Contribution of Live Heartworms Harboring in Pulmonary Arteries to Pulmonary Hypertension in Dogs with *Dirofilariasis*

Hitoshi KITAGAWA, Yoshihide SASAKI, Katsuya ISHIHARA, and Yuji HIRANO

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

(Received 14 November 1989/Accepted 7 August 1990)

ABSTRACT. To investigate whether adult heartworms harboring in the pulmonary arteries contribute to pulmonary hypertension, we determined the cardio-pulmonary values immediately before and after removal of heartworms from the pulmonary arteries and before and after insertion of live worms in their place. In 10 heartworm-infected dogs, 8 to 46 worms were removed. The mean pulmonary arterial pressure fell significantly from 24.5 ± 7.9 mmHg to 16.3 ± 4.9 mmHg ($p < 0.01$) immediately after removal. The right cardiac output decreased in 7 of the 10 cases. The total pulmonary resistance and right ventricular stroke work index also decreased. At 24 hours after removal, live heartworms were put back into the pulmonary arteries of their host dog. The mean pulmonary arterial pressure elevated significantly ($p < 0.01$) immediately after insertion. The right cardiac output further decreased in 7 of the 10 dogs, and the total pulmonary resistance and right ventricular stroke work index increased. Separate from this, 12 to 42 heartworms were transplanted into the pulmonary arteries of 5 heartworm-free dogs. Immediately after transplantation, the pulmonary arterial pressure did not show any significant change. However, the stroke volume decreased, and the total pulmonary resistance increased. These facts suggest a contribution of live heartworms to the pulmonary hypertension, although there is a complicated interaction among the presence of heartworms, the pulmonary lesions and the pulmonary hypertension.—**KEY WORDS:** dirofilariasis, heartworm, pulmonary hypertension.

Jpn. J. Vet. Sci. 52(6): 1211–1217, 1990

Pulmonary hypertension has been noticed in many dogs with heartworm disease [6, 8, 9, 12, 13], and it is regarded as the cause of many symptoms in dirofilariasis. The hypertension is produced by the pathologic changes within the pulmonary vasculature following severe and prolonged infection by the worms. The physical presence of adult heartworms and microfilariae do not contribute so greatly to the hypertension resulting from inserting heartworms into the pulmonary arteries of healthy dogs [7, 9]. However, the authors noted a reduction in pulmonary hypertension within a short period after heartworm removal from the pulmonary arteries [4], and considered that the worms themselves also might contribute to the hypertension. In the present study, in order to investigate whether the presence of heart-

worms contributes directly to the pulmonary hypertension, the pulmonary arterial pressure and other cardiopulmonary values were determined before and after heartworm removal from the pulmonary arteries and before and after insertion of live worms in heartworm-infected dogs. In the heartworm-free dogs, heartworms were also transplanted into the pulmonary arteries, and the cardiopulmonary values were determined before and after the treatment.

MATERIALS AND METHODS

Ten dogs infected spontaneously with heartworms and 5 heartworm-free dogs were investigated. They were provided by the regional dog pound. These dogs ranged in age from 7 months to 6 years old, and

weighed from 5.0 kg to 11 kg.

In heartworm-infected dogs, adult heartworms were removed from the pulmonary arteries through the jugular vein using a flexible alligator forceps without thoracotomy [5]. The heartworms removed were kept alive in Hank's solution with dog serum added at 4°C. On the next day (24 hr after removal), the worms were inserted into the pulmonary arteries of their original host using the flexible alligator forceps. In heartworm-free dogs, adult heartworms, which had been collected from other infected dogs, were transplanted surgically into the pulmonary arteries through the jugular vein. The location of heartworms was observed with convex-arrayed two-dimensional echocardiography (EUB-40, Hitachi Medical Corp. Tokyo), and it was confirmed that the worms located only in the pulmonary arteries.

The dogs were anesthetized with diazepam (Cercine, Takeda Chemical Industries Ltd., Osaka) and ketamine hydrochloride (Ketalar, Sankyo Co., Ltd., Tokyo) as described previously [4]. The cardiopulmonary values were determined immediately before and after removal and insertion of heartworms in heartworm-infected dogs, and immediately before and after trans-

plantation in heartworm-free dogs. The pulmonary arterial pressure was measured through a catheter connected with a blood pressure transducer and a carrier amplifier (TP-101T and AP-601G, Nihon Kohden Corp., Tokyo). The right cardiac output was determined with thermo-dilution method (Swan-Ganz catheter, 93-132-5F, Edwards Lab., Santa Ana, U.S.A., and Cardiac output computer, AH-611V and EQ-611V, Nihon Kohden Corp.). The stroke volume was calculated from the cardiac output and heart rate, the total pulmonary resistance from the mean pulmonary arterial pressure and cardiac index [8], and the right ventricular stroke work index from the stroke index and cardiac output [2]. The diameter of the pulmonary arterial trunk was measured by M-mode echocardiography. At the end of the experiment, all dogs were euthanatized by overdosing of the anesthetic, and the heartworms harbored were counted. All worms inserted or transplanted were recovered alive. Paired t-test was used for the statistical comparison of the data before and after treatments.

RESULTS

Table 1 shows the number of heartworms

Table 1. Number of heartworms removed, remaining and inserted in heartworm-infected dogs

Dog	Age	Sex	Body	Number of heartworms										
No.	(y)		weight	Removed			Remaining			Efficiency	Inserted			Re-harboring
				(kg)	Female	Male	Total	Female	Male	Total	(%)	Female	Male	Total
1517	3	Female	10.0	15	11	26	1	4	5	83.9	14	11	25	96.8
1557	4	Female	7.5	22	5	27	0	1	1	96.4	12	3	15	57.1
1618	3	Male	11.0	28	18	46	0	7	7	87.0	16	4	20	50.9
1657	3	Female	7.0	11	10	21	0	0	0	100	11	10	21	100
1678	6	Female	7.2	19	8	27	2	0	25	93.1	19	8	27	100
1681	5	Male	5.0	4	4	8	0	0	0	100	2	2	4	50.0
1688	4	Female	8.0	25	18	43	6	0	6	87.8	25	17	42	98.0
1707	5	Female	9.0	9	8	17	3	1	4	81.0	9	3	12	76.2
1722	2	Male	5.0	10	4	14	0	0	0	100	10	4	14	100
1729	2	Male	6.5	24	18	42	4	1	5	93.3	20	10	30	74.5

a) (No. of worms remaining+No. of worms inserted)/No. of worms harboring.

Table 2. Diameter of the pulmonary arterial trunk before and after removal and insertion of heartworms in heartworm-infected dogs

Measurement	n	Before removal	24 hr after removal ^{a)}	24 hr after insertion
Diameter of pulmonary arterial trunk at systolic phase (mm)	10	24.3 ± 3.2	19.4 ^{c)} ± 3.1	22.0 ^{d)} ± 2.7

a) Immediately before heartworm insertion.

b) Data are presented as mean±standard deviation.

c) Probability of significant difference from pre-removal level at $p<0.01$.d) Probability of significant difference from pre-insertion level at $p<0.01$.

Table 3. Changes in mean pulmonary arterial pressure after removal and insertion of heartworms in heartworm-infected dogs

Dog No.	Mean pulmonary arterial pressure (mmHg)			
	Removal		Insertion	
	Before	After ^{a)}	Before ^{b)}	After ^{c)}
1517	32.9	23.5	18.6	29.9
1557	24.4	13.2	15.1	16.2
1618	24.7	17.7	17.1	22.0
1657	13.3	14.6	14.2	21.4
1678	28.1	11.4	15.9	28.4
1681	34.8	18.0	18.3	36.5
1688	25.6	22.6	13.6	17.9
1707	31.4	19.9	15.3	22.4
1722	14.1	8.6	11.0	11.4
1729	15.4	13.1	9.9	16.4
Mean	24.5	16.3	14.9	22.3
SD	7.9	4.9	2.9	7.5
p<	—	0.01 ^{d)}	—	0.01 ^{e)}

a) Immediately after heartworm removal.

b) 24 hr after removal.

c) Immediately after heartworm insertion.

d) Probability of significant difference from pre-removal level.

e) Probability of significant difference from pre-insertion level.

removed, harboring and inserted in 10 heartworm-infected dogs. Eight to 46 worms were removed from the pulmonary arteries. The number of worms remaining was 0 to 7, and the removal efficiency ranged from 81.0% to 100%. Four to 42 worms were put back into the pulmonary arteries. The re-harboring rate, which was calculated from the sum of heartworms inserted and the remaining/total No. of worms harbored $\times 100$, ranged from 50.0%

to 100%. Not all of the worms which had been removed could be inserted into the pulmonary arteries, because the diameter of the pulmonary arterial trunk decreased after heartworm removal (Table 2). The trunk dilated significantly 24 hr after heartworm insertion.

Table 3 shows the mean pulmonary arterial pressure before and after removal and insertion of heartworms in heartworm-infected dogs. Immediately after removal, the pressure fell obviously in all 7 dogs having a pressure above 20 mmHg, but did not alter in 3 dogs with a normal pressure (Nos. 1657, 1722 and 1729). The mean in 10 cases fell significantly ($p<0.01$) from 24.5 mmHg to 16.3 mmHg. The pressure hardly changed at 24 hr after removal, immediately before insertion. Immediately after insertion, the pressure elevated in almost all cases, and the change in mean value was statistically significant ($p<0.01$). However, in cases with a normal pulmonary arterial pressure at pre-removal (Nos. 1722 and 1729) and a low re-harboring rate (Nos. 1557, 1618, 1681 and 1707), the pressure did not elevate much after insertion.

Table 4 shows the changes in other cardiopulmonary values in heartworm-infected dogs. The heart rate did not alter significantly throughout the experiment. The right ventricular end-diastolic and systolic pressures decreased immediately after heartworm removal, and elevated immediately after insertion. The changes in

Table 4. Changes in cardiopulmonary values after removal and insertion of heartworms in heartworm-infected dogs

Measurement	n	Removal		p< ^{a)}	Insertion		p< ^{b)}
		Before	After ^{c)}		Before ^{d)}	After ^{e)}	
Heart rate (beat/min)	10	154 ^{f)} ± 38	165 ± 51	NS ^{g)}	149 ± 31	153 ± 37	NS
Right ventricular end-diastolic pressure (mmHg)	10	1.94 ± 2.98	- 2.24 ± 2.62	0.01	- 0.80 ± 2.02	0.97 ± 1.82	0.01
Right ventricular systolic pressure (mmHg)	10	33.7 ± 10.0	24.4 ± 6.3	0.01	23.6 ± 4.2	32.5 ± 10.1	0.01
Right cardiac output (l/min)	10	2.39 ± 0.63	2.21 ± 0.84	NS	2.17 ± 0.58	2.02 ± 0.80	NS
Stroke volume (ml/beat)	10	15.8 ± 3.2	13.4 ± 3.2	0.05	14.4 ± 2.6	13.0 ± 3.5	NS
Total pulmonary resistance (dynes·sec·cm ⁻⁵ ·kg)	10	6203 ± 1945	4844 ± 2179	0.05	4315 ± 1377	6597 ± 2710	0.01
Right ventricular stroke work index (g/beat/kg)	10	0.70 ± 0.21	0.41 ± 0.17	0.01	0.39 ± 0.08	0.49 ± 0.15	NS

a) Probability of significant difference between the levels before and after heartworm removal. b) Probability of significant difference between the levels before and after heartworm insertion. c) Immediately after removal. d) 24 hr after removal. e) Immediately after insertion. f) Data are presented in mean±standard deviation. g) Not significant.

Table 5. Number of heartworms transplanted in heartworm-free dogs

Dog No.	Age (y)	Sex	Body weight (kg)	No. of heartworms transplanted			
				Female	Male	Total	Total/kg
1529	2.0	Male	9.0	9	8	17	1.89
1543	0.6	Male	6.5	7	5	12	1.85
1565	1.5	Female	6.0	15	10	25	4.17
1713	2.0	Male	5.0	8	6	14	2.80
1735	3.0	Female	11.0	17	5	22	2.00

the pressures showed the same tendency as those in the pulmonary arterial pressure. The right cardiac output tended to decrease, and the stroke volume decreased significantly after removal. The cardiac output and stroke volume tended to decrease further after insertion. The total pulmonary resistance decreased immediately after removal, and increased immediately after insertion. The right ventricular stroke work index

decreased significantly after removal, and did not change significantly after insertion.

Table 5 shows the number of heartworms transplanted into the pulmonary arteries of heartworm-free dogs. The dogs were given from 12 to 25 worms. After heartworm transplantation, the diameter of the pulmonary arterial trunk increased significantly (Table 6).

As shown in Table 7, the mean pulmon-

Table 6. Diameter of the pulmonary arterial trunk after transplantation of heartworms in heartworm-free dogs

Measurement	n	Before trans- plantation	24 hr after transplantation
Diameter of pulmonary arterial trunk at systolic phase (mm)	5	13.6 ^{a)} ± 3.5	18.0 ^{b)} ± 3.5

a) Data are presented as mean±standard deviation.

b) Probability of significant difference from pre-transplantation level at $p < 0.05$.

Table 7. Changes in mean pulmonary arterial pressure after heartworm transplantation in heartworm-free dogs

Dog No.	Mean pulmonary arterial pressure (mmHg)	
	Before	Immediately after
1529	11.9	14.5
1543	17.8	16.1
1565	15.4	16.9
1713	13.1	16.9
1735	8.6	12.1
Mean	13.4	15.2
SD	3.5	2.0
$p < ^a)$	—	NS ^{b)}

a) Probability of significant difference from pre-transplantation level.

b) Not significant.

ary arterial pressure elevated slightly or did not elevate immediately after transplantation in heartworm-free dogs. There were no dogs having a mean pulmonary arterial pressure above 20 mmHg. The elevation in mean value was slight (about 5 mmHg), and not statistically significant.

Table 8 shows the changes in the cardiopulmonary values in heartworm-free dogs. The heart rate did not alter immediately after transplantation. The right ventricular end-diastolic and systolic pressures elevated slightly, but these were not statistically significant. The right cardiac output tended to decrease, and the stroke volume decreased significantly. The total pulmonary resistance increased immediately after transplantation, but the right ventricu-

lar stroke work index did not alter significantly.

DISCUSSION

Heartworm infection produces many lesions in the pulmonary arteries such as proliferative and villous lesions with endarteritis, intimal hyperplasia, atherosclerosis and endothermal cushions, focal intimal hemorrhage, rupture of the arterial wall, obstructive fibrosis or granulomatous lesions and embolization [1, 3, 9–11]. Following formation of the lesions, the elasticity of the pulmonary vasculature is reduced, and the pulmonary vascular resistance increases, so pulmonary hypertension develops. It has been considered that the presence of adult heartworms does not contribute greatly to hypertension from the experimental data in heartworm-free dogs [7, 9].

Also in heartworm-free dogs of the present study, although the total pulmonary resistance increased slightly, the pulmonary arterial pressure did not elevate significantly immediately after heartworm transplantation. The contribution of heartworms to pulmonary hypertension might not be so great in heartworm-free dogs having no pulmonary arterial lesions. Besides, in dogs having the pulmonary arterial lesions, the pulmonary arterial pressure and total pulmonary resistance fell immediately after heartworm removal from the pulmonary arteries, and elevated immediately after insertion of worms into the arteries. These

Table 8. Changes in cardiopulmonary values after transplantation of heartworms in heartworm-free dogs

Measurement	n	Before	Immediately after	p< ^{a)}
Heart rate (beat/min)	5	162 ^{b)} ± 25	173 ± 54	NS ^{c)}
Right ventricular end-diastolic pressure (mmHg)	5	-2.23 ±2.85	0.17 ±1.94	NS
Right ventricular systolic pressure (mmHg)	5	22.6 ± 2.1	26.0 ± 7.2	NS
Right cardiac output (l/min)	5	2.57 ±1.18	2.15 ±0.93	NS
Stroke volume (ml/beat)	5	15.2 ± 5.0	12.5 ± 3.4	0.05
Total pulmonary resistance (dynes·sec·cm ⁻⁵ ·kg)	5	3399 ±1387	4535 ±1576	0.05
Right ventricular stroke work index (g/beat/kg)	5	0.36 ±0.08	0.35 ±0.06	NS

a) Probability of significant difference from pre-transplantation level. b) Data are presented as mean±standard deviation. c) Not significant.

facts indicated that the presence of live heartworms in the pulmonary arteries might cause directly the elevation of pulmonary arterial pressure due to the hindrance blood flow through the pulmonary arteries in cases having mild to severe pulmonary arterial lesions.

However, there was no significant correlation between the number of heartworms removed and changes in the pulmonary arterial pressure. The severity of the lesions and number and location of the worms in the pulmonary arteries may associate in a complex way with the occurrence of pulmonary hypertension in canine dirofilariasis.

The detailed mechanism of the decrease in the cardiac output, which was noted not only after heartworm removal but also after insertion, was unclear from the present study. It was considered that the reduction of the heart and vessel volume, which was

suggested from the findings on radiogram [4], may associate with the decrease in the cardiac output. Further investigations including the measurements of left-heart functions are required.

ACKNOWLEDGEMENTS. This study was supported in part by a Grant-in-Aid for encouragement of young scientists (No. 63760264) from the Ministry of Education, Science, and Culture, Japan.

REFERENCES

1. Adcock, J. L. 1961. Pulmonary arterial lesions in canine dirofilariasis. *Am. J. Vet. Res.* 22: 655-662.
2. Coma-Canella, I., Lopez-Sendon, J., and Gamallo, C. 1979. Low cardiac output syndrome in right ventricular infarction. *Am. Heart J.* 98: 613-620.
3. Hennigar, G. R. and Ferguson, R. W. 1956. Pulmonary sclerosis as a result of *Dirofilaria immitis* infection in dogs. *J. Am. Vet. Med. Assoc.* 131: 336-340.
4. Ishihara, K., Kitagawa, H., Sasaki, Y., and Yokoi, H. 1988. Changes in cardiopulmonary values after heartworm removal from pulmonary

- artery using flexible alligator forceps. *Jpn. J. Vet. Sci.* 50: 731-738.
5. Ishihara, K., Sasaki, Y., and Kitagawa, H. 1986. Development of flexible alligator forceps: a new instrument for removal of heartworms in the pulmonary arteries of dogs. *Jpn. J. Vet. Sci.* 48: 989-991.
 6. Knight, D. H. 1981. Evolution of pulmonary artery disease in canine dirofilariasis: Evaluation by blood pressure measurements and angiography. pp. 55-62. *In: Proceedings of the Heartworm Symposium '80* (Otto, G. F. ed.), Veterinary Medicine Publish Co., Edwardsville, Kansas.
 7. Rawlings, C. A. 1980. Acute response of pulmonary blood flow and right ventricular function to *Dirofilaria immitis* adults and microfilaria. *Am. J. Vet. Res.* 41: 244-249.
 8. Rawlings, C. A. 1980. Cardiopulmonary function in the dog with *Dirofilaria immitis* infection: During infection and after treatment. *Am. J. Vet. Res.* 41: 319-325.
 9. Rawlings, C. A. 1986. Heartworm Disease in Dogs and Cats. W. B. Saunders Co., Philadelphia.
 10. Rawlings, C. A., McCall, J. W., and Lewis, R. E. 1978. The response of the canine's heart and lungs to *Dirofilaria immitis*. *J. Am. Anim. Hosp. Assoc.* 14: 17-32.
 11. Sutton, R. H. 1988. Pathology and pathogenesis of dirofilariasis. pp. 99-132. *In: Dirofilariasis* (Boreham, P. F. L. and Atwell, R. B. eds.), CRC Press, Inc., Boca Raton, Florida.
 12. Wallace, C. R. and Hamilton, W. F. 1962. Study of spontaneous congestive heart failure in the dog. *Circ. Res.* 11: 301-314.
 13. Yarns, D. A. and Tashjian, R. J. 1967. Cardiopulmonary values in normal and heartworm-infected dogs. *Am. J. Vet. Res.* 28: 1461-1473.

要 約

肺動脈に寄生する犬糸状虫の肺高血圧に及ぼす影響：北川 均・佐々木栄英・石原勝也・平野勇二(岐阜大学農学部家畜内科学講座)——肺動脈に寄生する犬糸状虫が肺高血圧に直接関与するかどうかを検討する目的で、肺動脈から犬糸状虫を摘出する前後と肺動脈へ犬糸状虫を挿入する前後に肺動脈圧等を測定した。8から46匹の犬糸状虫が摘出された10例の犬糸状虫寄生犬では、平均肺動脈圧は、犬糸状虫摘出前の 24.5 ± 7.9 mmHg から摘出直後には 16.3 ± 4.9 mmHg に下降した。右心拍出量は7例で減少し、総肺血管抵抗及び右室仕事量も有意に減少した。犬糸状虫摘出24時間後、生きた状態で保存した犬糸状虫をもとの実験犬の肺動脈に挿入した。犬糸状虫挿入直後、平均肺動脈圧は有意に上昇した。右心拍量は7例でさらに減少したが、総肺血管抵抗及び右室仕事量は増加した。一方、12から42匹の犬糸状虫を肺動脈に挿入した5例の非寄生犬では、挿入直後に肺動脈圧は有意の変化を示さなかったが、1回拍出量は減少し、総肺血管抵抗は増加した。これらの結果は、犬糸状虫の存在と肺の病変が複雑に関与するが、肺動脈に寄生する犬糸状虫が肺高血圧に直接関与することを示唆する。