia. A, Mesenteric digital subtraction portogram “mask” demonstrating the selection of 3 regions of interest loosely based on left, central, and right regions of the liver, all representing normal hepatic parenchyma. B, Mesenteric digital subtraction portogram demonstrating peak contrast uptake in all regions of the liver with normal portal perfusion of the liver

hepatic parenchyma, defined as the regions of interest (ROIs), were measured using Horos (Horos, version 2.0.2, Horos Project, Open Source, available at: www.horosproject.org) (Figure 1). The ROIs were chosen subjectively based on areas of contrast opacification observed at peak intensity after mesenteric angiography, as well as areas of known hepatic tumor location observed by abdominal organ displacement and prior CTA. Greater opacification was correlated with higher blood flow to that region of tissue. Once these ROIs were chosen, they were propagated throughout the entire duration of the angiogram. The initial mask image (unopacified ROIs) was standardized (set to an equivalent baseline value). Similar ROI studies have been performed in people.^{27–29} A baseline ROI pixel count of 3012 (established by the Horos) was assigned for comparison of ROIs for tumor and normal hepatic tissue. Peak delta values for each dog then were calculated by subtracting the peak ROI pixel count values (acquired for normal and neoplastic liver ROIs) from the standardized baseline ROI pixel count of 3012. The ROI differences (deltas) between the tumor and the liver specimens then were averaged separately to acquire mean delta values for liver and neoplastic tissue and then were compared to each other.

2.1 | Statistical analysis

Between groups, analysis of baseline variables (peak ROI pixel count and the peak to baseline delta) was performed using analysis of variance as error residuals, and raw data were deemed normal by Kolmogorov-Smirnoff analyses. Hypothesized mean analyses were carried out by way of a Student's *t*-test. All analyses were deemed significant at $P < .05$ and carried out using SAS 9.4 (SAS software, version 9.4; SAS Institute Inc, Cary, North Carolina).

3 | RESULTS

At the Animal Medical Center, 5 dogs were identified that satisfied inclusion criteria for the study. Represented breeds included 2 Yorkshire Terriers, 1 Polish Hound, 1 Schnauzer mix, and 1 Goldendoodle. Dogs ranged from 8 to 13 years of age and consisted of 4 spayed females and 1 castrated male. Three dogs were presented for incompletely resectable well-differentiated HCCs, 2 that were centrally located, and 1 that was primarily right-sided. Two of these dogs had ascites. The 4th dog in the study had a central nonresectable adenoma or well-differentiated HCC (histopathology was equivocal). The 5th dog in the study had stage II splenic HSA treated by splenectomy and doxorubicin, and that required blood transfusion for recurrent hemoabdomen associated with multifocal hepatic metastases. This dog did not have ascites at the time of presentation.

All dogs had multiphase abdominal CTA performed, and results are summarized in Supporting Information Table 1. The CTs were performed as a general diagnostic evaluation for each dog to determine if the tumor could be resected. Computed tomography angiography studies of dogs with HCC and hepatocellular adenoma identified hypoattenuating masses on both arterial and portal venous phases. The CT for the dog with HSA disclosed multifocal, well-defined hepatic masses with a thin outer rim of contrast enhancement on the arterial phase.

Because of the incompletely resectable nature of these hepatic tumors, dogs were anesthetized for palliative procedures including hepatic vein stenting, abdominal port placement for ascites, TAE, TACE, or some combination of these, and mesenteric angiography ultimately was performed as previously described. Mesenteric portography was performed to determine the blood supply to each hepatic

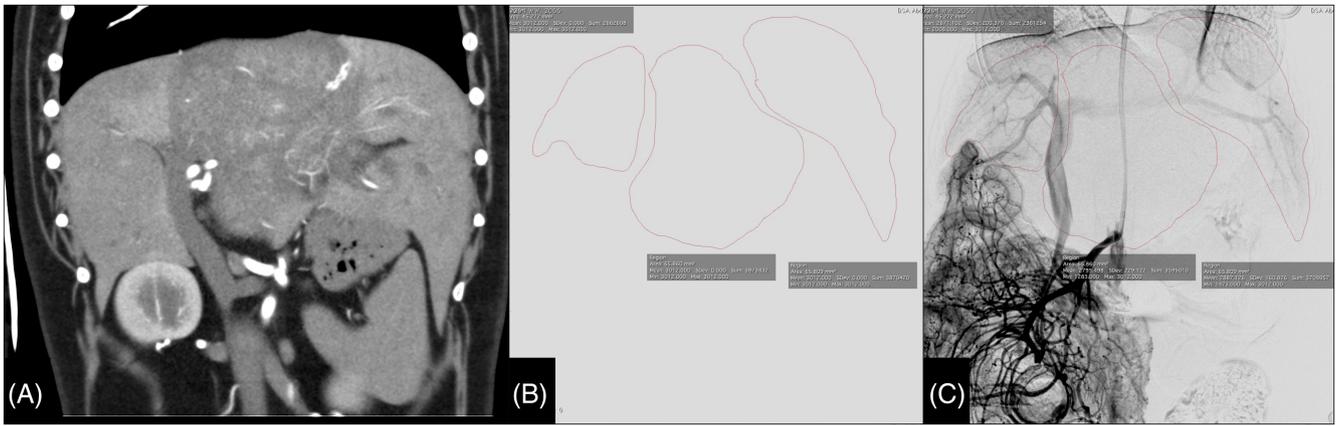


FIGURE 2 Dog 1. A 13-year-old female spayed Polish Hound with a centrally located hepatocellular carcinoma. A, Coronal reconstruction of a computed tomographic angiogram demonstrating slight hypoattenuation of the hepatic mass in the venous phase. B, Mesenteric digital subtraction portogram “mask” demonstrating the selection of 3 regions of interest, 2 of normal hepatic parenchyma, and 1 surrounding the hepatic mass. C, Mesenteric digital subtraction portogram demonstrating substantial peak contrast uptake in the areas of the normal hepatic parenchyma with no obvious contrast enhancement in the area of the centrally located hepatic tumor. The imaging also identifies penetrating towel clamps overlapping normal hepatic parenchyma

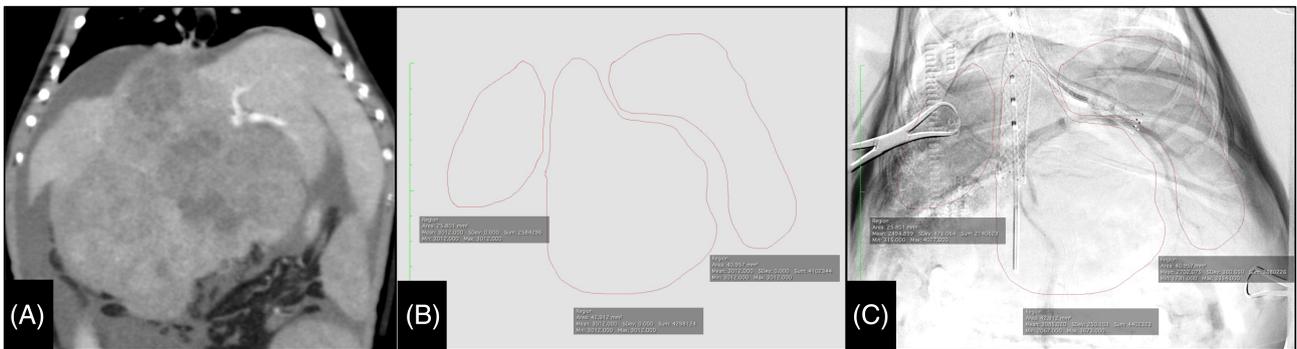


FIGURE 3 Dog 2. A 13-year-old female spayed Yorkshire Terrier with a centrally located hepatocellular carcinoma. A, Coronal reconstruction of a computed tomographic angiogram indicates hypoattenuation of the hepatic mass in the venous phase. B, Mesenteric digital subtraction portogram “mask” demonstrating the selection of 3 regions of interest, 2 of normal hepatic parenchyma, and 1 surrounding the central hepatic mass. C, Mesenteric digital subtraction portogram demonstrating substantial peak contrast uptake in the areas of the normal hepatic parenchyma with no substantial contrast enhancement in the area of the hepatic tumor. The imaging also identifies stents in the vena cava and left hepatic vein as well as penetrating towel clamps overlapping normal hepatic parenchyma

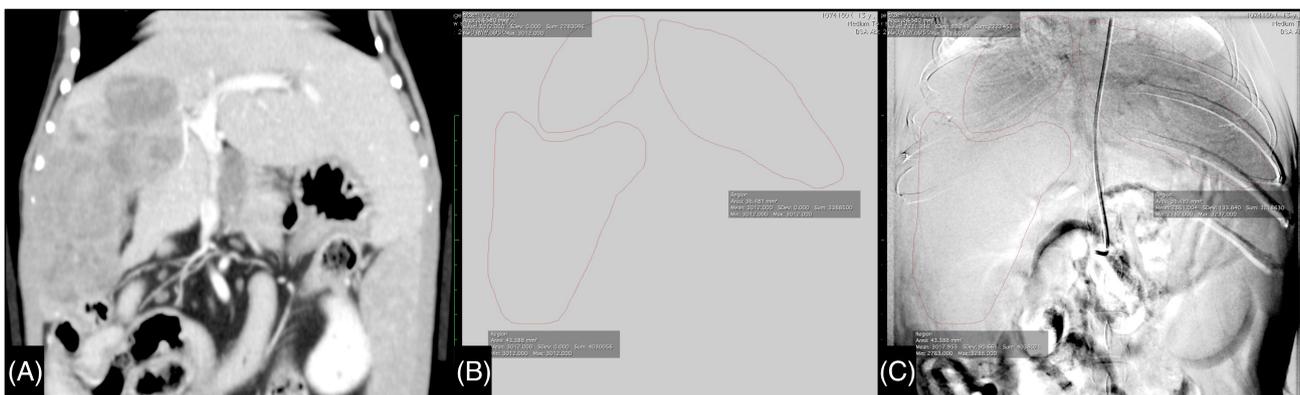


FIGURE 4 Dog 3. A 13-year-old female spayed Schnauzer mix with a right-sided hepatocellular carcinoma. A, Coronal reconstruction of a computed tomographic angiogram demonstrating hypoattenuation of the hepatic mass in the venous phase. B, Mesenteric digital subtraction portogram “mask” demonstrating the selection of 3 regions of interest, 2 of normal hepatic parenchyma, and 1 surrounding the right-sided hepatic mass. C, Mesenteric digital subtraction portogram demonstrating substantial peak contrast uptake in the areas of the normal hepatic parenchyma with no contrast enhancement in the area of the hepatic tumor

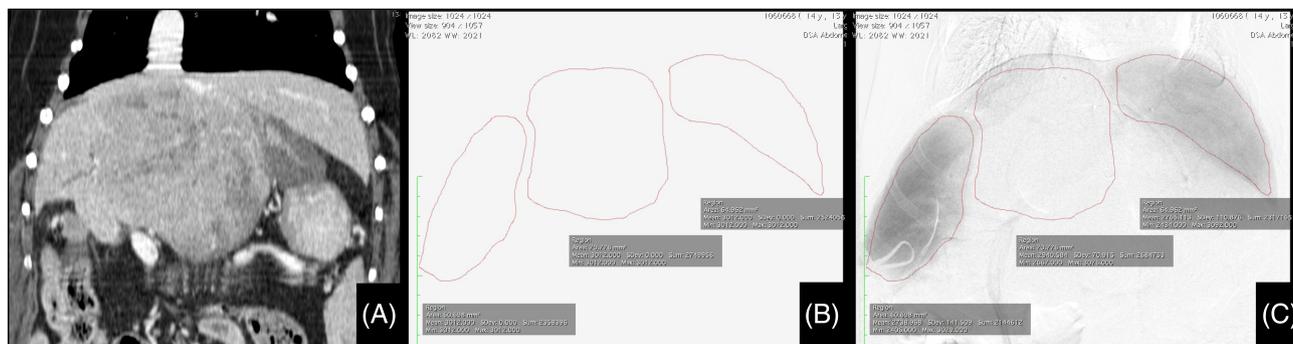


FIGURE 5 Dog 4. A 9-year-old female spayed Goldendoodle with a centrally located well-differentiated hepatocellular carcinoma or adenoma. A, Coronal reconstruction of a computed tomographic angiogram demonstrating general hypoattenuation of the hepatic mass in the arterial phase. B, Mesenteric digital subtraction portogram “mask” demonstrating the selection of 3 regions of interest, 2 of normal hepatic parenchyma, and 1 surrounding the hepatic mass. C, Mesenteric digital subtraction portogram demonstrating peak contrast uptake in the areas of the normal hepatic parenchyma with no obvious contrast enhancement in the area of the hepatic tumor

tumor to plan the treatment of these tumors using selective procedures such as embolization and chemoembolization. In each dog, portal blood flow was compared between hepatic tumors and regions of normal hepatic parenchyma by pixel density analysis of mesenteric angiography, as described in the previous section (Figures 2–6). Supporting Information Table 2 presents the individual pixel densities for tumor and normal parenchyma in comparison to background pixel densities. With these values, a significant difference was found between portal blood flow to normal hepatic parenchyma and hepatic masses, such that portal blood flow to hepatic tumors was markedly decreased ($P = .02$). No statistical difference was found when comparing regions of normal parenchyma ($P = .32$). The described statistical differences are reported in Table 1.

4 | DISCUSSION

Measurement of pixel intensity on imaging modalities, such as CT and ultrasonography, has proven to be a valuable, objective way of distinguishing significant differences in tissue composition and perfusion.^{28,30–33}

Pixel intensity of angiography has been studied more recently and has been used successfully in the field of cardiology to assess organ blood flow in various disease processes.^{27,29} In our study, the relative amount of blood supplied by the portal vein to a given hepatic mass was quantified using pixel intensity (Supporting Information Table 2). Regions of interest of a given hepatic mass and 2 different areas of surrounding hepatic parenchyma were compared for each dog (Figures 2–6), and it was found that the hepatic masses had significantly decreased portal blood flow compared to normal hepatic parenchyma when mesenteric portography was performed (Table 1). These findings are consistent with the human medical literature on hepatic tumor blood flow.^{7–11} In addition, the 2 different ROIs of normal hepatic parenchyma had no significant differences in mean pixel intensities (portal perfusion) when compared.

Multiphase CTA also was performed in all 5 dogs and identified inconsistencies in contrast enhancement compared to some reports listed above (Supporting Information Table 1). Four of the CTs, including those for all HCCs and the hepatocellular adenoma, disclosed centrally nonenhancing masses (hypoattenuating) on both arterial and portal venous phases. The CT for the dog with the HSA disclosed

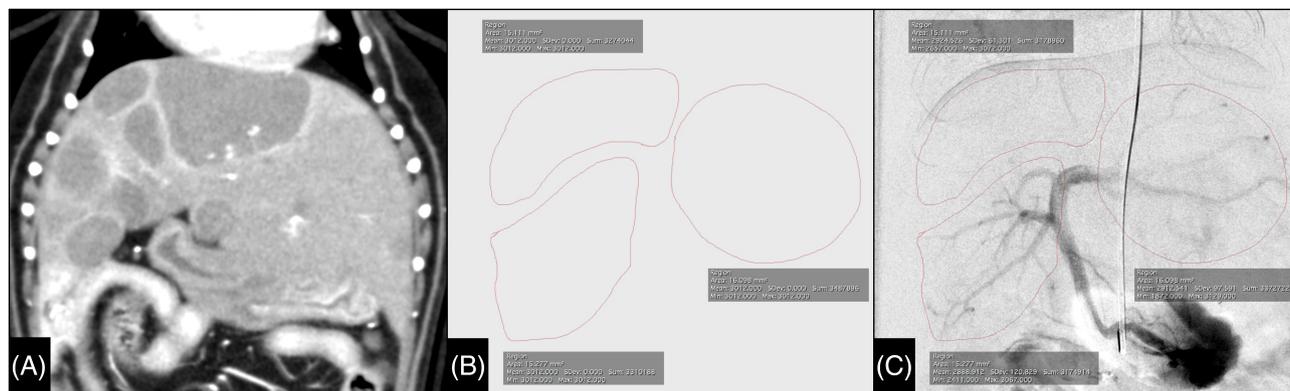


FIGURE 6 Dog 5. An 8-year-old male castrated Yorkshire Terrier with multifocal hepatic nodules diagnosed as hemangiosarcoma. A, Coronal reconstruction of a computed tomographic angiogram demonstrating hypoattenuation of the hepatic nodules with a rim of hyperattenuation around each nodule in a venous phase. B, Mesenteric digital subtraction portogram “mask” demonstrating the selection of 3 regions of interest, 2 of normal hepatic parenchyma, and 1 surrounding the region of hepatic nodules. C, Mesenteric digital subtraction portogram demonstrating substantial peak contrast uptake in the areas of the normal hepatic parenchyma with no substantial contrast enhancement in the area of the hepatic metastases

TABLE 1 Comparison of mean delta values for normal hepatic parenchyma (liver 1 and 2) with hepatic tumors

Mean delta from baseline, liver 1/2	Mean delta from baseline, tumor	Delta from liver 1/liver 2 versus tumor	Delta from liver 1 versus liver 2
219.9	39	$P = .02$	$P = .32$

There is a statistically significant difference in perfusion, as measured by pixel density, between normal hepatic parenchyma and the hepatic tumors. Liver 1 and 2 were not statistically different.

multifocal, well-defined hepatic masses with a thin outer rim of contrast enhancement on the arterial phase.

Computed tomography angiography is a useful method to assess hepatic tumor blood flow and has proved helpful in the detection of hepatic tumors.^{9,34–37} Although many studies have used dynamic CT imaging to identify differences in contrast enhancement of various hepatic tumors in dogs, the results of these studies have been inconsistent.^{1,37–41} Given these conflicting results, it seems that although CT is helpful in the detection of hepatic tumors, it is not sensitive for differentiating arterial and venous blood flow to (and from) these neoplasms, and use of other methods, such as mesenteric portography, may prove more helpful. Although CTA in these cases suggested more of an arterial blood supply to the hepatic tumors, portal perfusion was difficult to interpret. As tumors grow within the liver, normal portal triads are replaced by unorganized tumor tissue, and alterations in tumor vascularity should be anticipated.^{42,43} In comparison to CTA, mesenteric angiography offers more dynamic, extended periods of portal perfusion for evaluation. In addition, a CT venous phase typically contains some arterial enhancement, and both portal venous and hepatic venous structures are opacified concurrently, complicating differentiation of these latter structures, especially when normal anatomy is displaced by large tumors.^{43,44} We believe mesenteric angiography more accurately identifies the decreased portal blood supply to these neoplasms (Supporting Information Table 2).

Although our pilot study was successful in meeting the stated objective, it had some limitations. Our study was retrospective in nature, with no control population used for comparison of hepatic blood flow, and the study population was small. Because of the limited case number and the retrospective nature of the study, the protocol used for portography also was unable to be standardized among all patients. Although we attempted to select ROIs that best exemplified areas of hepatic neoplasia and normal hepatic parenchyma, the selections were subjective in nature. Intra-observer and interobserver variations also were not assessed in our study, and the small case number likely would not have allowed for accurate assessment of these variations during pixel intensity assessment. Overlying vessels, devices, and abdominal organs could not be fully eliminated in the calculations, given the limited detail of portography. In addition, ROIs and pixel density measurements have not been standardized for the canine liver and provide a crude objective measure of visibly different portal perfusions between neoplastic and normal hepatic tissue. Given the limited modalities available for more objective perfusion studies at our institution, the method chosen provided the best and most accurate available means of assessing the various extents of portal perfusion. Although the initial ROI pixel density for 3 of the hepatic tumors decreased, 2 slightly increased above baseline, which was unexpected

(Supporting Information Table 2). We believe that the increases may be explained by metallic equipment in the field as well as respiratory motion and gastrointestinal peristalsis changing the baseline mask image and therefore altering the ROIs (Figures 2 and 4). However, it is unlikely that these findings affected our conclusions because similar motion artifacts and surgical instruments were present in the normal hepatic parenchyma ROIs, likely resulting in similar pixel density adjustments. Surgical instruments also were observed in dog 2 (Figure 3), but pixel density for this hepatic tumor was decreased, as expected. To validate the findings of our study, further investigation must be performed to determine whether the use of mesenteric portography can be established as a dependable means of objectively assessing portal blood flow.

Our findings suggest that the blood supply to large, incompletely resectable hepatic tumors in dogs may be similar to that observed in humans, such that the majority of the tumor blood supply originates from the hepatic artery. The relationship between the tumor and its blood supply is useful in determining appropriate treatment for these tumors, especially when considering selective arterial therapies such as embolization or chemoembolization.

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CONFLICT OF INTEREST DECLARATION

Chick Weisse is a minority shareholder in a company that makes medical devices and consults for companies that make medical devices, but this manuscript does not relate to these other obligations, other than to suggest alternative treatment options should be explored.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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