Systemic Oxygen Delivery and Consumption in Dogs with Heartworm Disease

Hitoshi KITAGAWA, Katsuya KITOH, Kyouji YASUDA, and Yoshihide SASAKI

Laboratory of Internal Medicine, Division of Veterinary Medicine, Faculty of Agriculture, Gifu University, 1–1 Yanagido, Gifu 501–11, Japan

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ABSTRACT. To investigate systemic oxygen (O_2) transport, we calculated the oxygen delivery index ($\dot{D}o_2I$), oxygen consumption index ($\dot{V}o_2I$) and oxygen extraction ratio (ER) in dogs with heartworm (HW) disease. The $\dot{D}o_2I$ was 770±331 ml/min/kg in dogs mildly affected with pulmonary HW disease showing respiratory signs, mild anemia and mild cardiac insufficiency (n=34); 238±155 ml/min/kg in dogs with ascitic pulmonary HW disease (n=7); and 577±320 ml/min/kg and 333±263 ml/min/kg in dogs with caval syndrome (CS) which survived (n=15) or died (n=7) after surgical HW removal. The $\dot{D}o_2I$ was lower ($P<0.01$) in all HW-infected groups, especially in ascites and CS-non-surviving dogs, than in HW-free dogs (n=11, 1041±264 ml/min/kg). The $\dot{V}o_2I$ was higher in some mildly affected dogs (161±88 ml/min/kg), and lower ($P<0.01$) in ascitic dogs (45±53 ml/min/kg) than in HW-free dogs (123±44 ml/min/kg). The ER was higher ($P<0.01$) in all HW-infected groups than in HW-free dogs. The $\dot{D}o_2I$ correlated significantly with $\dot{V}o_2I$ ($r=0.84$, $P<0.01$), and the $\dot{V}o_2I$ correlated significantly with ER ($r=0.48$, $P<0.01$). The $\dot{D}o_2I$ correlated significantly with arterial O_2 tension ($r=0.33$), serum LDH ($r=-0.46$) and CK ($r=-0.46$) activities, serum urea nitrogen (UN, $r=-0.32$) and lactic acid (LA, $r=-0.39$) concentrations and cardiac index ($r=0.64$). The $\dot{V}o_2I$ correlated significantly with serum LDH (-0.43) and CK ($r=-0.41$) activities, serum UN ($r=-0.29$) and LA ($r=-0.37$) concentrations, cardiac index ($r=0.53$) and body weight ($r=-0.34$). The ER correlated significantly with mixed venous O_2 tension ($r=-0.38$) and serum ALT activity ($r=0.31$). The delivery and consumption of O_2 may be closely associated with organ injury in dogs with HW disease.—KEY WORDS: canine, extraction rate, heartworm disease, oxygen consumption, oxygen delivery.

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Heartworm (HW) disease is commonly recognized as a disease of circulatory disturbance in dogs [11, 13, 14]. The most important function of blood circulation is to deliver oxygen (O_2) to tissues. Therefore, a circulatory disorder is synonymous with O_2 transport disorder. It is self-evident that oxygen delivery and consumption relate closely with circulatory disturbance. However, there have been no data on O_2 transport in dogs with HW disease, one of the major circulatory diseases. In serial studies [7, 9, 10], we have reported cardiopulmonary function values and blood gas data in dogs with HW disease. In the present study, in order to clarify the significance of O_2 transport variables in dogs with HW disease, we calculated the O_2 delivery index ($\dot{D}o_2I$), O_2 consumption index ($\dot{V}o_2I$) and extraction ratio (ER, which indicated delivery and consumption of O_2 in the whole body) from cardiac output and blood gas values in dogs with pulmonary HW disease (PHWD) and caval syndrome (CS). Relationships between O_2 transport variables and laboratory or cardiopulmonary function values were also investigated.

MATERIALS AND METHODS

Dogs: Eleven HW-free dogs and 63 dogs with naturally acquired HW infection were studied. The age range was from 1 to 6 years in HW-free dogs, and from 2 to 12 years in HW-infected dogs. The latter were subdivided into 4 groups on the basis of the clinical signs of their disease; 1) mildly affected dogs (34 dogs with PHWD showing signs of slight to mild respiratory and cardiac insufficiency and anemia), 2) ascitic dogs (7 PHWD dogs exhibiting signs of right heart failure such as ascites, subcutaneous edema and/or jaundice), 3) CS-surviving dogs (15 CS dogs recovered after surgical HW removal using flexible alligator forceps [6]) and 4) CS-non-surviving dogs (7 CS dogs which died or were euthanatized after surgical treatment).

Blood gas analysis: Dogs were placed in right lateral recumbency under general anesthesia with diazepam and ketamine hydrochloride [9, 10]. While breathing room air, dogs had an arterial blood sampling from the femoral artery by a puncture, and had a mixed venous blood drawning from the pulmonary artery through a catheter. O_2 and carbon dioxide (CO_2) tensions and pH were determined, and O_2 saturation (SaO_2 or $S\bar{v}O_2$), O_2 content (CaO_2 or $C\bar{v}O_2$) and bicarbonate (HCO_3^-) concentration were calculated with an automated pH/blood gas analyzer (168 pH/Blood Gas Analyzer, Corning Ltd., Halstead, England). Blood gas values were corrected to the dog's rectal temperature and blood hemoglobin (Hb) concentration. The $\dot{D}o_2I$ was calculated from the equation: $CaO_2 \times$ cardiac index; $\dot{V}o_2I$ from the equation: $CaO_2 - C\bar{v}O_2 \times$ cardiac index; and ER from the equation: $\dot{V}o_2I/\dot{D}o_2I$ [5, 16].

Other measurement procedures: Blood Hb concentration was determined by the cyanmethemoglobin method, and white blood cells were counted with an automated cell counter (Model ZF, Coulter Electronics Inc., Hialeah, U.S.A.). We determined serum alanine transaminase (ALT), lactate dehydrogenase (LDH) and creatinine kinase (CK) activities, as well as urea nitrogen (UN) concentration with an autoanalyser (TDA-880, Toshiba Co., Ltd., Tokyo). Serum sodium, potassium and chloride concentrations were determined by the ion-electrode method and Volhard chloride estimation (Na/K ISE

Analyzer, Model 902, and 925 Chloride Analyzer, Corning Ltd.). Serum lactic acid concentration was determined with a commercial test kit (F-kit L-Lactic Acid, Boehringer Mannheim GMBH, Mannheim, Germany). Cardiopulmonary function measurements were performed by the same procedures described in our previous study [7, 9]. Dogs with ascites were weighed after elimination of ascitic fluid.

Statistical analysis: Data are expressed as mean± standard deviation. Duncan's new multiple range test was used for statistical comparison of the data among the 5 groups. Correlation coefficient was evaluated using the *t*-test. A p-value of less than 0.05 was selected as statistically significant.

RESULTS

Figures 1 to 3 show O_2 transport variables in HW-free dogs and dogs with HW disease. The $\dot{D}o_2$ I was 1041±264 ml/min/kg in HW-free dogs (n=11), 770±331 ml/min/kg in mildly affected dogs (n=34), 238±155 ml/min/kg in ascitic dogs (n=7), 577±320 ml/min/kg in CS-surviving dogs (n=15), and 333±263 ml/min/kg in CS-non-surviving dogs (n=7). The $\dot{D}o_2$I in dogs of all HW-infected groups was significantly (P<0.01) lower than in HW-free, ascitic and CS-non-surviving dogs. It was also significantly (P<0.01) lower than in mildly affected and CS-surviving dogs. The $\dot{V}o_2$I was distributed at the higher level in many mildly affected dogs, but was significantly (P<0.01) lower in ascitic dogs than in HW-free dogs. The ER was higher (P<0.01) in dogs of all HW-infected groups than in HW-free dogs.

Table 1 shows correlation coefficients among $\dot{D}o_2$I, $\dot{V}o_2$I and ER in 63 HW-infected dogs. The $\dot{D}o_2$I correlated positively with $\dot{V}o_2$I (r=0.84, P<0.01), but not with ER. The $\dot{V}o_2$I correlated positively with ER (r=0.48, P<0.01).

Table 2 shows blood gas variables. The PaO_2 was lower in ascitic and CS-non-surviving dogs, and the $P\bar{v}O_2$ was lower in all HW-infected groups. The SaO_2 was slightly lower in HW-infected dogs, but never below a value of 90% except in some CS-non-surviving dogs. The $S\bar{v}O_2$, CaO_2 and $C\bar{v}O_2$ were lower in dogs of HW-infected groups than in HW-free dogs, whereas the CaO_2 was not lower in the mildly affected group. The $a\bar{v}Do_2$ was higher only in CS-surviving dogs than in HW-free dogs.

Table 3 shows laboratory and cardiopulmonary function values. Table 4 indicates correlation coefficients between O_2 transport variables and laboratory and cardiopulmonary values in dogs with HW disease. The $\dot{D}o_2$I correlated positively with PaO_2, blood Hb concentration and cardiac index, and negatively with serum LDH activity, CK activity, UN concentration and lactic acid concentration. The $\dot{V}o_2$I correlated positively with blood Hb concentra-

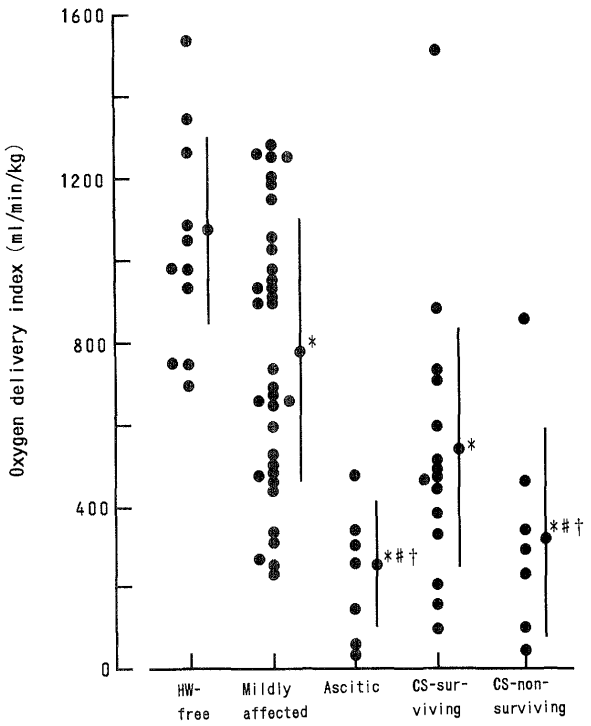

Fig. 1. Oxygen delivery index in heartworm-free dogs and dogs with heartworm disease. *, #, and †: Significantly (p<0.01) different from the value in HW-free dogs, mildly affected dogs, CS-surviving dogs, and CS-nonsurviving dogs, respectively.

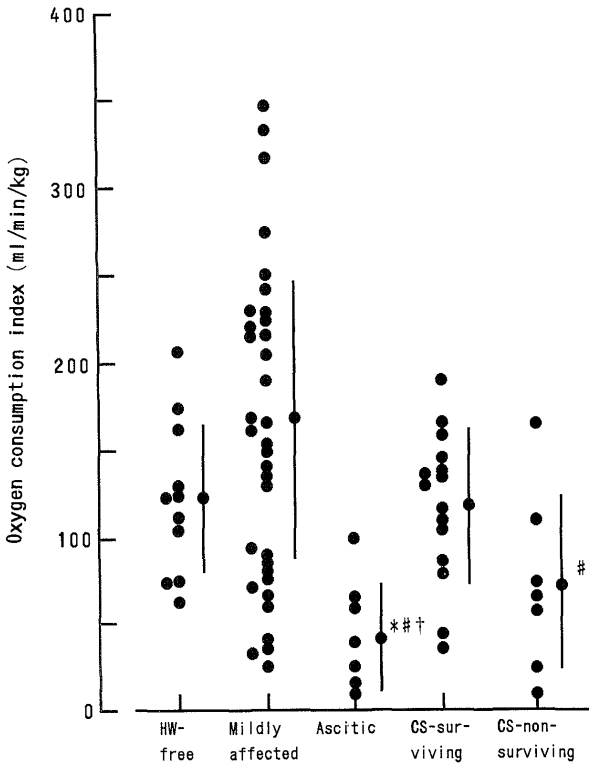

Fig. 2. Oxygen consumption index in heartworm-free dogs and dogs with heartworm disease. *, #, and †: Significantly (p<0.01) different from the value in HW-free dogs, mildly affected dogs, CS-surviving dogs, and CS-nonsurviving dogs, respectively.

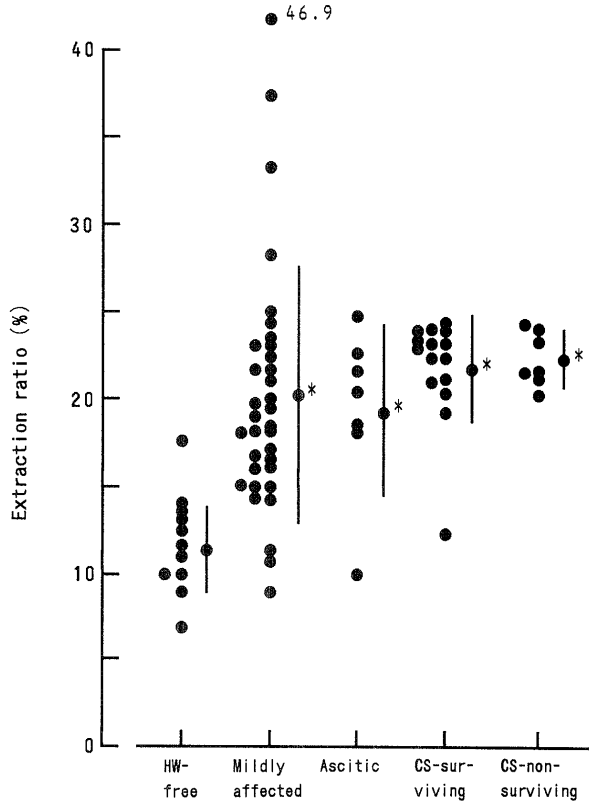

Fig. 3. Extraction ratio in heartworm-free dogs and dogs with heartworm disease. *: Significantly ($p<0.01$) different from the value in HW-free dogs.

tion and cardiac index, and negatively with serum LDH activity, CK activity, UN concentration, lactic acid concentration, and body weight. The $\dot{D}o_2I$ and $\dot{V}o_2I$ had a poor correlation with serum ALT activity, but the ER significantly correlated positively with serum ALT activity. The ER had a significantly negative correlation with $P\bar{v}O_2$.

DISCUSSION

The O_2 delivery was low in dogs with HW disease, possibly due to ventilation insufficiency in the lung and decreased cardiac output, both of which were mainly caused by lesions in the pulmonary arteries, parenchyma of the lung [15], HW residing in the pulmonary arteries and the tricuspid valve area [8, 9] and pulmonary hypertension [9, 11, 14]. Anemia also contributed to the decreased O_2 delivery. However, dogs with HW disease might cope with hypoxia by an increase in the O_2 extraction rate. When blood flow and Hb concentration decrease, O_2 consumption may initially be maintained by an increased oxygen extraction. A higher O_2 consumption in dogs with mildly affected PHWD might be consistent with this concept, and could be regarded as a compensatory mechanism protecting against tissue hypoxia [1]. The O_2 consumption was greater in some dogs of the mildly affected group, suggesting the hypermetabolic phase. In CS-surviving dogs, the $\dot{D}o_2I$ was less than in the HW-free group, but $\dot{V}o_2I$ showed almost the same level as in the HW-free group. Therefore, the $P\bar{v}CO_2$ level was lower

Table 1. Correlations among oxygen transport variables in dogs with heartworm disease

Variable	No. of dogs	Oxygen consumption index ($\dot{V}o_2I$)		Extraction rate (ER)	
Oxygen delivery index ($\dot{D}o_2I$)	63	0.84	0.01	−0.02	NS[a)]
Oxygen consumption index ($\dot{V}o_2I$)	63	—		0.48	0.01

Data are expressed as correlation coefficient and probability of significant correlation coefficient, a) Not significant.

Table 2. Blood gas variables in dogs with heartworm disease

Variable	HW[a)]-free	Pulmonary HW disease		Caval syndrome	
		Mildly-affected	Ascites	Surviving	Nonsurviving
PaO_2[c)] (mmHg)	11 91.7±10.3	34 87.0±8.4	7 78.1±13.3*#†	15 86.5±6.9	7 74.6±11.4*#†
$P\bar{v}O_2$[d)] (mmHg)	11 54.9±5.9	34 46.3±6.2*	7 42.1±10.6*	15 39.8±6.4*#	7 36.8±8.9*#
SaO_2[e)] (%)	11 95.7±2.2	34 94.6±2.4	7 93.3±3.2*	15 94.8±1.5	7 91.1±2.6*†
$S\bar{v}O_2$[f)] (%)	11 83.0±3.8	34 71.0±7.8*	7 66.4±14.6*	15 61.1±11.0*#	7 49.6±14.0*#|†
CaO_2[g)] (ml/dl)	11 18.9±2.6	34 16.5±3.6	7 11.3±3.5*#	15 13.9±3.0*#	7 13.4±3.8*#
$C\bar{v}O_2$[h)] (ml/dl)	11 16.3±2.3	34 11.7±2.7*	7 8.1±3.3*#	15 9.2±3.0*#	7 7.5±3.2*#
$a\bar{v}DO_2$[i)] (mmHg)	11 36.8±9.9	34 40.7±9.6	7 36.0±5.8	15 46.7±7.5*|	7 37.7±15.9†

Data are expressed as No. of dogs and mean±standard deviation. *: Significantly ($p<0.01$) different from the HW-free group, #: Significantly ($p<0.01$) different from the mildly-affected group, |: Significantly ($p<0.01$) different from the ascites group, †: Significantly ($p<0.01$) different from the CS-surviving group, a) Heartworm, b) Oxygen delivery index, c) Arterial oxygen tension, d) Mixed venous oxygen tension, e) Arterial oxygen saturation, f) Mixed venous oxygen saturation, g) Arterial oxygen content, h) Mixed venous oxygen content, i) Arterial-venous oxygen difference.

Table 3. Laboratory and cardiopulmonary function values in dogs with heartworm disease

Variable	HW[a]-free		Pulmonary HW disease				Caval syndrome			
			Mildly-affected		Ascites		Surviving		Nonsurviving	
Hemoglobin (g/dl)	11	14.0±1.9	34	11.5±2.6	7	8.5±2.7	15	10.4±2.2	7	10.7±3.5
WBC ($\times 10^4/\mu l$)	11	136±48	27	163±88	7	268±163	10	212±126	4	335±200
ALT (IU/l)	10	37±17	22	89±90	7	157±200	10	119±154	4	50±33
LDH (IU/l)	10	89±48	23	102±61	7	360±269	10	372±321	4	231±216
CK (IU/l)	8	108±46	9	135±62	7	325±296	7	218±189	3	356±220
Urea nitrogen (mg/dl)	10	17.4±8.9	25	4.6±2.4	7	40.4±29.5	10	16.4±5.4	4	49.0±35.8
Sodium (mmol/l)	11	143±11	21	137±7	7	134±6	11	142±6	4	138±14
Potassium (mmol/l)	11	3.60±0.36	21	3.54±0.42	7	3.35±0.98	11	3.64±0.59	4	4.32±0.87
Chloride (mmol/l)	11	115±5	21	114±3	7	113±8	11	114±5	4	109±10
HCO_3^- (mmol/l)	11	20.3±2.0	34	17.6±2.2	7	16.2±1.6	15	16.4±3.5	4	14.3±2.2
Lactic acid (mg/dl)	11	1.65±0.78	21	1.41±0.66	7	2.38±1.03	10	1.92±1.13	4	2.35±0.59
Heart rate (beat/min)	11	109±22	33	139±43	7	143±21	15	138±36	7	144±38
Mean pulmonary arterial pressure (mmHg)	11	13.0±3.0	33	21.1±9.6	7	33.2±12.5	15	29.1±10.5	7	34.8±12.7
Cardiac index (l/min/kg)	11	296±55	34	304±84	7	169±26	15	290±84	7	180±87
Number of HW/kg body weight	11	0±0	33	2.97±2.64	7	2.11±2.07	7	4.79±2.68	4	4.48±5.80
Body weight (kg)	11	9.9±3.1	34	9.6±2.6	7	12.8±4.2	15	8.2±4.7	7	6.9±2.6

Data are expressed as No. of dogs and mean±standard deviation, a) Heartworm.

Table 4. Correlations between oxygen transport variables and other parameters in dogs with heartworm disease

Variable	Oxygen delivery index			Oxygen consumption index			Extraction rate		
Heart rate	55	−0.08	NS[a]	55	0.03	NS	55	0.14	NS
MPAP[b]	63	−0.20	NS	63	−0.17	NS	63	0.10	NS
Cardiac index	63	0.64	0.01	63	0.53	0.01	63	0.02	NS
PaO_2[c]	63	0.33	0.01	63	0.23	NS	63	−0.14	NS
$P\bar{v}O_2$[d]	63	0.21	NS	63	0.08	NS	63	−0.38	0.01
$a\bar{v}DO_2$[e]	63	0.16	NS	63	0.18	NS	63	0.15	NS
Heartworm/kg	51	−0.17	NS	51	−0.06	NS	51	0.25	NS
Body weight	63	−0.09	NS	63	−0.34	0.01	63	−0.14	NS
Hemoglobin	63	0.71	0.01	63	0.54	0.01	63	−0.14	NS
WBC	48	−0.26	NS	48	−0.25	NS	48	0.05	NS
ALT	43	−0.16	NS	43	−0.09	NS	43	0.31	0.05
LDH	45	−0.46	0.01	45	−0.43	0.01	45	0.15	NS
Creatine kinase	26	−0.46	0.05	26	−0.41	0.05	26	0.20	NS
Urea nitrogen	53	−0.32	0.05	53	−0.29	0.05	53	0.12	NS
Sodium	43	0.08	NS	43	0.03	NS	43	0.03	NS
Potassium	43	−0.06	NS	43	−0.09	NS	43	0.14	NS
Chloride	43	0.20	NS	43	0.10	NS	43	−0.28	NS
Bicarbonate	63	0.20	NS	63	0.09	NS	63	−0.22	NS
Lactic acid	42	−0.39	0.05	42	−0.37	0.05	42	0.06	NS

Data are expressed as No. of dogs, correlation coefficient and probability of significant correlation coefficient, a) Not significant, b) Mean pulmonary arterial pressure, c) Arterial oxygen tension, d) Mixed venous oxygen tension, e) Arterial-mixed venous oxygen difference.

and $a\bar{v}Do_2$ was greater in CS-surviving dogs than in mildly affected dogs. Besides, the $\dot{D}o_2I$ and $\dot{V}o_2I$ were lower in ascitic and CS-non-surviving dogs, indicating a hypometabolic state. Ascitic dogs, which were considered to have chronic HW disease, had a severely diminished cardiac output and low blood Hb concentration, and had been exposed the risk of a long-term hypoxia and venous congestion. In order to adjust to critically reduced O_2 delivery or reduced metabolic activity, the O_2 consumption was reduced in ascitic dogs. Nonsurviving dogs with CS tended to harbor a small number of worms, and having a severe pulmonary thromboembolism resulted in pulmonary hypertension [9]. In these dogs, it was considered that the causes of severe circulatory disturbance were tricuspid valve dysfunction resulting from the presence of worms, worm-coiling to the tricuspid chordae and severe pulmonary hypertension. Low O_2 delivery and consumption might be atributable to perfusion insufficiency, pulmonary shunt and circulatory disorder. A more severe reduction in cardiac output would necessarily result in reduced O_2 consumption in dogs with heartworm disease.

Oxygen transport is expressed as the product of cardiac output and arterial O_2 content [1]. Low O_2 delivery was generally accompanied by low O_2 consumption. In order to compensate for low O_2 delivery, dogs with HW disease had a higher ER than HW-free dogs. The low $\dot{V}o_2I$ might result from low $\dot{D}o_2I$ and high ER.

In a state of low cardiac output and low oxygen distribution, maldistribution of systemic blood flow may also limit tissue oxygenation [2]. Disruption of cellular integrity by hypoxia allows soluble cytosolic enzymes to escape into the surrounding fluid and blood serum [12]. An increase in serum UN concentration may reflect an accelerated rate of protein catabolism or decreased urinary excretion of urea [4]. The significant and negative correlation between the O_2 transport variables ($\dot{D}o_2$ and $\dot{V}o_2$) and serum enzyme activities such as LDH and CK or serum UN concentration could confirm that hypermetabolism and organ injuries might correlate with delivery and consumption of O_2 in HW disease. Besides, the $\dot{D}o_2I$ and $\dot{V}o_2I$ did not correlate significantly with serum ALT activity. The liver plays an important role in internal blood flow regulation, and two thirds of normal O_2 supply comes from the already desaturated hemoglobin in the portal

vein [3]. Low O_2 supply might induce liver injury. However, serum ALT activity levels were not particularly high in dogs of the ascites and CS-non-surviving groups. Therefore, the enzyme activity might not express the magnitude of liver injury in dogs with HW disease, since the ALT release decreased from an extremely injured liver. The reason for the significant correlation between ER and ALT activity was unknown.

The data in the present study suggest the effectiveness of O_2 inhalation in dogs severely affected with HW disease. However, attention must be paid to hypoxia-reoxidation injuries of tissues.

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