Relationship between Pulmonary Arterial Pressure and Lesions in the Pulmonary Arteries and Parenchyma, and Cardiac Valves in Canine Dirofilariasis

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ABSTRACT. The relationship between pulmonary hypertension and lesions was examined in 41 dogs infested naturally with heartworms, which consisted of 28 cases with pulmonary heartworm disease and 13 cases with caval syndrome. Pulmonary arterial pressure (PAP) was measured before and 1 or 7 days after heartworm removal with a flexible alligator forceps. In these dogs, lesions were examined after the last measurement of PAP. The mean PAP was 28.2±16.0 mmHg (10.9 to 81.4 mmHg in range) at post-removal phase. Pulmonary arterial intimal lesions, pulmonary thromboemboli, pneumonic lesions, tricuspid valvular lesions and mitral valvular lesions were macroscopically recognized in 95, 59, 39, 54 and 56% of cases, respectively. These lesions were classified by severity and the relationship with PAP was examined by the multiple correlation analysis. The multiple coefficient correlation was found the highest between PAP and thromboemboli, followed by mitral valvular lesion, tricuspid valvular lesion, and pneumonic lesion. There was no significant correlation between PAP and intimal lesions. The coefficient of determination showed the highest value in thromboemboli when one variable was used, and increased only very slightly when a variable of thromboemboli was added to those of other lesions. The cases with high PAP had fresh thromboemboli in large pulmonary arteries. From these evidences, it was concluded that thromboemboli following natural death of heartworm was the most important factor causing an increase in PAP and developing clinical signs in canine heartworm disease.—KEY WORDS: dirofilariasis, heartworm, hemodynamics, pulmonary hypertension, thromboembolism.

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Pulmonary hypertension is the most important factor in the development of clinical signs in canine dirofilariasis (heartworm disease). It has been considered that pulmonary hypertension in heartworm disease occurs due to various factors, such as intimal lesion of the pulmonary arteries [9, 14], thromboemboli associated with dead adult heartworms [9] and lung parenchymal lesions (pneumonic lesion) [18]. However, live worms are probably not involved in pulmonary hypertension [9, 14, 15]. The authors demonstrated that live adult worms were dominant causative agents of pulmonary hypertension, because pulmonary arterial pressure (PAP) fell significantly after heartworm removal with a flexible alligator forceps [8, 17]. Thromboemboli are also suspected to be an important factor of pulmonary hypertension in heartworm disease, since there was extremely high PAP after heartworm removal in cases in which severe thromboemboli associated with dead worms were noticed [6, 17]. Tricuspid and mitral valve lesions are found frequently in dogs with heartworm disease [3, 11], and mitral valve regurgitation causes an increase in PAP [3, 18]. The dogs infected spontaneously with heartworms have above lesions concomitantly. Therefore, these lesions might be involved together to induce pulmonary hypertension in heartworm disease, but the contributive rate of each lesion to PAP has not been clarified yet.

This paper describes the relationships between PAP after heartworm removal and lesions in the pulmonary arteries, pulmonary parenchyma and cardiac valve in canine heartworm disease by the multiple correlation analysis.

MATERIALS AND METHODS

Forty-one dogs of both sexes of various bleeding, weighing 3 to 15 kg, aged 3 to 12 years were used. The dogs were infested with heartworms naturally. Twenty-eight of them were pulmonary heartworm disease, which were detected heartworms only in the pulmonary arteries by ultrasonography. On physical examination, no signs were detected in 13 of the dogs, mild signs such as slight anemia, coughing and systolic cardiac murmur were noticed in 13 dogs, and severe signs such as ascites and subcutaneous edema in addition to those of mild signs were found in 2 dogs. Thirteen of 41 dogs were caval syndrome (CS), which were found heartworm in the tricuspid

valve orifice by ultrasonography. On physical examination on the dogs with CS, systolic cardiac murmur and hemoglobinuria were detected in almost all of them before heartworm removal, and the systolic cardiac murmur remained in 9 dogs, ascites in 4 dogs and coughing in 4 dogs 1 or 7 days after heartworm removal.

Heartworms were removed with a flexible alligator forceps from the pulmonary arteries and/or tricuspid valve orifice through the jugular vein in all dogs. PAP was measured before and 1 or 7 days after heartworm removal under diazepam-ketamine anethesia using the same methods cited in our previous report [4]. All dogs were euthanatized by overdosing of anesthetics after the final measurement of PAP, and the remaining live heartworms and lesions were examined.

Severity of each lesion was classified by the following criteria. In the intimal lesions in the pulmonary arteries, slight lesion had sandy vegetation on the intimal surface, moderate lesion had grainy, rugose and/or villous vegetation on the intimal surface, and severe lesion had strictures of the vessel lumen owing to large grainy or villous vegetation. In the thromboemboli in the pulmonary arteries, slight lesion had a few small-chronic emboli in the peripheral arteries which were barely detected by palpation from the surface of the lungs, and the emboli tightly adhered to the vessel wall, containing small worm fragments. Moderate lesion had a small number of emboli in the middle or small arteries, which were grayish or brownish fibrinoid substance surrounding relative fresh worm fragments and adhering to the vessel wall in several lobes. Severe lesion had fresh and large thromboemboli in the large and middle size arteries. In the pneumonic lesion, slight lesion had scattered small consolidations in the lobes, moderate lesion had consolidation or pneumonic lesion occupying less than quarter of entire lobes, and severe lesion had pneumonia occupying over one-fourth of the entire lobes. In the cardiac valvular lesion, slight lesion had sandy or grainy nodules or slight edema in the valvular leaves but were not accompanied by deformation, moderate lesion showed deformation of the valvular leaves by grainy or coalesced nodules or moderate edema, and severe lesion had shrunken valvular leaves and chord above the lesions, or coiling of heartworm. Systolic cardiac murmur was detected in all cases with moderate and severe valvular lesions. Histopathological examination was performed on the lungs in 20 cases with various grade of PAP to examine the possible correlation between microemboli and pulmonary hypertension.

Each lesion except microemboli was scored by the severity; no change was counted as 1, slight lesion as 2, moderate lesion as 3, and severe lesion as 4. The correlation coefficient between lesions and PAP was examined by the multiple correlation analysis.

RESULTS

The number of heartworms and change in PAP before and after heartworm removal were shown in Table 1. In cases with pulmonary heartworm disease, the average number of heartworms removed was 39, with 6 worms remaining, and a removal rate of 88%. The mean PAP was 34.3 mmHg before heartworm removal, which fell significantly to 22.1 mmHg afterward. There were no significant correlations between PAP before worm removal and the total number of worms, or between the fall in PAP and the number of worms removed. In CS cases, the number of worms removed and the removal rate were almost the same as those of the dogs with pulmonary heartworm disease. The mean PAP of

Table 1. Number of heartworms removed and pulmonary arterial pressure before and after heartworm removal

Type of heartworm disease	No. of dogs	No. of worms removed		No. of remaining worms	Removal rate (%)	Mean pulmonary arterial pressure (mmHg)		
		Tricuspid valve orifice	Pulmonary arteries			Pre-removal	Post-removal[a)]	Fall value[b)]
Pulmonary	28	0	39±26[c)] (9~112)[d)]	6±8 (0~11)	88±13 (56~100)	34.3±10.9 (14.6~58.6)	22.1±8.0** (10.9~42.1)	12.2±6.8 (−1.2~28.2)
Caval	13	20±17 (2~72)	11±14 (0~44)	5±7 (0~37)	88±17 (39~100)	44.6±18.0 (15.6~71.4)	41.5±19.7 (12.2~81.4)	3.1±7.0 (−14.0~12.4)
Pulmonary and Caval	41	7±13 (0~112)	31±26 (0~3)	5±7 (0~37)	88±0.1 (39~100)	37.6±14.4 (14.6~71.4)	28.4±16.0 (10.9~81.2)	9.3±8.0 (−14.0~28.2)

a) One or seven days post-removal. b) Fall value=Pre-removal value−Post-removal value. c) Mean±standard deviation. d) Range. **: Significant difference ($p<0.01$) from pre-removal value.

Table 2. Incidences of lesions in the pulmonary arteries, lungs and cardiac valves in experimental dogs

Type of heartworm disease	No. of dogs	Intimal lesion				Thromboemboli				Pneumonia				TV[a] lesion				MV[b] lesion			
		−	+	++	+++[c]	−	+	++	+++	−	+	++	+++	−	+	++	+++	−	+	++	+++
Pulmonary	28	2[d]	17	5	4	16	5	7	0	17	8	2	1	17	5	3	3	16	7	5	0
		(7)[e]	(61)	(18)	(14)	(57)	(18)	(25)		(61)	(29)	(7)	(4)	(61)	(18)	(11)	(11)	(57)	(25)	(18)	
Caval	13	0	4	6	3	1	4	3	5	8	3	2	0	2	3	6	2	2	3	8	0
			(31)	(46)	(23)	(8)	(31)	(23)	(38)	(62)	(23)	(15)		(15)	(23)	(46)	(15)	(15)	(23)	(62)	
Total	41	2	21	11	7	17	9	10	5	25	11	4	1	19	8	9	5	18	10	13	0
		(5)	(51)	(27)	(17)	(41)	(22)	(24)	(12)	(61)	(27)	(10)	(2)	(46)	(20)	(22)	(12)	(44)	(24)	(32)	

a) Tricuspid valvular. b) Mitral valvular. c) Severity of lesions: −... no change, +... slight, ++... moderate, +++... severe. d) Number of dogs. e) Percentage.

Table 3. Correlation matrix of each lesion and pulmonary arterial pressure

	Intimal lesion	Thrombo-emboli	Pneumonia	Tricuspid valvular lesion	Mitral valvular lesion	Pulmonary arterial pressure
Intimal lesion	1.000					
Thromboemboli	0.214	1.000				
Pneumonia	0.140	0.138	1.000			
Tricuspid valvular lesion	0.354*	0.330*	0.352*	1.000		
Mitral valvular lesion	0.404**	0.474**	0.320*	0.785**	1.000	
Pulmonary arterial pressure	0.129	0.673**	0.275*	0.388*	0.431*	1.000

*: $P<0.05$. **: $P<0.01$.

Table 4. Results of multiple regression analysis between pulmonary arterial pressure and lesions

Item	Multiple correlation coefficient	Coefficient of determination	ΔR^2	F value
Te[a]	0.67319	0.45318	—	32.32150***
Te·Mv[b]	0.68509	0.46935	0.01617	16.80480***
Te·Mv·Tv[c]	0.69569	0.48399	0.01464	11.56790***
Te·Mv·Tv·Pn[d]	0.70850	0.50197	0.01798	9.07113***
Te·Mv·Tv·Pn·In[e]	0.71225	0.50730	0.00535	7.20730***

a) Thromboemboli. b) Mitral valvular lesion. c) Tricuspid valvular lesion. d) Pneumonic lesion. e) Intimal lesion. ***: $p<0.005$.

CS cases were higher than that of pulmonary heartworm disease cases before and after worm removal. The difference in the mean PAP before and after worm removal was not significant. As to the relationships between clinical signs and PAP, the cases with ascites and/or cardiac murmur always indicated a high PAP (40.3 to 81.2 mmHg) after worm removal, but some other cases with high PAP showed no clinical signs.

Intimal lesions were found in almost all the cases, and thromboemboli, pneumonic lesions, tricuspid valvular and mitral valvular lesions were observed in about 40 to 60% of the cases (Table 2). The incidence or severity of each lesion was higher and severer in the CS cases than in the pulmonary heartworm disease cases. The correlation in the incidence of each lesion was examined in a case with concomitant several lesions (Table 3). There was a slight correlation between tricuspid and mitral valvular lesion and intimal lesion, thromboemboli and pneumonic lesion. A high correlation was observed between tricuspid and mitral valvular

lesions; the severity of the tricuspid valvular lesion roughly corresponded to that of the mitral valvular lesion in the majority of cases.

The highest multiple correlation coefficient was observed between PAP and thromboemboli ($R=0.673$, $P<0.01$), followed by mitral valvular lesion ($R=0.431$, $P<0.05$), tricuspid valvular lesion ($R=0.388$, $P<0.05$) and pneumonic lesions ($R=0.275$, $P<0.05$). Intimal lesions showed no significant multiple correlation coefficient with PAP (Table 3). Thromboemboli also exhibited the highest coefficient determination (contribution rate) when one variable was used between lesions and PAP (Table 4). The coefficient of determination increased when a variable of thromboemboli was added to those of mitral valvular, tricuspid valvular, pneumonic and intimal lesions, but the either difference (ΔR^2) was very small.

The relationship between PAP and the severity of thromboemboli in individual dogs was presented in Fig. 1. PAP tended to increase with the severity except in a few cases. In cases with mild or no thromboemboli, the mean PAP was within the control or slightly higher values in the majority of cases, but 4 cases displayed a moderately high PAP (30 to 40 mmHg) and one case a high PAP (60.2 mmHg). One case with moderately high PAP and without thromboemboli had a severe pneumonic lesion and moderate mitral and tricuspid valvular lesions, and the 3 other cases with moderately high PAP had moderate mitral and tricuspid valvular lesions and intimal lesions, but no pneumonic lesions. One case with high PAP and mild thromboemboli had a severe mitral valvular and moderate tricuspid valvular lesions and slight intimal lesion but no pneumonic lesion. In moderate thromboemboli, the majority of cases showed slightly to moderately high PAP. One case showed very high PAP (81.2 mmHg), which rose after worm removal. In this case, there were moderate pneumonic and intimal lesions and slight valvular lesions, but no other severe lesions. A small number of microemboli without dead worms were detected in 11 cases with no correlation to PAP.

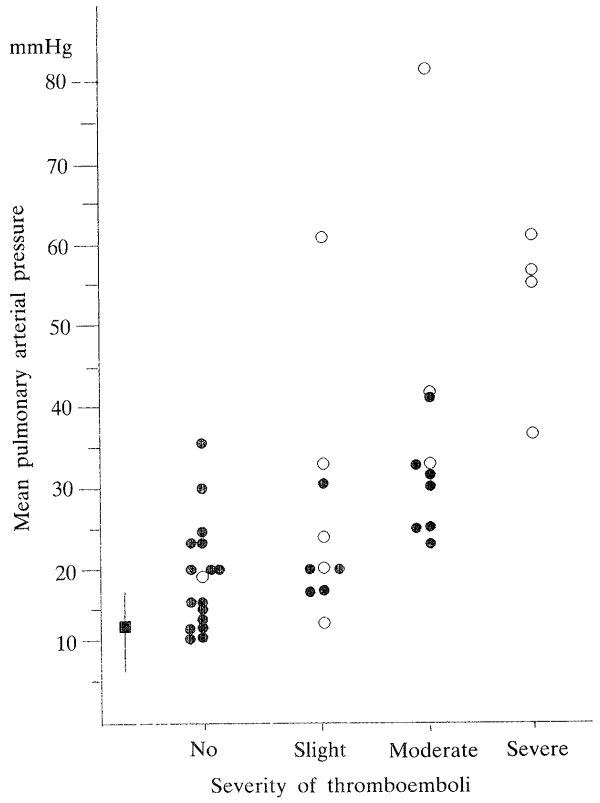

Fig. 1. Relationship between pulmonary arterial pressure and severity of thromboemboli. ●: Pulmonary heartworm disease. ○: Caval syndrome. ■: Control value, obtained from 15 dogs infected with no heartworms. Vertical bar indicates standard deviation.

DISCUSSION

Since the cases with ascites and heart murmur always had pulmonary hypertension in this study, it was reaffirmed that pulmonary hypertension contributed to development of clinical signs in heartworm disease. PAP fell significantly after removal of adult live worms in the pulmonary heartworm disease cases, and live worms was considered one of the causative agents for pulmonary hypertension, just as in the previous reports [8, 17]. In the CS cases, PAP did not fall significantly after worm removal, possibly because the majority of worms in the pulmonary arteries, which caused PAP to rise, migrated from the pulmonary arteries to the right atrium and tricuspid valve orifice before surgical removal. Therefore, it was suspected that they had higher PAP before the onset of CS. PAP after worm removal in CS cases was higher than that in pulmonary heartworm disease cases, possibly owing to the influence of severe lesions. CS was induced by heartworm migration from the pulmonary arteries to the right atrium following the change in hemodynamics by many causes [5, 7]. The authors, however, considered that thromboembolism associated with dead worms might be the most important factor in spontaneous CS [6, 7].

The multiple regression analysis of the rela-

tionship between PAP and lesions showed that thromboembolus had the strongest correlation to PAP, followed by mitral valvular lesion, tricuspid valvular lesion and pneumonic lesion in this order. Moreover, the coefficient of determination was the largest in thromboembolus, and the value increased slightly when variables of other lesions were added to that of thromboembolus. This result indicated that thromboemboli were the most important factor in pulmonary hypertension in heartworm disease. Severe pulmonary hypertension in cases with relatively fresh thromboemboli in large pulmonary arteries was found to accompany moderate to severe intimal lesions. This could be explained by the following evidences. It is well known that thromboemboli associated with dead worms interfere the blood flow, cause a sharp rise in PAP and lead to right-side congestive heart failure [10]. However, PAP and clinical signs recover gradually following the development of recanalization and collateral circulation with time [10, 12]. On the other hand, pulmonary hypertension by emboli is not explained simply by the mechanical blockage of blood flow [16]. Increased PAP is noted more often in cases in which microemboli are induced in the widespread small pulmonary arteries or arteriolae than cases in which thromboemboli are induced in the relatively large pulmonary arteries of experiment animals [16]. Microthromboemboli in the pulmonary small vessels are noticed often in dogs with heartworm disease [1]. A small number of pulmonary microthromboemboli were also recognized by microscopic findings in some cases in the present study, but they had no relation with the severity of pulmonary hypertension. The previous damage to the cardiac and pulmonary-vascular system has a role in inducing pulmonary hypertension in thromboembolism [16]. Therefore, terms of the time since worms died, the number of dead worms, the location of thromboemboli, and the previous intimal lesions in the pulmonary arteries should be considered in the onset of pulmonary hypertension by thromboemboli associated with dead worms. Intimal lesions in the pulmonary arteries were reported to be the most important factor in pulmonary hypertension in canine heartworm disease [9, 14]. However, the intimal lesion showed the least effects on the pulmonary hypertension in the present study. There is no doubt that the intimal lesion interferes the blood flow and cause the vascular elasticity and compliance to decrease [14, 17]. Although pulmonary hypertension might occur when other factors such as live worms or thromboemboli were complicated with it.

It has been well known that pulmonary parenchymal hemorrhage, and red-brownish or gelatinous consolidations occur around thromboemboli associated with dead worms [1, 2]. These lesions were recognized in some cases, but the frequency and severity were not remarkable. Hence, no statistical correlations could be observed between pneumonic lesions and PAP in this study. However, moderate pulmonary hypertension was noticed in a case with severe pneumonic lesions but no thromboembolus.

The effects of tricuspid valvular lesions on pulmonary hypertension have not been well known, but mitral valvular lesion induce moderate pulmonary hypertension [3]. Mitral and tricuspid valvular lesions occurred together in almost all of the cases, and the effects of mitral valvular lesion on tricuspid valvular lesion could be expressed statistically. The valvular lesion effects on PAP were relatively clear in some cases with little or no thromboemboli. Thus, the lesions in the pulmonary arteries, lungs and cardiac valve were considered to cause PAP increase, but pulmonary hypertension could not be explained sufficiently in some cases by only these lesions. These cases might include other factors such as hypoxemia [13].

It follows from what has been indicated that heartworms died naturally quite often, and thromboemboli associated with dead worms are the most important factors causing the PAP increase and developing clinical signs in heartworm disease.

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