FULL PAPER *Surgery*

Arterial blood gas anomaly in canine hepatobiliary disease

Yasuyuki KANEKO[1)], Shidow TORISU[1)]*, Takumi KOBAYASHI[2)], Shinya MIZUTANI[1)], Nao TSUZUKI[3)], Hiroko SONODA[4)], Masahiro IKEDA[4)] and Kiyokazu NAGANOBU[1)]

[1)]*Veterinary Teaching Hospital, Faculty of Agriculture, University of Miyazaki, 1–1 Gakuen Kibanadai-nishi, Miyazaki-shi, Miyazaki 889–2192, Japan*
[2)]*Oji Pet Clinic, 1–22–9 Toshima, Kita-ku, Tokyo 114–0003, Japan*
[3)]*Laboratory of Veterinary Surgery, Faculty of Agriculture, University of Miyazaki, 1–1 Gakuen Kibanadai-nishi, Miyazaki-shi, Miyazaki 889–2192, Japan*
[4)]*Department of Veterinary Pharmacology, Faculty of Agriculture, University of Miyazaki, 1–1 Gakuen Kibanadai-nishi, Miyazaki-shi, Miyazaki 889–2192, Japan*

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ABSTRACT. Arterial blood gas analysis is an important diagnostic and monitoring tool for respiratory abnormalities. In human medicine, lung complications often occur as a result of liver disease. Although pulmonary complications of liver disease have not been reported in dogs, we have frequently encountered hypoxemia in dogs with liver disorders, especially extrahepatic biliary obstruction. In addition, respiratory disorders account for 20% of perioperative fatalities in dogs. Therefore, in this study, we evaluated the respiratory status in dogs with hepatobiliary disease by arterial blood gas analysis. PaO_2 and $PaCO_2$ were measured. Alveolar-arterial oxygen difference ($AaDO_2$), the indicator of gas exchange efficiency, was calculated. Compared to healthy dogs (control group), hepatobiliary disease dogs had significantly lower PaO_2 and higher $AaDO_2$. Hypoxemia (PaO_2 of ≤80 mmHg) was observed in 28/71 dogs with hepatobiliary disease. $AaDO_2$ was higher (≥30 mmHg) than the control group range (11.6 to 26.4 mmHg) in 32/71 hepatobiliary disease dogs. By classifying type of hepatobiliary disease, dogs with extrahepatic biliary obstruction and chronic hepatitis showed significantly lower PaO_2 and higher $AaDO_2$ than in a control group. Dogs with chronic hepatitis also had significantly lower $PaCO_2$. The present study shows that dogs with hepatobiliary disease have respiratory abnormalities more than healthy dogs. Preanesthetic or routine arterial blood gas analysis is likely beneficial to detect the respiratory abnormalities in dogs with hepatobiliary disease, especially extrahepatic biliary obstruction and chronic hepatitis.

KEY WORDS: arterial blood gas, canine, chronic hepatitis, extrahepatic biliary obstruction, hepatobiliary disease

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Arterial blood gas (ABG) analysis is an important diagnostic and monitoring tool for respiratory abnormalities, and measurement of partial pressure of arterial oxygen (PaO_2) and carbon dioxide ($PaCO_2$) provides information on pulmonary function [7]. In human medicine, lung and other organ complications often occur as a result of liver disease [9]. In liver cirrhosis, for example, more than 70% of patients evaluated for liver transplantation complained of dyspnoea [19]. In screening studies of human patients with chronic liver disease, arterial blood gas abnormalities are found in as many as 45% of patients [12]. Hepatopulmonary syndrome has been reported as a respiratory complication of hepatic disease in human medicine. Hepatopulmonary syndrome is well-recognized in humans and defined by the presence of 1) liver disease, 2) hypoxemia or high alveolar-arterial oxygen gradient ($AaDO_2$) and 3) intrapulmonary vasodilatation [11, 21, 23]. Although pulmonary complications of liver disease have not been reported in dogs, we have frequently encountered hypoxemia in dogs with liver disorders, especially extrahepatic biliary obstruction. In addition, respiratory disorders account for 20% of perioperative fatalities in dogs, while 55% of deaths are attributable to either respiratory or cardiovascular disorders according to a study of perioperative deaths in small animals [5]. These observations indicate the importance of preoperative screening for respiratory abnormalities in dogs with hepatobiliary disease. For these reasons, we routinely analyzed ABG preoperatively in patients with hepatobiliary disease. To our knowledge, ABG profiles in dogs with hepatobiliary disease have not been reported. Therefore, in this study, we evaluated the respiratory status in dogs with hepatobiliary disease by analyzing ABG. In addition, we classified hepatobiliary disease to congenital portosystemic shunt, hepatic mass, gallbladder disease without jaundice, extrahepatic biliary obstruction and chronic hepatitis, and evaluated each result of ABG, vital signs and blood test.

MATERIALS AND METHODS

Animals: Seventy–one client-owned dogs referred to our hospital for evaluation of hepatobiliary disease between February 2010 and August 2014. These dogs were included in the study after definitive diagnosis of the disease and confirmation of the absence of clinical signs of cardiopulmonary disease. The presence or absence of cardiopulmo-

*CORRESPONDENCE TO: TORISU, S., Veterinary Teaching Hospital, Faculty of Agriculture, University of Miyazaki, 1–1 Gakuen Kibanadai-nishi, Miyazaki-shi, Miyazaki 889–2192, Japan.
e-mail: torisu@cc.miyazaki-u.ac.jp

nary disease was determined by auscultation and thoracic radiography. Dogs with hepatobiliary disease were classified as congenital portosystemic shunt (n=17), hepatic mass (n=13), gallbladder disease without jaundice (GBD) (n=12), extrahepatic biliary obstruction (EHBO) (n=18) and chronic hepatitis (CH) (n=11). All cases were presented as surgical candidates and underwent surgery under general anesthesia, except for 2 cases of GBD and one case of EHBO. Hepatic mass included hepatocellular carcinoma (n=6), nodular hyperplasia (n=3) and one case each of fibrosarcoma, undifferentiated malignancy, carcinoma and hepatocellular adenoma. GBDs were gallbladder mucoceles (n=5), biliary sludge (n=4) and cholelithiasis (n=3). The causes of EHBO were gallbladder mucoceles (n=9), cholelithiasis (n=6) and biliary sludge (n=3). Fourteen client-owned healthy dogs with no abnormalities in complete blood count, blood urea nitrogen, serum creatinine, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase as well as in auscultation and other physical examination findings were also included in the study as controls. Informed owner consent was obtained before arterial blood collection in all cases.

ABG analysis: Arterial blood samples were obtained in room air after fasting and before operation in surgical cases. The animal was placed and rested in lateral recumbency, and blood was drawn from the femoral artery using a 25-gauge needle and a heparinized 1-m*l* syringe (a small amount of heparin sodium was drawn into a syringe to wet the entire syringe and expelled to the fullest extent possible). ABG analysis (i-STAT 300F analyzer; Fuso Pharmaceutical Industries, Osaka, Japan with i-STAT CG4+ or EG7+ cartridges; Abbott Laboratories, Abbott Park, IL, U.S.A.) was performed within one min after sample collection. PaO_2, $PaCO_2$ and pH were measured. Base excess (BE) and bicarbonate (HCO_3^-) concentration were calculated automatically by ABG analyzer. $AaDO_2$, the indicator of gas exchange efficiency, was calculated based on PaO_2 and $PaCO_2$ with the fractionated inspiratory oxygen (FiO_2) of 0.21 (for room air), barometric pressure (P_B) of 765 mmHg, water vapor pressure (P_{H2O}) of 50 mmHg and respiratory exchange ratio (R) of 0.8 using the following formula: $AaDO_2=FiO_2 \times(P_B-P_{H2O})-PaCO_2/R-PaO_2$.

Agitated saline contrast transthoracic echocardiography: Agitated saline contrast transthoracic echocardiography is a simple and highly sensitive diagnostic procedure for the detection of intrapulmonary vasodilatation [1, 3, 20]. When 2 m*l* of saline solution, 0.2 m*l* of blood and a small amount of air are agitated and intravenously injected, the bubbles are initially detected in the right heart and then move to the pulmonary vascular bed, but they cannot pass the pulmonary capillary circulation because they are larger (≥15 μm) than the diameter of the capillaries (5 to 8 μm in humans and 6.5 μm in dogs) [10]. Thus, immediate detection of bubbles in the left heart indicates congenital malformation in the heart, such as an atrial septal defect or ventricular septal defect [21, 23]. On the other hand, if bubbles appear in the left heart after 4 to 6 heartbeats after visualization in the right heart, it suggests the presence of intrapulmonary vasodilatation [21]. In this study, agitated saline contrast transthoracic echocardiography was performed in eight cases of CH to examine whether the pulmonary vasodilation exists.

Statistical analysis: All statistical analyses were conducted using statistical processing software (JMP 9, SAS Institute Japan, Tokyo, Japan). By the Shapiro-Wilk test for normality, the data did not follow a normal distribution. Therefore, all data were expressed as median and range (minimum to maximum) and analyzed by nonparametric methods. Mann-Whitney *U* test was used for comparison of two independent groups. Kruskal-Wallis test was used for comparison of more than two groups, and when significant differences were found, Steel-Dwass test was performed on each pair. Statistical significance was set at $P<0.05$.

RESULTS

There were 7 intact males and 7 females (4 intact and 3 neutered) in the control group with a median age of 3.0 years (0.7 to 10.0 years) and median body weight of 14.1 kg (6.6 to 26.9 kg). For 71 hepatobiliary disease dogs [22 males (15 intact and 7 neutered) and 49 females (27 intact and 22 neutered)], the median age was 8.8 years (0.3 to 14.0 years), and the median body weight was 5.3 kg (1.6 to 32.0 kg). The median age of the control group was significantly younger than that of the hepatobiliary disease group ($P=0.006$). No significant differences were found in sex ratio and median body weight.

The median PaO_2 was significantly lower in the hepatobiliary disease group [84 mmHg (57 to 120 mmHg) than in the control group [91 mmHg (81 to 100 mmHg)] ($P=0.0016$) (Fig. 1A). $AaDO_2$ was significantly higher in the hepatobiliary disease group [29.4 mmHg (5.0 to 59.7 mmHg)] than in the control group [21.5 mmHg (11.6 to 26.4 mmHg)] ($P<0.001$) (Fig. 1B). $PaCO_2$ did not show significant difference. In the hepatobiliary disease group, 28 dogs (39.4%) were hypoxemic with $PaO_2 \leq 80$ mmHg, and 32 dogs (45.1%) had $AaDO_2 \geq 30$ mmHg, which were deviations from the control group range (11.6 to 26.4 mmHg) and indicative of pulmonary disease [6].

As the result of evaluation on each group of hepatobiliary disease, the EHBO and CH groups showed significantly lower PaO_2 [77 mmHg (57 to 98 mmHg) and 80 mmHg (64 to 89 mmHg), respectively] compared to the control group ($P=0.024$ and $P=0.038$, respectively) (Fig. 2A). For $PaCO_2$, the CH group [26.5 mmHg (21.7 to 32.2 mmHg)] had a significantly lower value than the control group [30.9 mmHg (25.1 to 38.3 mmHg)] ($P=0.046$) (Fig. 2B). $AaDO_2$ was significantly higher in the EHBO group [32.1 mmHg (15.0 to 59.7 mmHg)] and in the CH group [37.0 mmHg (28.6 to 54.9 mmHg)] than in the control group ($P=0.003$ and=0.0004, respectively) (Fig. 2C). In groups of congenital portosystemic shunt, hepatic mass and GBD, no significant differences were seen in PaO_2, $AaDO_2$ and $PaCO_2$ compared to the control group. No significant difference was found in pH, BE and HCO_3^- between the control group and any of the hepatobiliary disease types (Fig. 2D–2F).

The results of the vital signs and blood tests of each dis-

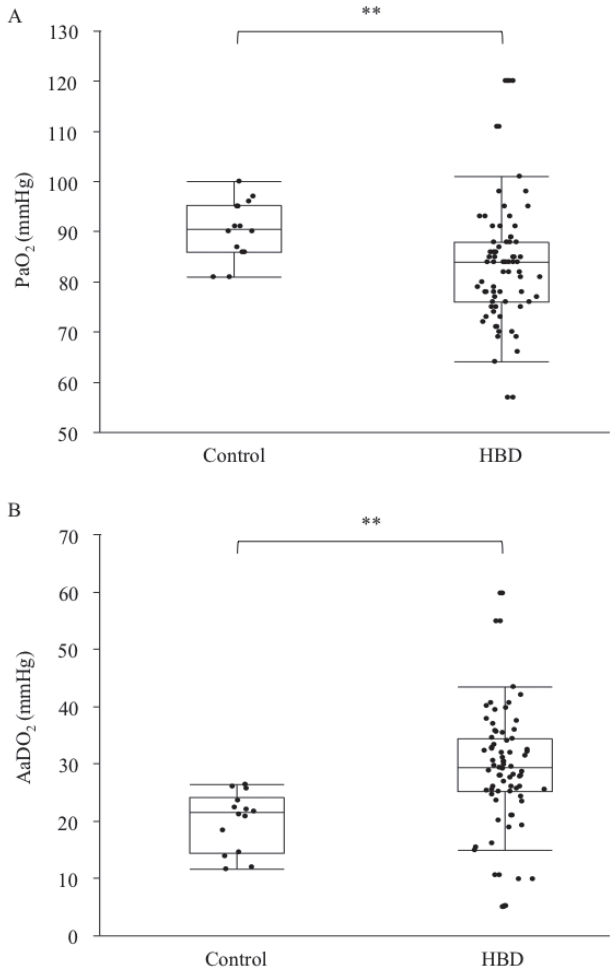

Fig. 1. Comparison of (A) PaO_2 and (B) $AaDO_2$ between control (n=14) and dogs with hepatobiliary disease (HBD) (n=71). Individual values are indicated by dots. The horizontal line in the middle of each box indicates the median, while the top and bottom borders of the box indicate the 25th and 75th percentiles. The dots outside the whiskers are outliners beyond 1.5 times the interquartile range above the 75th percentile or 1.5 times the interquartile range below the 25th percentile. Significant differences (P<0.01) are indicated (**). Note significantly lower PaO_2 and higher $AaDO_2$ in the hepatobiliary disease group.

ease group are shown in Fig. 3. No significant difference was found in body temperature, heart rate and respiration rate between any of the hepatobiliary disease types (Fig. 3A–3C). In respiration rate, data recorded as "panting" were represented with 200 bpm. The median white blood cell count was significantly higher in the EHBO group [25,923 /μl (5,800 to 68,900 /μl)] and in the CH group [14,300 /μl (3,800 to 25,300 /μl)] than in the GBD group [8,000 /μl (4,100 to 15,000 /μl)] (P=0.004 and P=0.037, respectively) (Fig. 3D). C-reactive protein was significantly higher in the EHBO group [3.9 mg/dl (0.3 to 14.0 mg/dl)] than in the GBD group [0.6 mg/dl (0 to 5.0 mg/dl)] and in the CH group [0.8 mg/dl (0.3 to 13.3 mg/dl)] (P=0.0097 and P=0.033, respectively) (Fig. 3E). Aspartate aminotransferase was significantly higher in the EHBO group [156 U/l (35 to 1,000 U/l)] than in the CPSS group [50 U/l (38 to 272 U/l)], the HM group [35 U/l (27 to 409 U/l)] and the GBD group [32 U/l (14 to 212 U/l)] (P=0.013, P=0.030 and P=0.001 respectively). Also, the CH group was significantly higher [98 U/l (46 to 348 U/l)] compared to the GBD group (P=0.0097) (Fig. 3F). Alanine aminotransferase was significantly higher in the EHBO group [616 U/l (47 to 2,986 U/l)] than in the CPSS group [91 U/l (34 to 606 U/l)] and the GBD group [220 U/l (15 to 575 U/l)] (P=0.0101 and P=0.0306, respectively) (Fig. 3G). Alkaline phosphatase was significantly higher in the EHBO group [4,561 U/l (2,417 to 11,551 U/l)] than in the CPSS group [359 U/l (84 to 1,244 U/l)], the HM group [925 U/l (132 to 10,500 U/l)], the GBD group [356 U/l (112 to 4,605 U/l)] and the CH group [1,383 U/l (303 to 5,857 U/l)] (P=0.0001, P=0.0062, P=0.0003 and P=0.0072 respectively). Also, the CH group was significantly higher compared to the CPSS group (P=0.0140) (Fig. 3H). Total protein was significantly lower in the CPSS group [5.5 g/dl (3.4 to 6.5 g/dl)] than in the HM group [7.3 g/dl (6.1 to 7.8 g/dl)] and the EHBO group [6.45 g/dl (5.7 to 8.4 g/dl)] (P=0.003 and P=0.047, respectively) (Fig. 3I). Albumin was significantly lower in the CPSS group [2.6 g/dl (1.7 to 3.3 g/dl)] than in the GBD group [3.5 g/dl (2.7 to 3.8 g/dl)] (P=0.019) (Fig. 3J)

Agitated saline contrast transthoracic echocardiography was performed in eight cases of CH. The bubbles made with agitated saline were detected in the right heart immediately after injection and then in the left heart after the 5th heartbeat in three cases.

DISCUSSION

In the present study, we evaluated the respiratory status in dogs with hepatobiliary disease by analyzing ABG. In human medicine, lung complications often occur as a result of liver disease [9]. However, pulmonary complications of liver disease have not been reported in dogs. In this study, significantly decreased PaO_2 and increased $AaDO_2$ were observed in dogs with hepatobiliary disease. In addition, hypoxemia and/or high $AaDO_2$ were observed in approximately 45% of dogs with hepatobiliary disease. Therefore, this is the first report that describes deteriorations in PaO_2 and $AaDO_2$ in dogs in association with hepatobiliary disease.

As compared to a control, significantly lower PaO_2 and higher $AaDO_2$ were observed in EHBO and chronic hepatitis. Decreased $PaCO_2$, however, was found in dogs with chronic hepatitis, but not in dogs with EHBO. In addition, chronic hepatitis and EHBO present different etiological and pathophysiological states. Therefore, different mechanisms are likely involved in the abnormal respiratory statuses observed in these two conditions.

In extrahepatic biliary obstruction, bacterial translocation and endotoxemia may stimulate systemic inflammatory responses and thus the generation of free oxygen radicals, which may lead to lung injury [2, 6, 15, 22]. The accumulation of stimulated inflammatory cells in small airways and

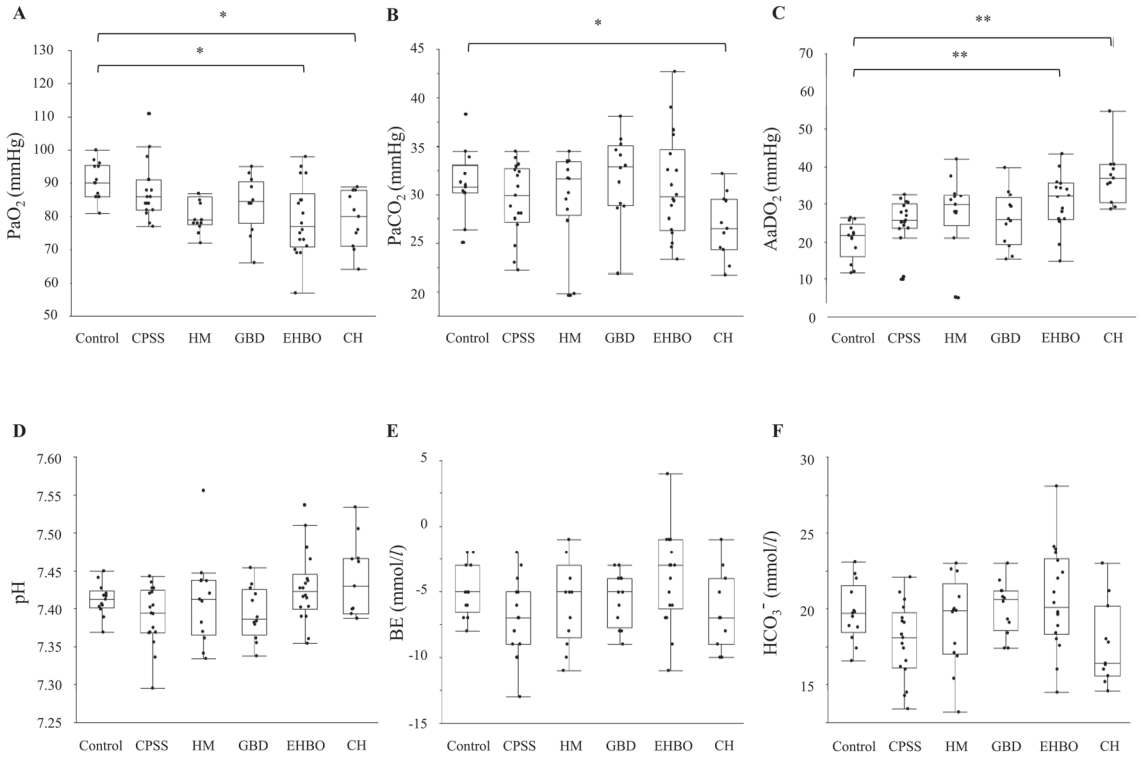

Fig. 2. Comparison of (A) PaO_2, (B) $PaCO_2$, (C) $AaDO_2$, (D) pH, (E) BE and (F) HCO_3^- between control and hepatobiliary disease types. Individual values are indicated by dots. The boxes define the 25th and 75th percentiles, with the median indicated as a horizontal line in the box. The dots outside the whiskers are outliners beyond 1.5 times the interquartile range above the 75th percentile or 1.5 times the interquartile range below the 25th percentile. Significant differences ($P<0.05$ and $P<0.01$) are indicated (*, **). Note significantly lower PaO_2 in dogs with extrahepatic biliary obstruction (EHBO) and chronic hepatitis (CH), significantly lower $PaCO_2$ in dogs with CH and significantly increased $AaDO_2$ in dogs with EHBO and CH. No significant difference was found in pH, BE and HCO_3^- between the control group and any of the hepatobiliary disease types. CPSS: congenital portosystemic shunt, HM: hepatic mass, GBD: gallbladder disease without jaundice.

pulmonary spaces can also cause impairments in the alveolar epithelial function and microcirculation. If these conditions persist, acute respiratory distress syndrome may develop [17]. Furthermore, in experimental rat models with common bile duct ligation, it histologically demonstrated bronchiolar fluid accumulation and peribronchiolar neutrophil infiltration [8]. We did not perform lung biopsy in the present study, because this study was conducted in client-owned dogs. However, high white blood cell count and C-reactive protein were observed in the EHBO group. Therefore, it is possible that a similar mechanism of lung injury was involved in the hypoxemia observed in dogs with EHBO.

In chronic liver disease, the development of pulmonary complications, most notably hepatopulmonary syndrome, is well documented in humans [11, 21, 23]. Hepatopulmonary syndrome has been known since 1966 [4] and characterized by the presence of 1) liver disease, 2) hypoxemia or increased $AaDO_2$ and 3) intrapulmonary vasodilatation. Although the exact mechanism is not understood, it has been proposed that ventilation-perfusion mismatch arising from intrapulmonary vasodilatation or arteriovenous fistula formation is the cause of hypoxemia in hepatopulmonary syndrome. Reportedly, hepatopulmonary syndrome occurs in 10 to 30% of cirrhotic patients [11]. However, this syndrome has not been described in dogs. In the present study, agitated saline contrast transthoracic echocardiography was performed in eight cases of CH. In three cases, the bubbles made with agitated saline appear in the left heart after 5 heartbeats after visualization in the right heart. It suggests the presence of intrapulmonary vasodilatation. Therefore, there is a possibility that the hepatopulmonary syndrome also exists in dogs. Also, decreased PaO_2 and $PaCO_2$ and increased $AaDO_2$ were observed in the CH group in this study. These results are consistent with those reported in human chronic hepatitis cases with intrapulmonary vasodilatation [3].

It is also noteworthy that perioperative mortality was high value as 28 to 64% in dogs with EHBO [14]. In the present study, the death of perioperative (up to one week post surgery) was not observed in 17 EHBO dogs that had undergone surgery. At our hospital, arterial blood gas analysis is routinely performed before and/or after surgery, and if necessary, animals are given oxygen therapy in the intensive care unit, although it is not clear whether these perioperative management practices have contributed to the low mortality.

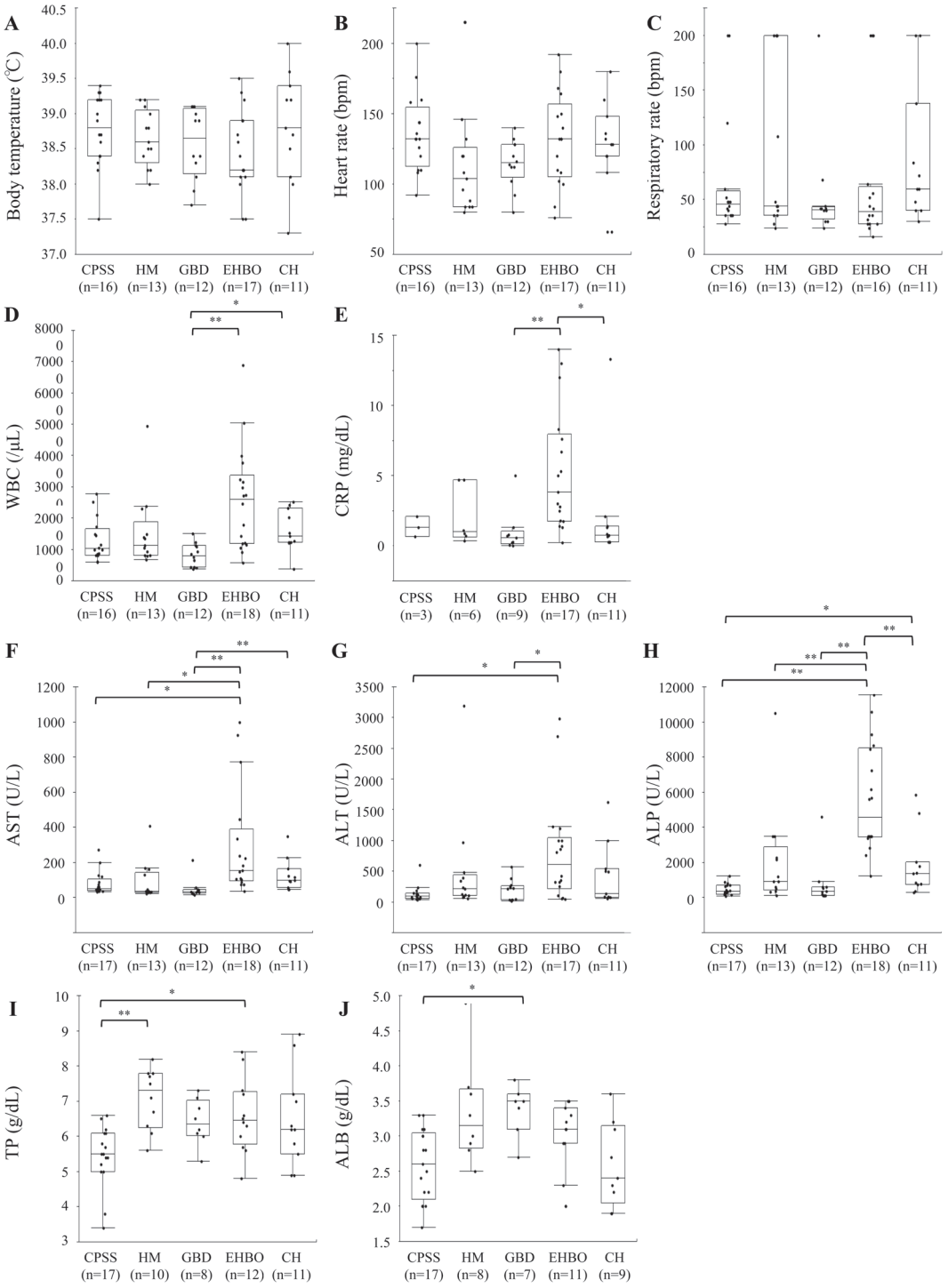

Fig. 3. Comparison of (A) Body temperature, (B) Heart rate, (C) Respiration rate, (D) White blood cell (WBC), (E) C-reactive protein (CRP), (F) Aspartate aminotransferase (AST), (G) Alanine aminotransferase (ALT), (H) Alkaline phosphatase (ALP), (I) Total protein (TP) and (J) Albumin (ALB) between hepatobiliary disease types. Number of cases was shown under the disease types. Individual values are indicated by dots. The boxes define the 25th and 75th percentiles, with the median indicated as a horizontal line in the box. The dots outside the whiskers are outliners beyond 1.5 times the interquartile range above the 75th percentile or 1.5 times the interquartile range below the 25th percentile. No significant difference was found in body temperature, heart rate and respiration rate between any of the hepatobiliary disease types. Note significantly higher WBC in dogs with extrahepatic biliary obstruction (EHBO) and chronic hepatitis (CH), significantly higher CRP in dogs with EHBO. Also, note significantly higher AST in dogs with EHBO and CH, significantly higher ALT in dogs with EHBO, significantly higher ALP in dog with EHBO and CH, and significantly lower TP and ALB in dog with congenital portosystemic shunt (CPSS). HM: hepatic mass, GBD: gallbladder disease without jaundice.

In the investigation of deaths related to anesthesia, given that 20% of perioperative deaths are associated with respiratory disorders in dogs [5] and that many of the dogs with hepatobiliary disease in this study had markedly low PaO_2 and high $AaDO_2$, it seems important to include blood gas analysis as part of the preanesthetic screening with hepatobiliary disease. Furthermore, hepatopulmonary syndrome is associated with poor prognosis in human cirrhotic patients [18]. Therefore, respiratory status of dogs with chronic hepatitis should be reassessed.

In the present study, pre-existing cardiopulmonary disease was ruled out by physical examination, auscultation and thoracic radiography. More detailed evaluations, such as ultrasonography and computed tomography, may be necessary in future studies. Also, the median age of the hepatobiliary diseases population was significantly higher than that of the control dogs. In dogs, however, the influence of age on arterial blood gasses seems negligible. Previous studies have reported that PaO_2 and $AaDO_2$ levels are similar in young (age not reported) and senior dogs (≥8 years of age) [13], and fasting PaO_2 and $PaCO_2$ also are not significantly different between young (1 year of age) and senior dogs (10 to 12 years of age) [16]. As the dogs with hepatobiliary disease in our study population were median of 8.8 years, the influence of age was considered minimal.

In conclusion, this study shows that respiratory complications may occur in dogs with hepatobiliary diseases, especially extrahepatic biliary obstruction and chronic hepatitis. Preanesthetic or routine arterial blood gas analysis is likely beneficial to detect the respiratory abnormalities in these dogs.

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