Plasma Renin Activities, Angiotensin II Concentrations, Atrial Natriuretic Peptide Concentrations and Cardiopulmonary Function Values in Dogs with Severe Heartworm Disease

Hitoshi KITAGAWA, Katsuya KITO, Hideaki INOUE, Yasunori OHBA, Fumiaki SUZUKI¹⁾ and Yoshihide SASAKI

Laboratory of Internal Medicine, Division of Veterinary Medicine, Faculty of Agriculture, ¹⁾Molecular Genetics Research Center, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

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ABSTRACT. Relationships among plasma renin activities (PRA), plasma angiotensin II (ATII) concentrations, atrial natriuretic peptide (ANP) concentrations and cardiopulmonary function values were examined in dogs with ascitic pulmonary heartworm disease and acute- and chronic-vena caval syndrome (CS). PRA, plasma ATII concentration and plasma ANP concentration tended to be higher or were significantly higher in dogs with ascites, acute- and chronic-CS. PRA correlated significantly with plasma ATII concentration, WBC count, ALP activity, plasma concentrations of urea nitrogen, creatinine, sodium, potassium, and chloride, right ventricular endodiastolic pressure and right atrial pressure. Plasma ATII concentration correlated significantly with WBC count, plasma concentrations of urea nitrogen, sodium, and potassium, right ventricular endodiastolic pressure and right atrial pressure. Plasma ANP concentration did not correlate with PRA or ATII concentration, but correlated significantly only with pulmonary arterial pressure.—KEY WORDS: ANP, heartworm disease, renin-angiotensin.

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It has been widely acknowledged that the renin-angiotensin system should be activated in animals with heart failure, and vasoconstriction owing to activation of the renin-angiotensin system contributes to a worsening of circulatory disturbances [7]. Atrial natriuretic peptide (ANP) is released from the atrium in response to atrial pressure [12–14]. Heartworm disease (HWD) is one of the common circulatory diseases in dogs [2, 10, 15]. Evidence observed in HWD, such as low cardiac output, high pulmonary arterial pressure, and high right atrial pressure [2, 8–10, 15], suggest activation of the renin-angiotensin system and ANP excretion. Although there have been some data on the renin-angiotensin system and ANP in dogs with HWD [3, 18], no data exist on the relationship among renin-angiotensin, ANP and cardiopulmonary function values. To clarify the pathophysiology of HWD, we simultaneously determined plasma renin activity (PRA), and concentrations of angiotensin II (ATII) and ANP as well as laboratory values and cardiopulmonary function values in dogs with naturally acquired severe HWD.

Thirty-six dogs diagnosed as naturally acquired HWD were used. They were classified into 3 groups based on clinical signs and the locations of heartworms: 1) ascites group (10 dogs) in which dogs showed obvious ascites as well as liver congestion, anemia, and respiratory signs, with heartworm echoes detected only in the pulmonary arteries; 2) acute-caval syndrome (CS) group (11 dogs) in which a sudden onset of caval murmur, jugular pulsation, hemoglobinuria, anemia, and prostration were observed, and heartworm echoes were detected at the tricuspid valve area; and 3) chronic-CS group (15 dogs), in which heartworm echoes could be detected at the tricuspid valve area, and caval murmur and venous congestion were observed, but

the disease course was chronic. Eleven normal adult mixed breed dogs without heartworm infection were used as controls (control group). Heartworm infection was diagnosed by the detection of circulating microfilariae and circulating antigen (SNAP Heartworms, IDEXX Laboratories, Tokyo), echocardiography, and radiography. For measurement of blood pressure, a Berman angiographic balloon catheter (7F, Arrow Co., Ltd., Tokyo) was inserted into the pulmonary arteries and right atrium under general anesthesia with diazepam (0.5–1.5 mg/kg, Cercine, Takeda Chemical Industries, Osaka) and ketamine hydrochloride (5–10 mg/kg, IM, Ketalar, Sankyo Co., Ltd., Tokyo) at the surgical removal of heartworms with flexible alligator forceps. PRA was calculated from the production rate of ATI [17]. Plasma ATII (Nichols Institute Diagnostics, B.V., Netherlands) and ANP concentrations (Shionoria, Shionogi, Tokyo) were measured with radioimmunoassay kits. Differences in the data among the groups were tested using the one-way ANOVA test.

Table 1 shows PRA, and ATII and ANP concentrations, laboratory test results, and cardiopulmonary function values. Mean PRA was 4.3 ± 1.8 ATI ng/ml/hr in the control group, but tended to be higher in the ascites and acute-CS groups, and significantly ($P < 0.01$) higher in the chronic-CS group. Mean plasma ATII concentration was 104 ± 67 pg/ml in dogs of the control group. Plasma ATII concentration varied in individual dogs, but tended to be higher in dogs with ascites and both CS groups than in the control group. Plasma ANP concentration was 31 ± 30 pg/ml in dogs of the control group. By comparison, plasma ANP concentrations tended to be higher in the ascites and acute-CS groups, and significantly ($P < 0.01$) higher in dogs of the chronic-CS group. RBC counts were lower in the 3 groups

Table 1. Cardiopulmonary function values, plasma renin activities, angiotensin II concentrations, atrial natriuretic peptide concentrations in dogs with heartworm disease

Variable	Group							
	Control		Ascites		Acute-CS		Chronic-CS	
	n	Mean $\pm$ SD	n	Mean $\pm$ SD	n	Mean $\pm$ SD	n	Mean $\pm$ SD
Plasma renin activity (ATI ng/ml/hr)	10	4.3 $\pm$ 1.8	9	10.8 $\pm$ 8.3	11	6.9 $\pm$ 8.4	15	11.1 $\pm$ 11.4**
Angiotensin II concentration (pg/ml)	11	103.8 $\pm$ 67	9	471.2 $\pm$ 764	11	422.6 $\pm$ 868	13	520.4 $\pm$ 563
Atrial natriuretic peptide concentration (pg/ml)	11	31 $\pm$ 30	10	89 $\pm$ 66	11	71 $\pm$ 64	15	120 $\pm$ 102**
Red blood cell count ($\times 10^4$ /ml)	11	733 $\pm$ 116	9	587 $\pm$ 159*	11	530 $\pm$ 112*	15	576 $\pm$ 159**
White blood cell count ($\times 10^2$ /ml)	11	154 $\pm$ 33	9	203 $\pm$ 85	11	235 $\pm$ 105*	15	199 $\pm$ 89
Alanin transaminase activity (IU/l)	10	57 $\pm$ 46	10	77 $\pm$ 68	11	356 $\pm$ 488 [†]	15	119 $\pm$ 191
Alkaline phosphatase activity (IU/l)	10	132 $\pm$ 92	10	293 $\pm$ 255	11	481 $\pm$ 609	15	407 $\pm$ 1013
Urea nitrogen concentration (mg/dl)	10	9.5 $\pm$ 2.7	10	52.9 $\pm$ 56.7*	11	71.4 $\pm$ 71.1**	15	40.5 $\pm$ 23.0
Creatinine concentration (mg/dl)	10	0.8 $\pm$ 0.2	10	1.4 $\pm$ 1.4	11	1.8 $\pm$ 2.0	15	1.0 $\pm$ 0.5
Sodium concentration (mEq/l)	10	145 $\pm$ 3	9	142 $\pm$ 6	11	143 $\pm$ 8	14	141 $\pm$ 6
Potassium concentration (mEq/l)	10	4.2 $\pm$ 0.4	9	4.1 $\pm$ 0.7	11	4.0 $\pm$ 0.7	14	4.3 $\pm$ 0.7
Chloride concentration (mEq/l)	10	110 $\pm$ 2	9	108 $\pm$ 5	11	107 $\pm$ 10	14	107 $\pm$ 9
Mean pulmonary arterial pressure (mmHg)	11	12.0 $\pm$ 2.8	10	51.0 $\pm$ 26.4**	11	50.2 $\pm$ 17.9**	15	55.9 $\pm$ 10.0**
Right ventricular endodiastolic pressure (mmHg)	11	-0.15 $\pm$ 1.90	10	6.47 $\pm$ 10.4	11	102 $\pm$ 10.2**	15	13.7 $\pm$ 8.2**
Maximum right atrial pressure (mmHg)	11	1.3 $\pm$ 1.10	10	14.6 $\pm$ 11.8**	11	17.3 $\pm$ 13.5**	15	17.7 $\pm$ 5.4**
No. of heartworms removed/kg body weight	11	0 $\pm$ 0	10	0.66 $\pm$ 0.57**	11	3.8 $\pm$ 3.0** ^{††}	14	0.79 $\pm$ 0.72**

* and **: Significantly different from control value ($P < 0.05$ and 0.01 , respectively).

[†] and ^{††}: Significantly different from ascites group value ($P < 0.05$ and 0.01 , respectively).

: Significantly different from acute CS group value ($P < 0.01$).

CS: caval syndrome; SD: standard deviation.

with heartworm infection. Plasma ALT activity was higher in dogs of the acute-CS group. Plasma urea nitrogen (UN) concentration was higher in the ascites and acute-CS groups. Dogs in the ascites, acute-CS, and chronic-CS groups had a higher mean pulmonary arterial pressure (MPAP) than the control group. Right ventricular endodiastolic pressure (RVEDP) was higher in dogs of the acute- and chronic-CS groups, and pressures in the right atrium were significantly higher in all HWD groups than in the control group. The number of heartworms removed per kg body weight was greater in dogs of the acute-CS group.

As shown in Table 2, PRA correlated significantly ($P < 0.01$) with plasma ATII concentration as well as with WBC count, plasma ALP activity, plasma concentrations of UN, creatinine, sodium, potassium and chloride, RVEDP, and maximum right atrial pressure. Plasma ATII concentration correlated significantly with WBC counts, plasma concentrations of UN, sodium and potassium, RVEDP and right atrial pressure. However, plasma ANP concentration did not correlate significantly with PRA or plasma ATII concentration, but only with MPAP.

It has been reported that the renin-angiotensin system is activated in dogs with HWD [3]. In the present study as well, PRA and plasma ATII concentrations tended to be higher, and correlated significantly with cardiopulmonary function values such as RVEDP and right atrial pressure. These data suggested that peripheral vasoconstriction and sodium reabsorption in the kidney [5] owing to the activation of the renin-angiotensin system might also be associated with congestive heart failure in dogs with HWD. Plasma ANP levels were high, and correlated with pulmonary

arterial pressures, right atrial pressures and RVEDP in dogs with mild heartworm infection [18]. In dogs with HWD at a severer stage, plasma ANP concentration differed among individual dogs in the present study, but tended to be high, and correlated significantly with pulmonary arterial pressure. Dogs with severer HWD had a considerably higher atrial pressure because of pulmonary hypertension and tricuspid valve insufficiency [8, 9]. Circulatory disturbance was very acute in dogs with acute-CS, but chronic in dogs with chronic-CS and ascitic pulmonary HWD, and there might be differences in the response of ANP excretion to circulatory disturbance. ANP is released to circulation responding to an increase in left atrial pressure [13, 14], and the excretion of ANP may be different between right-side and left-side heart failures.

In dogs with HWD, PRA, plasma ATII concentration, and ANP concentration tended to be high as in human patients with congestive heart failure [16], and tended to correlate with right atrial pressure and pulmonary arterial pressure, respectively. However, there were no significant correlations between PRA or plasma ATII concentration and plasma ANP concentration. ANP has diuretic and vasorelaxant properties, and acts to decrease venous congestion [4, 6, 12]. ANP acts suppressively on the renin-angiotensin system [1, 11]. Although that system and ANP may be activated simultaneously, they may act dependently in HWD. Circulatory disturbances involve many factors such as pulmonary and systemic vascular resistances, circulating blood volume, and pumping ability of the heart. A variety of negative and positive feedback mechanisms, including the renin-angiotensin system and ANP, might be

Table 2. Correlations among the plasma renin activities, angiotensin II concentrations, atrial natriuretic peptide concentrations and laboratory and cardiopulmonary function variables

Variable	Plasma renin activity			Angiotensin II concentration			Atrial natriuretic peptide concentration		
	n	r	P<	n	r	P<	n	r	P<
Angiotensin II concentration	42	0.67	0.01		—			—	
Atrial natriuretic peptide concentration	44	0.02	NS	45	-0.06	NS		—	
Red blood cell count	44	-0.06	NS	43	-0.10	NS	46	0.23	NS
White blood cell count	44	0.30	0.05	43	0.39	0.01	46	-0.08	NS
Alanin transaminase activity	44	0.24	NS	43	0.004	NS	46	-0.16	NS
Alkaline phosphatase activity	44	0.64	0.01	43	0.27	NS	46	-0.03	NS
Urea nitrogen concentration	44	0.40	0.01	43	0.34	0.05	46	-0.14	NS
Creatinine concentration	44	0.32	0.05	43	0.23	NS	46	-0.20	NS
Sodium concentration	43	-0.55	0.01	41	-0.31	0.05	44	-0.01	NS
Potassium concentration	43	0.41	0.01	41	0.40	0.01	44	-0.10	NS
Chloride concentration	43	-0.52	0.01	41	-0.25	NS	44	-0.03	NS
Mean pulmonary arterial pressure	44	0.17	NS	43	0.23	NS	44	-0.03	NS
Right ventricular endodiastolic pressure	45	0.34	0.05	44	0.51	0.01	47	0.26	NS
Maximum right atrial pressure	45	0.34	0.05	44	0.47	0.01	47	0.20	NS
No. of heartworms removed/kg body weight	44	-0.20	NS	43	-0.18	NS	46	-0.16	NS

n: No. of dogs; r: correlation coefficient; P: probability of significant coefficient; NS: not significant.

activated in response to circulatory disturbance. Moreover, kidney and liver dysfunctions at the terminal phase might result in excretions of renin, angiotensin and ANP. The pathophysiology of HWD is not simple. However, treatments to suppress the renin-angiotensin system and to activate the ANP system may also be effective in dogs with HWD.

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