Received: 19 June 2019 | Accepted: 29 October 2019

DOI: 10.1111/jvim.15661

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

# Plasma renin activity and aldosterone concentration in dogs with acquired portosystemic collaterals

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## Abstract

**Background:** The renin-angiotensin-aldosterone system (RAAS) is activated in humans with portal hypertension (PH) associated with liver disease. However, involvement of RAAS in dogs with intrahepatic PH is not clear.

**Objective:** To measure plasma renin activity (PRA) and plasma aldosterone concentration (PAC) in dogs with PH (chronic hepatitis [CH] and primary hypoplasia of the portal vein [PHPV]), dogs with extrahepatic congenital portosystemic shunt (EH-CPSS), and healthy dogs and to determine whether the RAAS is activated in dogs with PH.

**Animals:** Twenty-seven dogs with acquired portosystemic collaterals (APSCs; 15 dogs with CH, 12 dogs with PHPV), 9 dogs with EH-CPSS, and 10 healthy dogs.

**Methods:** Retrospective study. Plasma renin activity and PAC were measured by radioimmunoassay.

**Results:** Plasma renin activity was significantly higher in the CH group (median, 4.4 ng/mL/h) than in the EH-CPSS (median, 1.0 ng/mL/h; $P < .01$) and the healthy (median, 1.1 ng/mL/h; $P < .01$) groups. No significant differences were found between the PHPV group (median, 2.2 ng/mL/h) and other groups. Plasma aldosterone concentration was significantly higher in the CH (median, 111.0 pg/mL) and PHPV (median, 89.5 pg/mL) groups than in the EH-CPSS (median, 1.0 pg/mL; $P < .001$, $P < .01$, respectively) and healthy (median, 14.5 pg/mL; $P < .001$, $P < .05$, respectively) groups.

**Conclusions and Clinical Importance:** Activation of the RAAS contributes to the pathophysiology of intrahepatic PH in dogs, suggesting that spironolactone may not only be effective for the treatment of ascites but also for the suppression of intrahepatic PH.

KEYWORDS

canine, chronic hepatitis, portal hypertension, primary hypoplasia of the portal vein, renin-angiotensin-aldosterone system

## 1 | INTRODUCTION

Portal hypertension (PH) is caused by excessive resistance to blood flow in the portal circulation, and can be classified into 3 types: prehepatic, intrahepatic, and posthepatic.[1,2] In dogs, chronic hepatitis (CH) and

**Abbreviations:** ACE, angiotensin-converting enzyme; APSCs, acquired portosystemic collaterals; AT-II, angiotensin-II; CH, chronic hepatitis; CT, computed tomography; EH-CPSS, extrahepatic congenital portosystemic shunt; PAC, plasma aldosterone concentration; PH, portal hypertension; PHPV, primary hypoplasia of the portal vein; PRA, plasma renin activity; RAAS, renin-angiotensin-aldosterone system; SPP, splenic pulp pressure; TGF-β, transforming growth factor-β.

primary hypoplasia of the portal vein (PHPV) are the primary causes of intrahepatic PH.[1] Affected dogs often have acquired portosystemic collaterals (APSCs) that develop as a compensatory response to increased portal vein pressure.[2-4] Therefore, APSCs can serve as an indirect indicator of intrahepatic PH in dogs. In contrast, extrahepatic congenital portosystemic shunts (EH-CPSS) with large-caliber vein are not typically associated with PH in dogs.[1,5] The combination of PH and moderate hypoalbuminemia because of liver dysfunction often induces ascites in dogs with CH and PHPV.[3,4,6] Abdominal effusion however is uncommon in dogs with EH-CPSS because they typically do not have severe hypoalbuminemia or PH.

The renin-angiotensin-aldosterone system (RAAS) is a physiological regulator of blood pressure, electrolyte balance, and fluid homeostasis,[7] and its activation often is assessed by measurement of plasma renin activity (PRA) and plasma aldosterone concentration (PAC) in dogs with cardiovascular and renal diseases.[7] Increased PRA associated with these diseases is an important determinant promoting aldosterone secretion. The RAAS is involved in the development of ascites associated with liver disease.[2] Plasma renin activity and PAC frequently are increased in human patients with liver cirrhosis,[8,9] which is considered a compensatory response to systemic and splanchnic arterial vasodilatation and decreased extracellular fluid volume caused by ascites retention associated with PH.[9,10] However, to the best of our knowledge, activation of the RAAS has not been evaluated in dogs with liver disease. Therefore, our aim was to determine whether the RAAS is activated in dogs with APSCs compared with healthy dogs and dogs with EH-CPSS. We hypothesized that PRA and PAC would be increased in dogs with intrahepatic PH.

## 2 | MATERIALS AND METHODS

### 2.1 | Animals

We assessed 36 client-owned dogs with liver disease that were presented to the Nihon University Animal Medical Center between 2009 and 2019. Twenty-seven dogs underwent laparoscopic liver biopsy and were diagnosed histopathologically with CH or PHPV by a board-certified veterinary pathologist. In these dogs, APSCs were confirmed by computed tomography (CT) angiography or laparoscopic splenoportography, as previously described.[11,12] As control animals for the dogs with APSCs caused by intrahepatic disease, we used 9 dogs diagnosed with EH-CPSS by CT angiography.[11] All dogs were free of concurrent diseases, such as congestive heart failure, pulmonary disease, or renal failure, based on clinical signs, auscultation, laboratory testing, and diagnostic imaging findings. Informed consent was obtained from the owner of each dog before enrollment of the dog in the study.

The study controls were 10 beagle dogs (7 males and 3 females) that were confirmed as healthy based on the findings of clinical examination, CBC, serum biochemistry, and thoracic and abdominal radiography and ultrasonography. The median age and body weight of dogs in the control group were 0.8 years (range, 0.8-2.8 years) and 10.9 kg (range, 9.4-11.8 kg), respectively. The College of Bioresource Sciences, Nihon University, granted ethical approval for the use of the control dogs, and the study was performed in accordance with the institution's Guide for Animal Experimentation.

### 2.2 | Blood samples

Blood samples obtained from the jugular vein of dogs in a sitting position were collected in EDTA tubes for PRA and PAC measurements and in heparin tubes for biochemical blood testing. Samples were centrifuged at 15 800 rpm for 90 seconds and the plasma obtained was stored immediately at −20°C. These samples were sent to SRL Co (Tokyo, Japan) within 24 hours and measurement of PRA and PAC was performed that day.

### 2.3 | Measurements of PRA and PAC and biochemical blood tests

Both PRA and PAC were measured using a radioimmunoassay kit (SRL renin kit; FUJIREBIO Inc, Tokyo, Japan and Spac-S aldosterone; FUJIREBIO Inc) in accordance with the manufacturer's instructions.[13,14] All samples were analyzed in duplicate by personnel blinded to dog identity, and the mean values of the data obtained were used for analyses. Heparinized plasma was tested immediately after centrifugation. Liver enzyme activity, and albumin, bilirubin, blood urea nitrogen, creatinine, fasting serum bile acid, ammonia, sodium, potassium, and chloride concentrations were measured using a biochemical auto-analyzer (LABOSPECT 003; Hitachi High-Technologies Co, Ltd, Tokyo, Japan).

### 2.4 | Histopathology

In the CH and PHPV groups, the liver samples were obtained using 5-mm cup forceps during laparoscopy, as previously described.[15] Liver biopsy samples were fixed in 10% neutral buffered formalin and embedded in paraffin. All sections were prepared and stained with hematoxylin and eosin, and histologically diagnosed as CH or PHPV in accordance with the criteria developed by the World Small Animal Veterinary Association Liver Standardization Group.[1]

### 2.5 | Statistical analysis

All variables measured were assessed for conformity to normal distributions by using the Kolmogorov-Smirnov and Shapiro-Wilk normality tests. Because the data were not normally distributed, we have reported the median and range. Differences in PRA and PAC between the APSCs and healthy groups, between the APSCs and EH-CPSS groups, and between dogs with and without ascites in the APSCs group were statistically analyzed using the Mann-Whitney test. Plasma renin activity and PAC were compared between groups using the Kruskal-Wallis test in conjunction with Dunn's multiple comparison post hoc test. Correlations between PRA and PAC in the APSCs group were evaluated using Spearman's

correlation coefficient. All data were analyzed using GraphPad PRISM for Mac OS X version 5.0b software (GraphPad Software Inc, La Jolla, California). Differences were considered significant for *P*-values <.05.

## 3 | RESULTS

Thirty-six cases were separated into APSCs (n = 27) and EH-CPSS (n = 9) groups. The characteristics of the CH (n = 15), PHPV (n = 12), and EH-CPSS groups are shown in Table 1. Twelve dogs in the CH group and 5 dogs in the PHPV group had ascites, whereas in contrast no dogs in the EH-CPSS group had ascites. Among the dogs in the CH group that had ascites, 1 had received spironolactone (0.5 mg/kg PO q12h) and furosemide (0.5 mg/kg PO q12h), 1 had received spironolactone (1 mg/kg PO q12h), and 2 had received furosemide (0.5 mg/kg PO q24h and 1 mg/kg PO q12h, respectively) until 1 day before blood sampling for PRA and PAC measurements. In addition,

**TABLE 2** PRA and PAC in APSCs and healthy groups

| | APSCs group (n = 27) | Healthy group (n = 10) | *P* value |
|---|---|---|---|
| PRA (ng/mL/h) | 4.3 (0.8-19.0) | 1.1 (0.3-3.1) | <.001 |
| PAC (pg/mL) | 101.0 (11.0-723.0) | 14.5 (1.0-42.0) | <.001 |

Abbreviations: APSCs, acquired portosystemic collaterals; PAC, plasma aldosterone concentration; PRA, plasma renin activity.

**TABLE 1** Animal characteristics

| | APSCs group (n = 27) | | |
|---|---|---|---|
| | CH group (n = 15) | PHPV group (n = 12) | EH-CPSS group (n = 9) |
| Breed | American Cocker Spaniel (3) | Miniature Dachsund (3) | Toy Poodle (2) |
| | English Cocker Spaniel (2) | Maltese (2) | Mixed-breed (2) |
| | Miniature Dachsund (2) | Bichon Frise (1) | Bichon Frise (1) |
| | Mixed-breed (2) | Chihuahua (1) | Cavalier King Charles Spaniel (1) |
| | Chihuahua (1) | German Shepherd (1) | Shih Tzu (1) |
| | Golden retriever (1) | Italian Greyhound (1) | Welsh Corgi (1) |
| | Jack Rassell Terrier (1) | Jack Russell Terrier (1) | Whippet (1) |
| | Labrador Retriever (1) | Welsh Corgi (1) | |
| | Toy Poodle (1) | Yorkshire Terrier (1) | |
| | West Highland White Terrier (1) | | |
| Sex | 4M, 4MC, 7FS | 6MC, 4F, 2FS | 2M, 3MC, 2F, 2FS |
| Age (years) | 9.1 (2.2-11.1) | 5.1 (0.9-14.4) | 1.3 (0.3-4.0) |
| BW (kg) | 7.5 (1.6-28.6) | 4.6 (2.4-37.0) | 3.2 (1.8-8.5) |
| ALT (U/L) | 186 (50-1838) | 176 (21-1340) | 77 (33-835) |
| ALP (U/L) | 250 (65-958) | 111 (64-1079) | 247 (55-2246) |
| AST (U/L) | 98 (38-397) | 72 (26-273) | 70 (24-103) |
| GGT (U/L) | 12 (8-29) | 7 (0-24) | 5 (0-37) |
| Albumin (g/dL) | 2.1(1.3-2.6) | 2.4 (1.6-2.8) | 2.4 (1.4-3.3) |
| Total bilirubin (mg/dL) | 0.5 (0.1-1.3) | 0.2 (0.0-0.5) | 0.1 (0.0-0.5) |
| Glucose (mg/dL) | 88 (63-144) | 91 (80-111) | 84 (61-109) |
| BUN (mg/dL) | 8 (3-27) | 7 (3-21) | 14 (3-21) |
| Creatinine (mg/dL) | 0.7 (0.3-1.7) | 0.6 (0.3-1.2) | 0.4 (0.1-0.8) |
| SBA (fasting) (μmol/L) | 44.2 (7.8-611.4) | 63.0 (38.4-285.3) | 42.9 and 195.4 |
| Ammonia (μmol/L) | 37 (3-123) | 47 (31-111) | 150 (19-293) |
| Sodium (mEq/L) | 147 (138-153) | 148 (145-151) | 145 (144-150) |
| Chloride (mEq/L) | 112 (105-118) | 115 (107-118) | 111 108-120) |
| Potassium (mEq/L) | 3.9 (3.1-4.9) | 3.8 (2.8-4.5) | 4.3 (3.8-4.8) |

*Notes*: Data are expressed as the median (range). Numbers in parentheses indicate number of dogs of that breed. SBA values from 13/15 dogs in CH group, 9/12 dogs in PHPV group, and 2/9 dogs with EH-CPSS; other values were missing. Ammonia values from 10/12 dogs in PHPV group; other values were missing.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; APSCs, acquired portosystemic collaterals; AST, aspartate aminotransferase; BUN, blood urea nitrogen; BW, body weight; CH, chronic hepatitis; EH-CPSS, extrahepatic congenital portosystemic shunt; F, female; FS, female-spayed; GGT, gamma-glutamyltranspeptidase; M, male; MC, male-castrated; PHPV, primary hypoplasia of the portal vein; SBA, serum bile acid.

3 dogs with CH had received prednisolone (2 mg/kg PO q24h, 0.5 mg/kg PO q24h, and 0.4 mg/kg PO q24h, respectively) until 1 day before blood sampling.

Plasma renin activity and PAC were significantly higher in the APSCs group than in the healthy group (Table 2). In dogs with APSCs, PRA and PAC were found to be significantly higher than in dogs with EH-CPSS ($P$ = .004, $P$ < .001, respectively). In the APSCs group, no difference was found between dogs with or without ascites with respect to PRA and PAC (Table 3). Moreover, a weakly significant correlation was found between PRA and PAC in the APSCs group ($r_s$ = .51; $P$ = .006; n = 27).

The PRA and PAC results in each group are shown in Figures 1 and 2, respectively. Plasma renin activity was significantly higher in the CH group (median, 4.4 ng/mL/h; range, 1.4-18.0 ng/mL/h) than in the EH-CPSS group (median, 1.0 ng/mL/h; range, 0.3-5.4 ng/mL/h; $P$ < .01) and the healthy group (median, 1.1 ng/mL/h; range, 0.3-3.1 ng/mL/h; $P$ < .01). No significant differences were found between the PHPV group (median, 2.2 ng/mL/h; range, 0.8-19.0 ng/mL/h) and the other groups. Plasma aldosterone concentration was significantly higher in the CH (median, 111.0 pg/mL; range, 29.9-723.0 pg/mL) and PHPV (median, 89.5 pg/mL; range, 11.0-375.0 pg/mL) groups than in the EH-CPSS group (median, 1.0 pg/mL and range, 1.0-23.7 pg/mL; $P$ < .001 and $P$ < .01, respectively) and the healthy group (median, 14.5 pg/mL and range, 1.0-42.0 pg/mL; $P$ < .001 and $P$ < .05, respectively). No significant difference in PAC was found between the CH and PHPV groups.

**TABLE 3** PRA and PAC in ascites and non-ascites APSCs groups

| | Ascites (n = 17) | Non-ascites (n = 10) | *P* value |
|---|---|---|---|
| PRA (ng/mL/h) | 5.3 (0.8-19.0) | 2.4 (0.9-6.0) | .05 |
| PAC (pg/mL) | 143.0 (26.3-723.0) | 89.5 (11.0-226.0) | .11 |

Abbreviations: APSCs, acquired portosystemic collaterals; PRA, plasma renin activity; PAC, plasma aldosterone concentration.

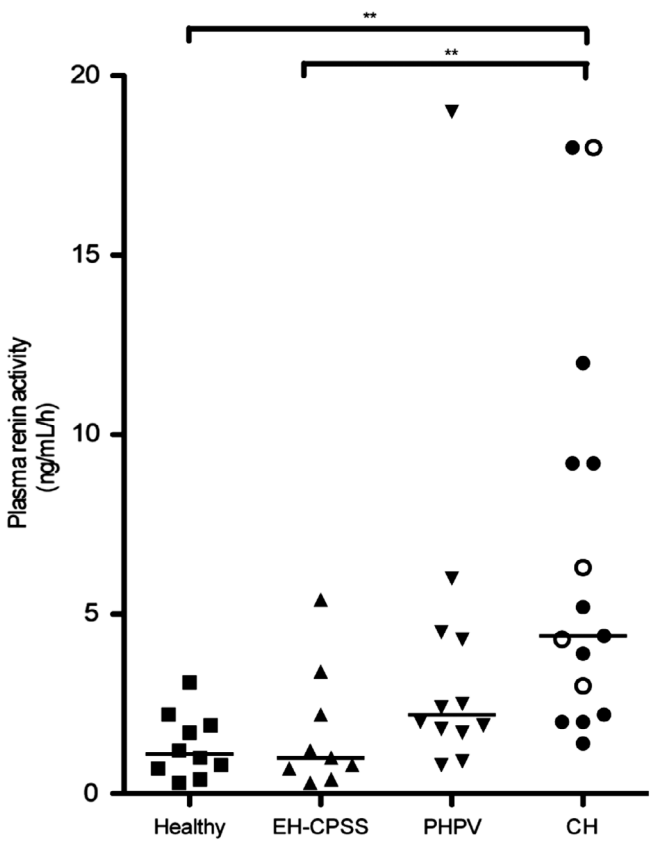


**FIGURE 1** Plasma renin activity in the healthy (n = 10), EH-CPSS (n = 9), PHPV (n = 12), and CH (n = 15) groups. Plasma renin activity was significantly higher in the CH group than in the EH-CPSS ($P$ < .01) or healthy ($P$ < .01) groups. There were no significant differences between the PHPV group and other groups. Symbols; ■ healthy group, ▲ EH-CPSS group, PHPV group, ● CH group (◯ dogs had received diuretics). Lines indicate the median values. **$P$ < .01. CH, chronic hepatitis; EH-CPSS, extrahepatic congenital portosystemic shunt; PHPV, primary hypoplasia of the portal vein

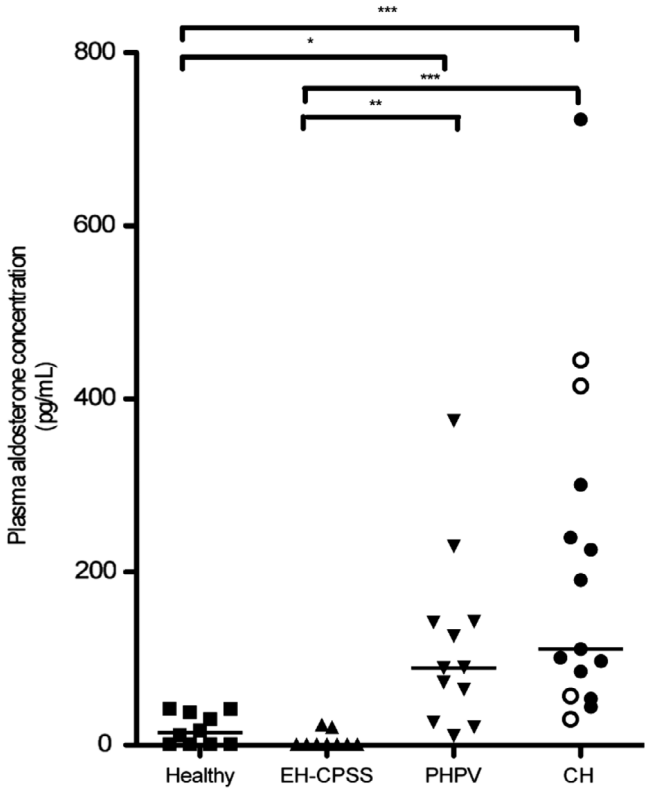


**FIGURE 2** Plasma aldosterone concentration in the healthy (n = 10), EH-CPSS (n = 9), PHPV (n = 12), and CH (n = 15) groups. Plasma aldosterone concentration was significantly higher in the CH and PHPV groups than in the EH-CPSS ($P$ < .001, $P$ < .01, respectively) and healthy ($P$ < .001, $P$ < .05, respectively) groups. There was no significant difference in PAC between the CH group and PHPV group. Symbols; ■ healthy group, ▲ EH-CPSS group, PHPV group, ● CH group (◯ dogs had received diuretics). Lines indicate the median values. ***$P$ < .001, **$P$ < .01, *$P$ < .05. CH, chronic hepatitis; EH-CPSS, extrahepatic congenital portosystemic shunt; PHPV, primary hypoplasia of the portal vein

## 4 | DISCUSSION

We found that PRA and PAC were significantly higher in dogs in the APSCs (PH) group than in those in the healthy group. In humans, the effective circulating blood volume is lower in patients with cirrhosis because of splanchnic arterial vasodilatation caused by PH and a decrease in extracellular fluid volume caused by ascites, which activates the RAAS.[8,16,17] Dogs with cirrhosis and ascites also have splanchnic arterial vasodilatation and decreased extracellular fluid volume.[18] However, in our study, PRA and PAC were not significantly different between dogs in the PH group with and without ascites. Thus, in dogs with liver disease, RAAS may be activated by splanchnic arterial vasodilatation before ascites accumulation rather than because of a decrease in extracellular fluid volume. Furthermore, we detected a weak but significant correlation between PRA and PAC in the APSCs group. A similar moderate correlation between renin and aldosterone has been observed in humans with cirrhosis.[19] In dogs with PH, the balance between PRA and PAC may be affected by their clearance in the liver and negative feedback mechanisms.

Plasma renin activity and PAC were not significantly different between the EH-CPSS group and the healthy group. Portal vein pressure is low or normal in dogs with EH-CPSS because portal blood flow enters the venous system directly via the large shunting vessel.[5] Therefore, for dogs without PH, RAAS activation may be normal. Hepatic encephalopathy is common in dogs with congenital or acquired portosystemic shunting, and leads to neuroendocrine derangements.[20] High serum bile acid concentrations because of shunting also inhibit aldosterone receptors.[21] In addition, liver dysfunction may lead to increased PRA and PAC because endogenous hormones are metabolized in the liver.[19] Although these events may contribute to hyperaldosteronism, PRA and PAC were not high in the dogs with EH-CPSS. Thus, the presence of shunting vessels may not be directly associated with RAAS activation.

Primary hypoplasia of the portal vein is a congenital liver disorder of dogs characterized by decreased portal vein diameter and arteriolar proliferation without inflammation.[22] Portal hypertension and loss of hepatic function occurs in severe cases of PHPV with fibrosis. This disorder has many histological features in common with EH-CPSS, and APSCs develop in PHPV as a consequence of PH.[22] In the PHPV group with APSCs, only PAC was significantly increased compared with the EH-CPSS and healthy groups. Circulating angiotensin-converting enzyme (ACE), an important molecule in the RAAS, is related to portal fibrosis in humans with hepatoportal sclerosis, which has characteristics similar to PHPV with PH in dogs.[23] Although we detected no increase in PRA and did not measure ACE in our PHPV group, we suspect that RAAS may be activated by intrahepatic PH in dogs without inflammation, in a process similar to that which occurs in humans.

Chronic hepatitis is a common primary hepatic disease in dogs characterized by hepatocellular apoptosis or necrosis, inflammatory infiltration, regeneration and fibrosis, and cirrhosis, and end-stage CH often is associated with PH.[1,3] We found that both PRA and PAC were significantly higher in the CH group than in the EH-CPSS and healthy groups, respectively. In humans, PRA is correlated with the severity of PH and the extent of liver dysfunction,[9] and thus high PRA represents an independent risk factor for mortality in humans with cirrhosis. Activation of angiotensin II (AT-II) is associated with increased intrahepatic resistance because of contraction and proliferation of hepatic stellate cells and deposition of fibrous tissue.[24] In addition, transforming growth factor β (TGF-β) is involved in liver fibrosis in dogs,[25-27] and TGF-β expression in humans is increased by AT-II.[24] Plasma aldosterone concentration also is increased by decreased aldosterone clearance because of liver failure.[19] Given that the increase in aldosterone has been associated with an increase in portal venous inflow associated with sodium and water retention,[28] we hypothesize that these mechanisms potentially can aggravate PH and that the RAAS plays a pivotal role in dogs with PH associated with CH.

Previously, portal vein pressure has been found to be higher in dogs with APSCs than in dogs with CPSS,[2] and also higher in dogs with APSCs associated with CH and PHPV than in in healthy dogs and dogs with EH-CPSS.[5] In addition, portal vein pressure tends to be higher in dogs with CH than in dogs with PHPV.[5] Therefore, increased portal vein pressure might underlie the increase in PRA we observed in the CH group compared with the PHPV group. In the present study, however, we were unable to measure portal vein pressure. The activation of aldosterone has been associated with hepatic inflammation and fibrosis,[10,29] and in our APSCs group, we observed that the PAC in dogs with CH tended to be higher than that in dogs with PHPV, indicating that increased PAC also might be related to inflammation in the liver. Activation of the RAAS in dogs with increased portal vein pressure suggests that spironolactone, a competitive antagonist of aldosterone, might not only be effective for the treatment of ascites but also for the suppression of intrahepatic PH.

Our study had some limitations. First, our study was retrospective and had a small sample size, and thus the breed, age, and sex of the dogs were not matched.[30] Second, because some dogs with CH had received prednisolone for hepatic inflammation before sampling, the actual PAC concentrations may be higher than those that we actually measured. However, the RAAS does not appear to be affected by anti-inflammatory dosages of corticosteroids.[16] Moreover, in some dogs, PRA and PAC may have been increased by low doses of diuretics. However, in human patients, it has been found that PAC is not affected by the administration of spironolactone,[19] whereas in healthy dogs treated with 4 mg/kg furosemide daily for 2 weeks, PAC was significantly increased compared with healthy dogs that had not received furosemide.[31] Although in the our study drugs for CH and ascites were administered at low doses and for short periods, these treatments may have affected the results of the study.

In conclusion, both PRA and PAC were high in dogs with APSCs, and we believe that activation of the RAAS was caused by splanchnic artery vasodilatation associated with PH rather than to ascites. Further studies are needed to determine the role of the RAAS in the pathophysiology and management of dogs with PH.

### ACKNOWLEDGMENT

This study was partially presented at the 28th Annual Congress of the European College of Veterinary Internal Medicine - Companion Animals, September 6–8, 2018, Rotterdam, the Netherlands.

## CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

## OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

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

Nihon University granted ethical approval for use of the control dogs, and the study proceeded in accordance with the institution's Guide for Animal Experimentation.

## HUMAN ETHICS APPROVAL DECLARATION

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

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**How to cite this article:** Sakamoto Y, Sakai M, Sato K, Watari T. Plasma renin activity and aldosterone concentration in dogs with acquired portosystemic collaterals. *J Vet Intern Med*. 2020;34:139–144. https://doi.org/10.1111/jvim.15661