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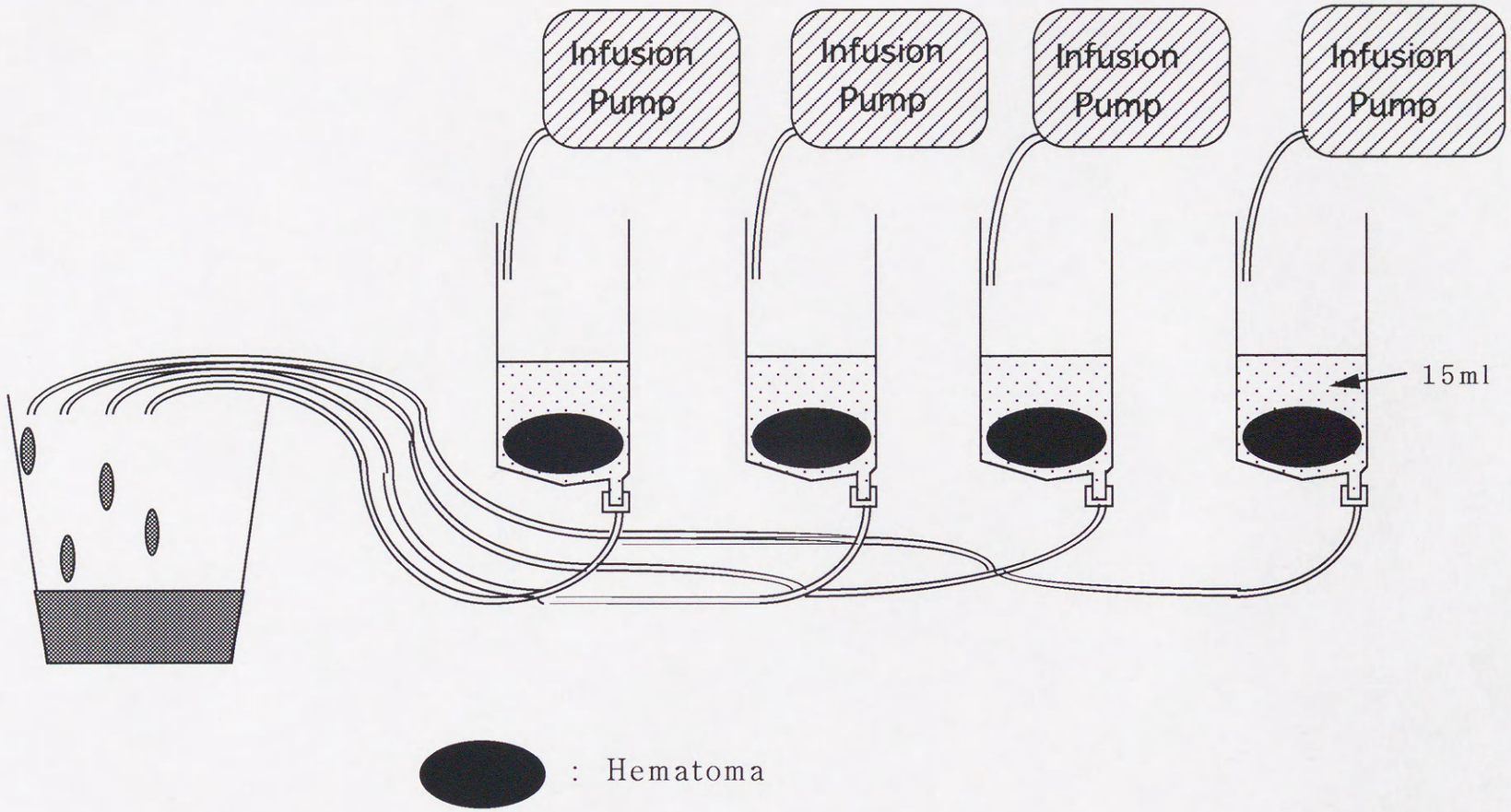


Fig. 1 *in vitro* Subarachnoid hematoma model.

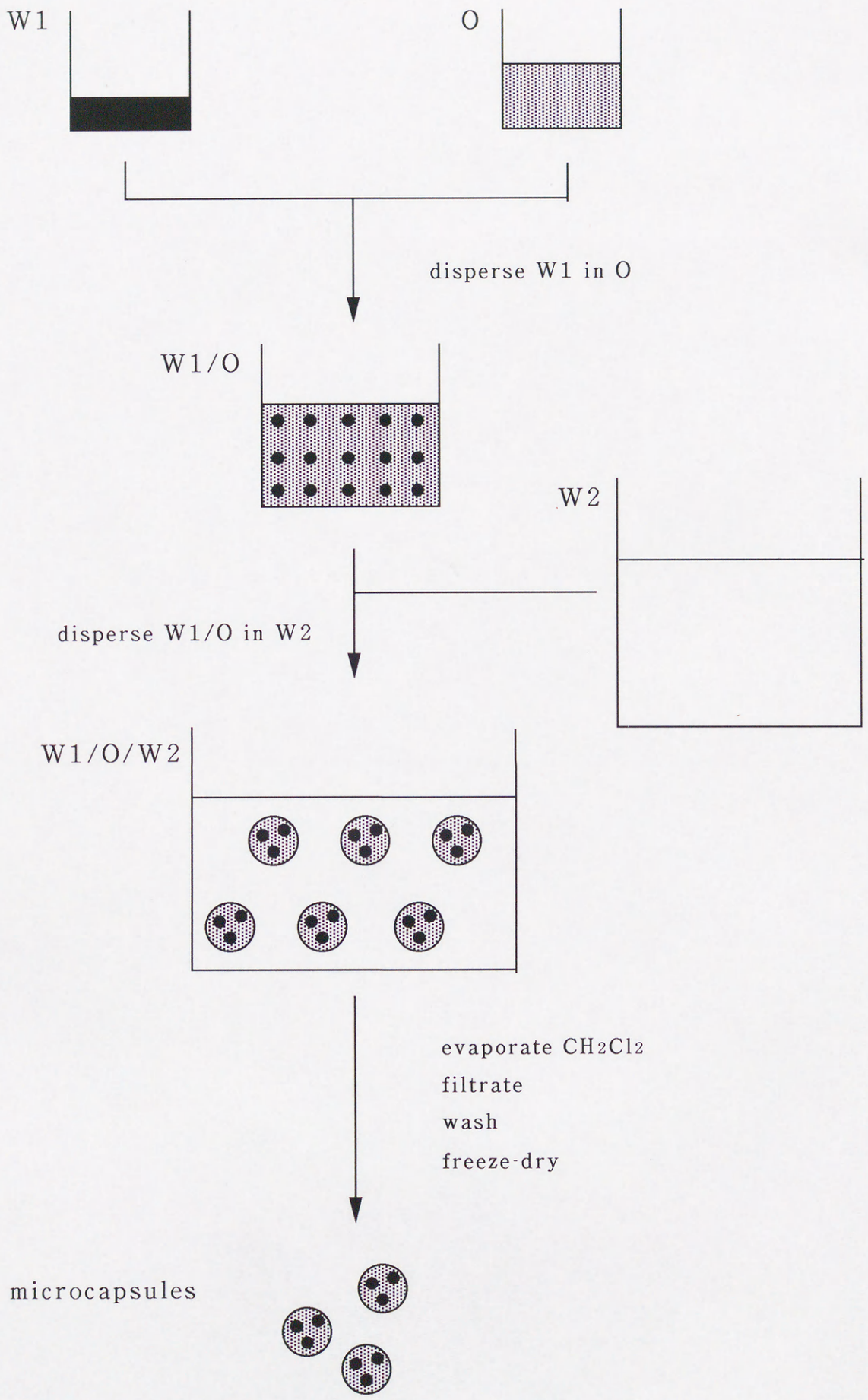


Fig.2 Schematic diagram for microcapsule preparation by water drying method

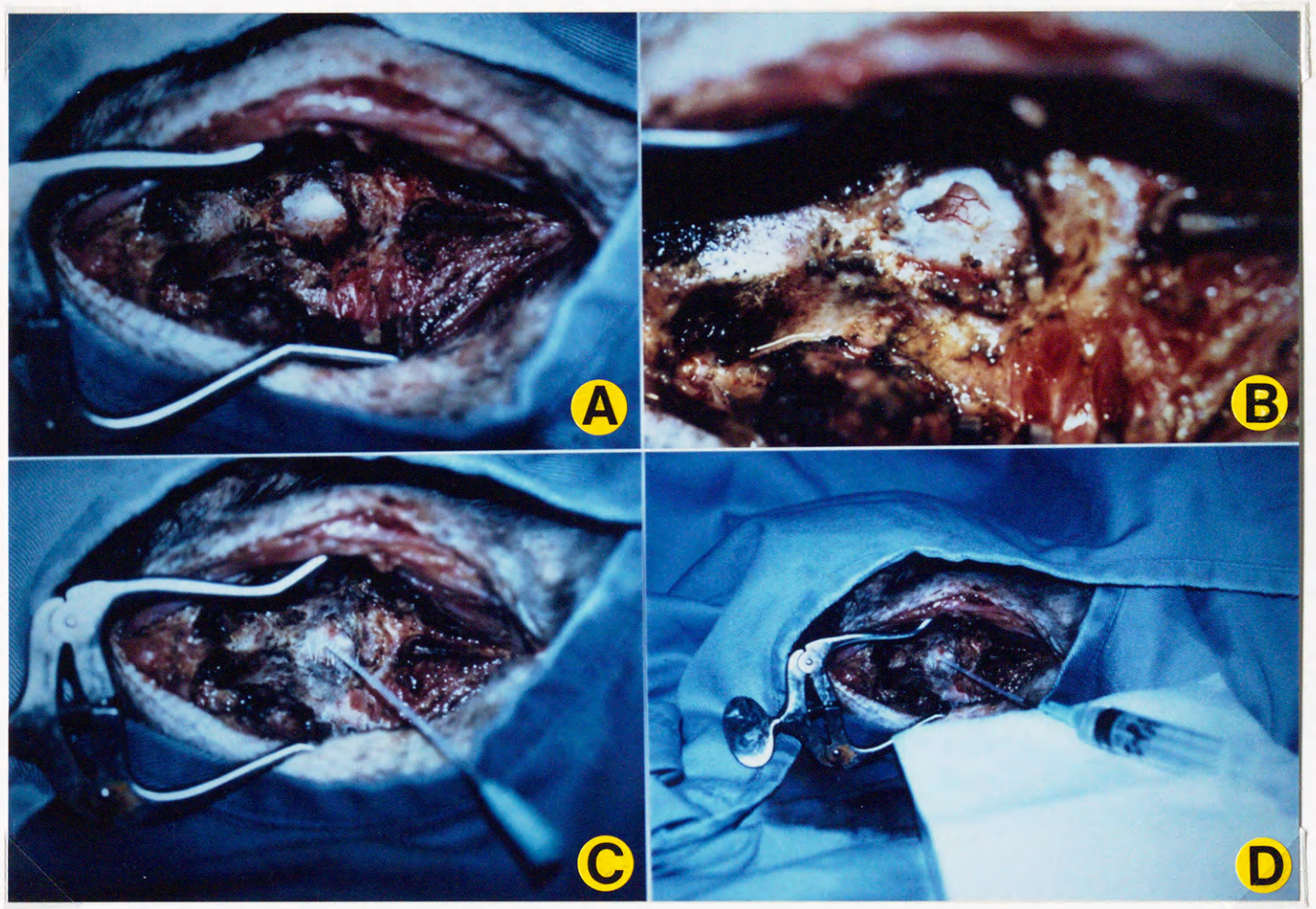


Fig. 3 Experimental procedure for the cisternal administration of t-PA or t-PA MC*

MC* = microcapsule

A : Dura mater between occipital bone and atlas B : Medulla oblongata and cisterna magna

C : Canulation into cisterna magna D : Cisternal administration of t-PA or t-PA MC*

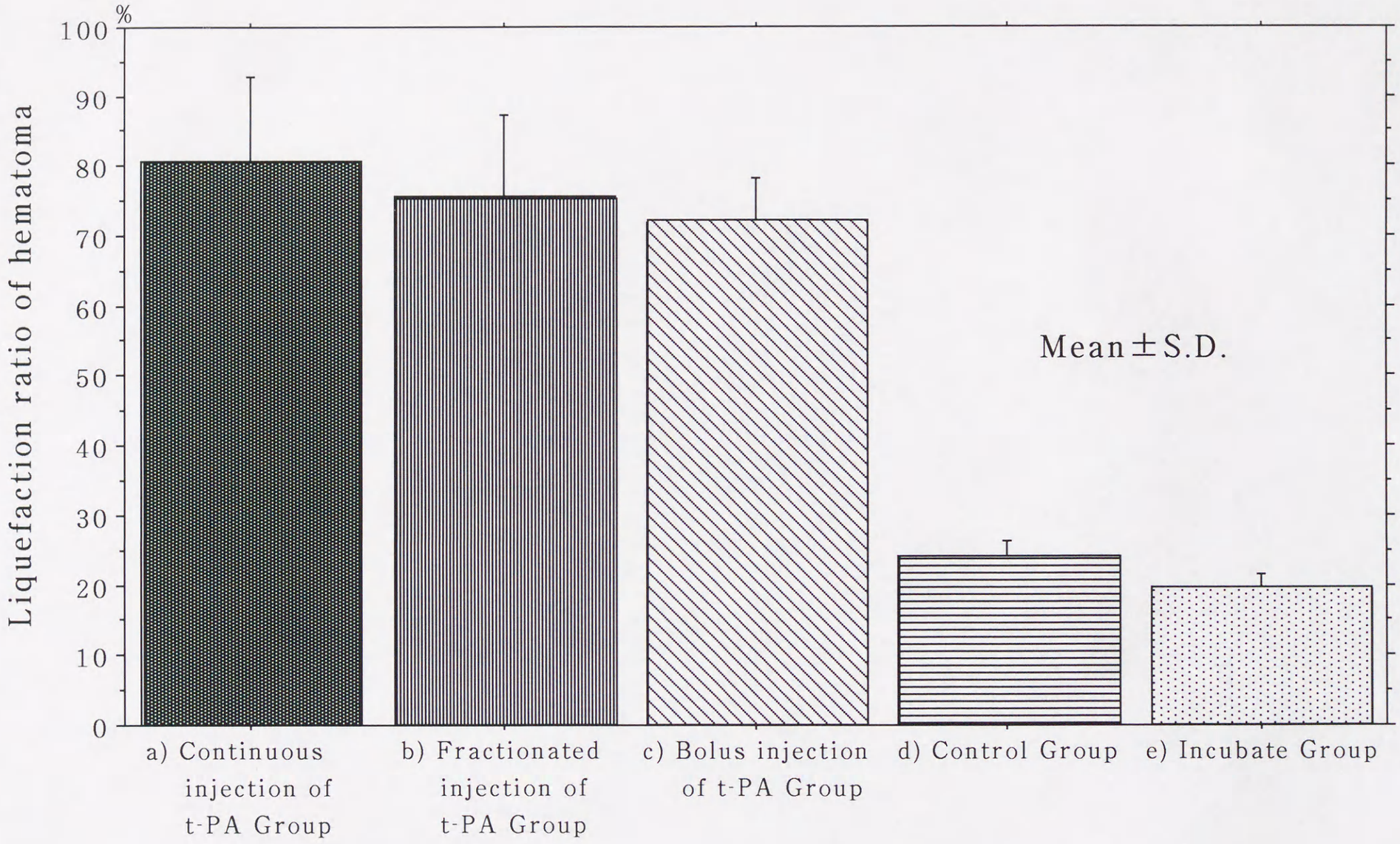


Fig. 4 Liquefaction ratio of canine arterial blood hematoma .

a) Continuous injection of t-PA Group tend to liquefy hematoma mostly in all group.

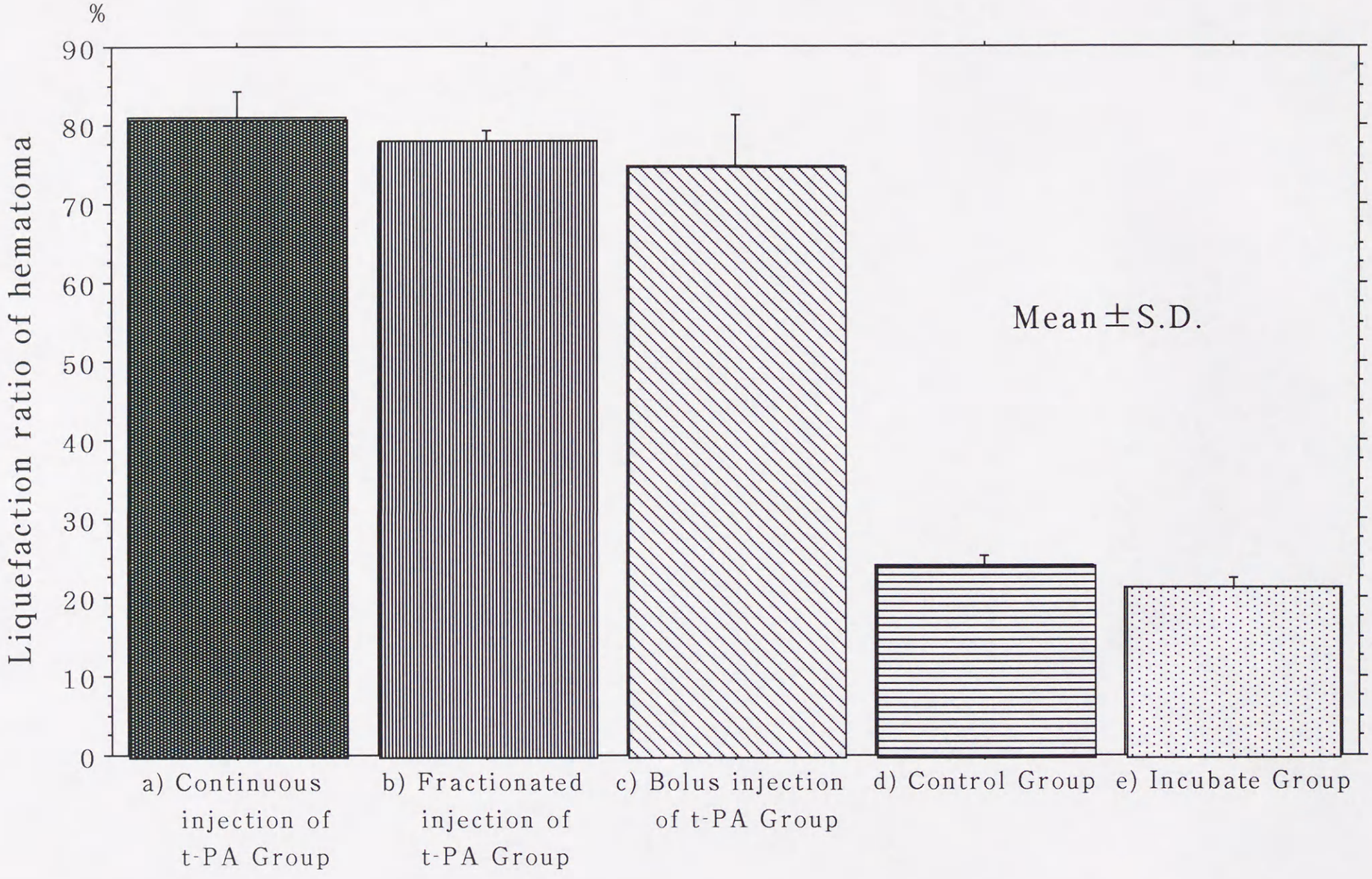


Fig. 5 Liquefaction ratio of human venous blood hematoma.

a) Continuous injection of t-PA Group tend to liquefy hematoma mostly in all group.

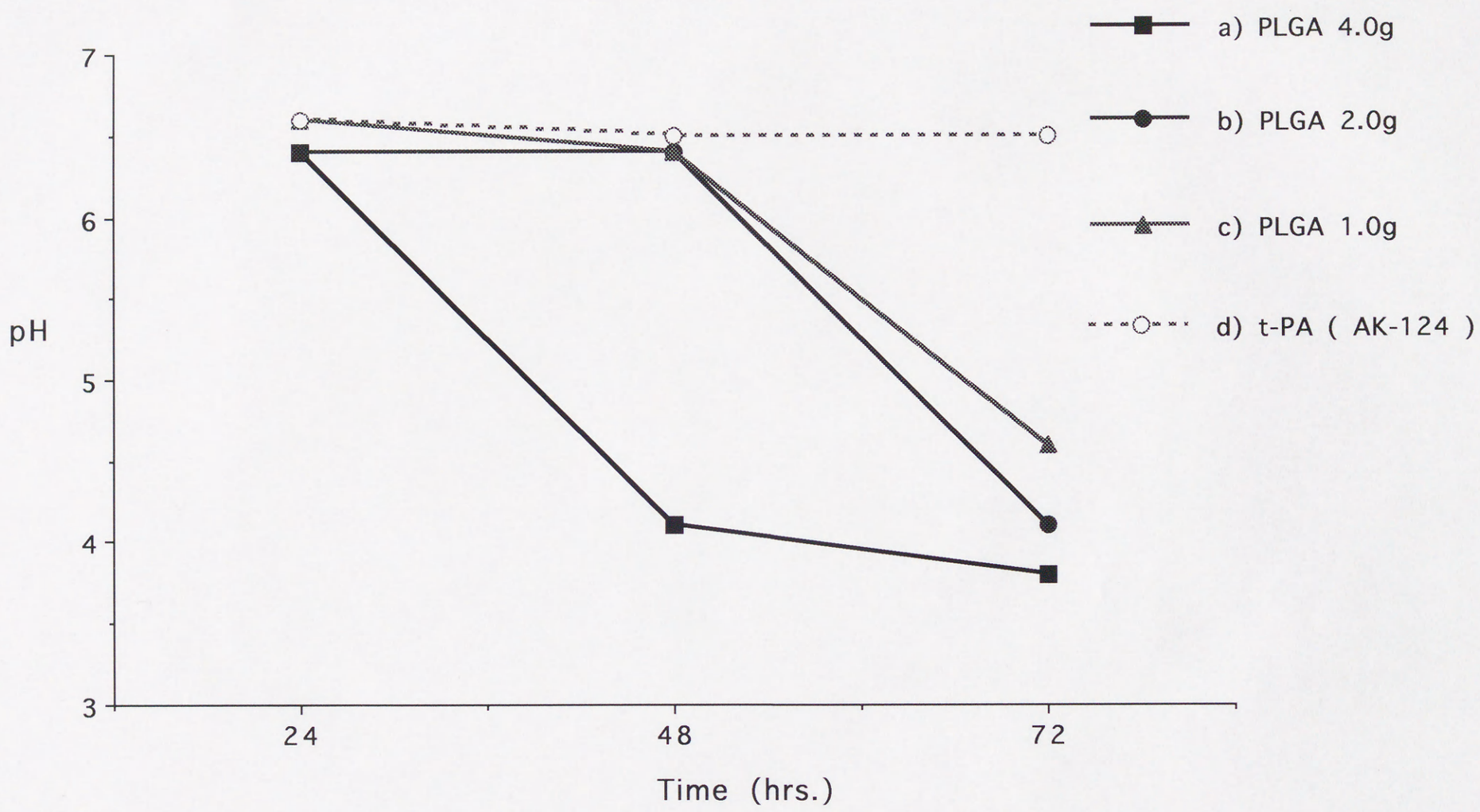


Fig. 6 Serial pH changes of the three kinds of t-PA MC suspension and t-PA (AK-124)solution.

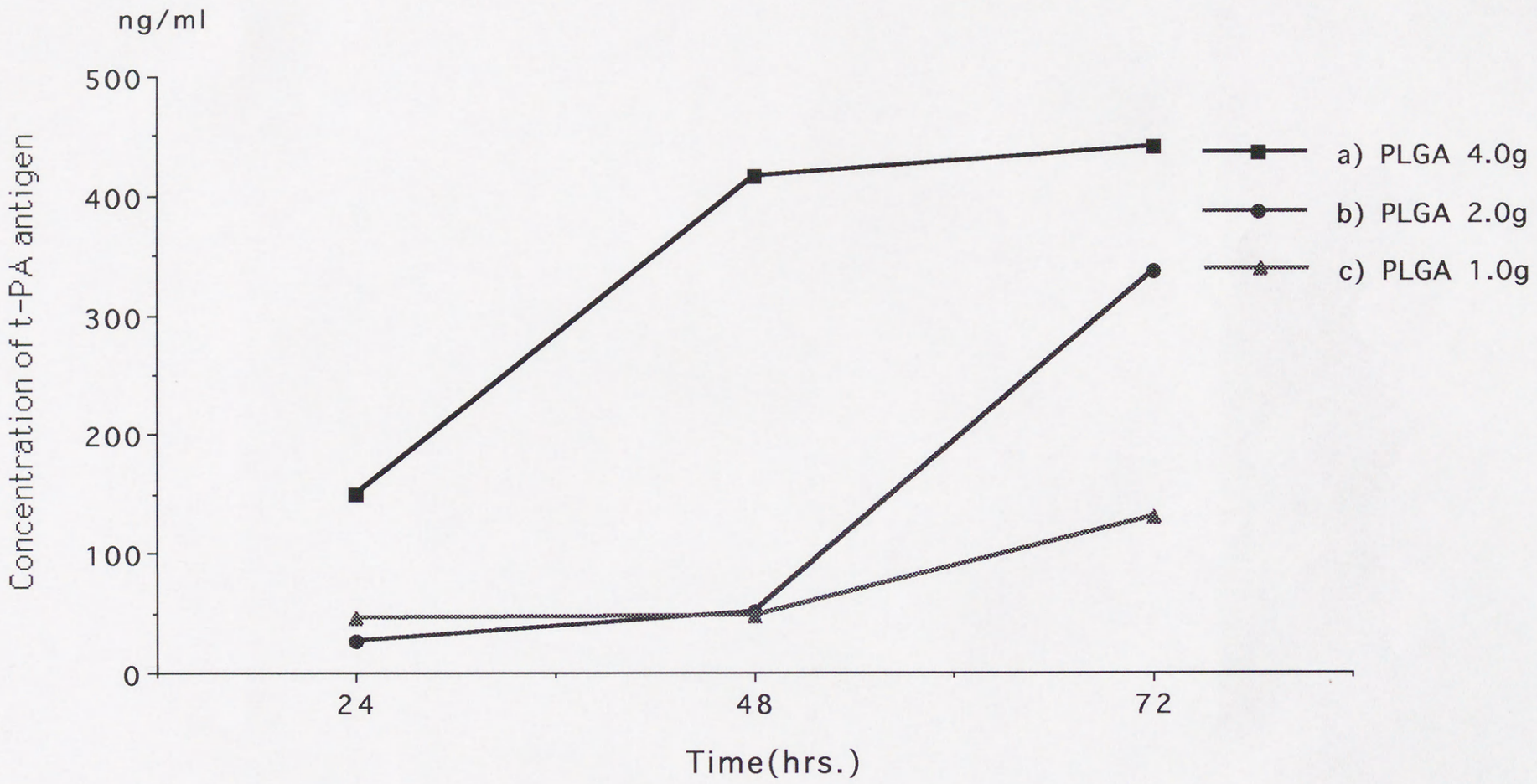


Fig. 7 Serial concentration changes of the three kinds of t-PA MC suspension.

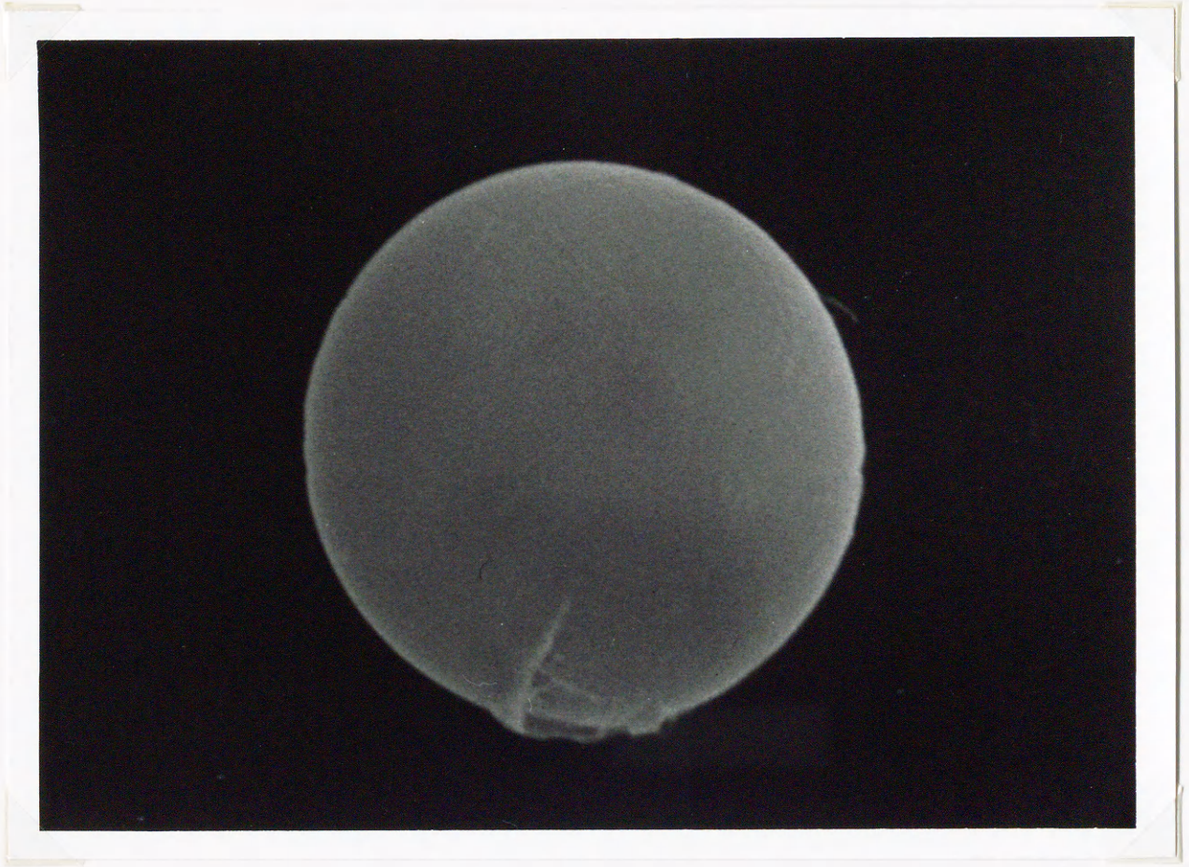


Fig. 8 Scanning electron micrograph of t-PA MC*

t-PA MC* = t-PA microcapsules prepared by water drying method

Fig. 9 Photograph of t-PA MC* prepared by water drying method
t-PA MC* = tissue plasminogen activator microcapsules

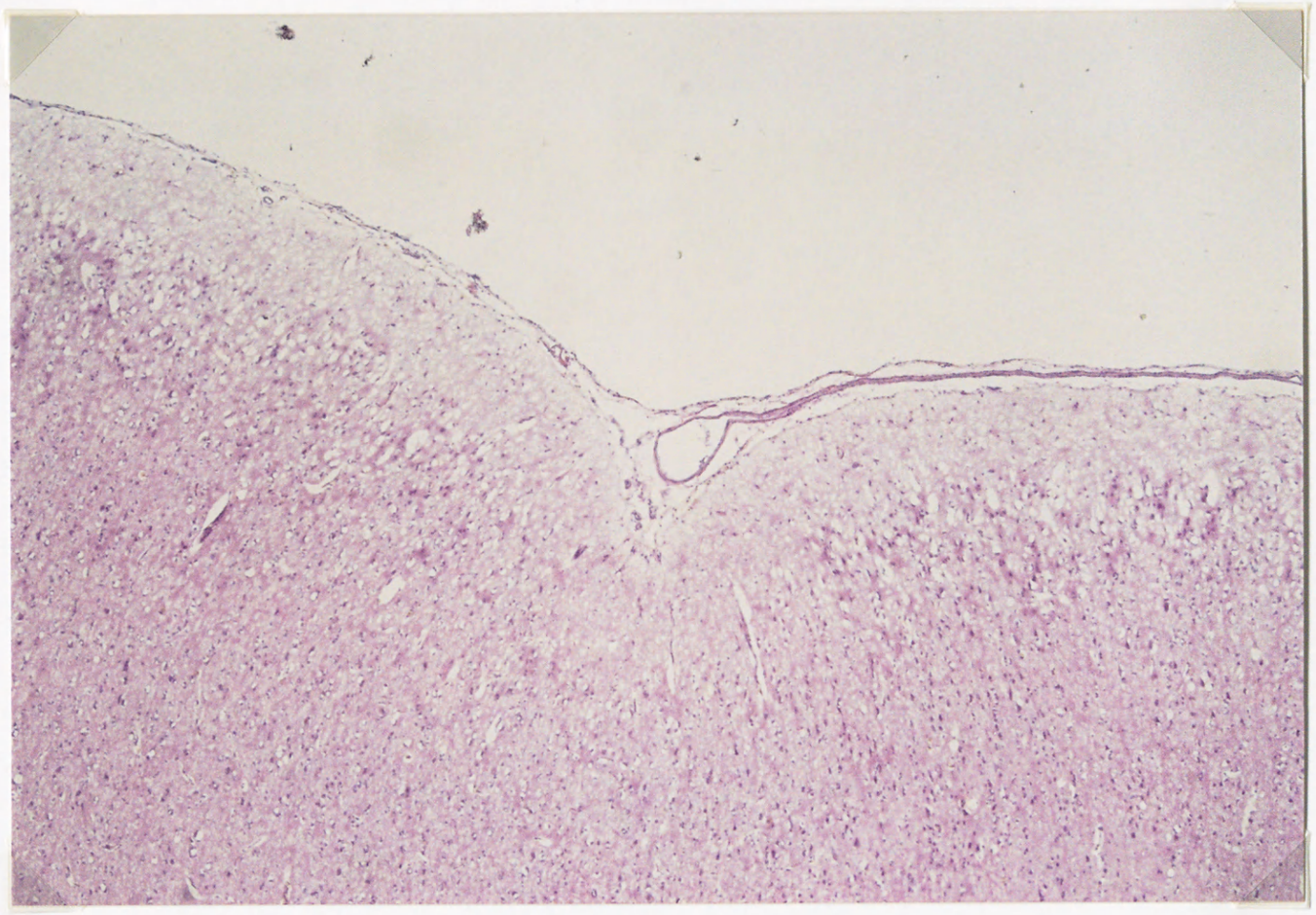


Fig. 10 Light micrograph of cerebral cortex

Abnormal findings indicating neurotoxicity of the cisternal administration of t-PA MC* could be observed neither in arachnoid membrane nor in cerebral tissue.

MC* = microcapsules, H&E, ×40.

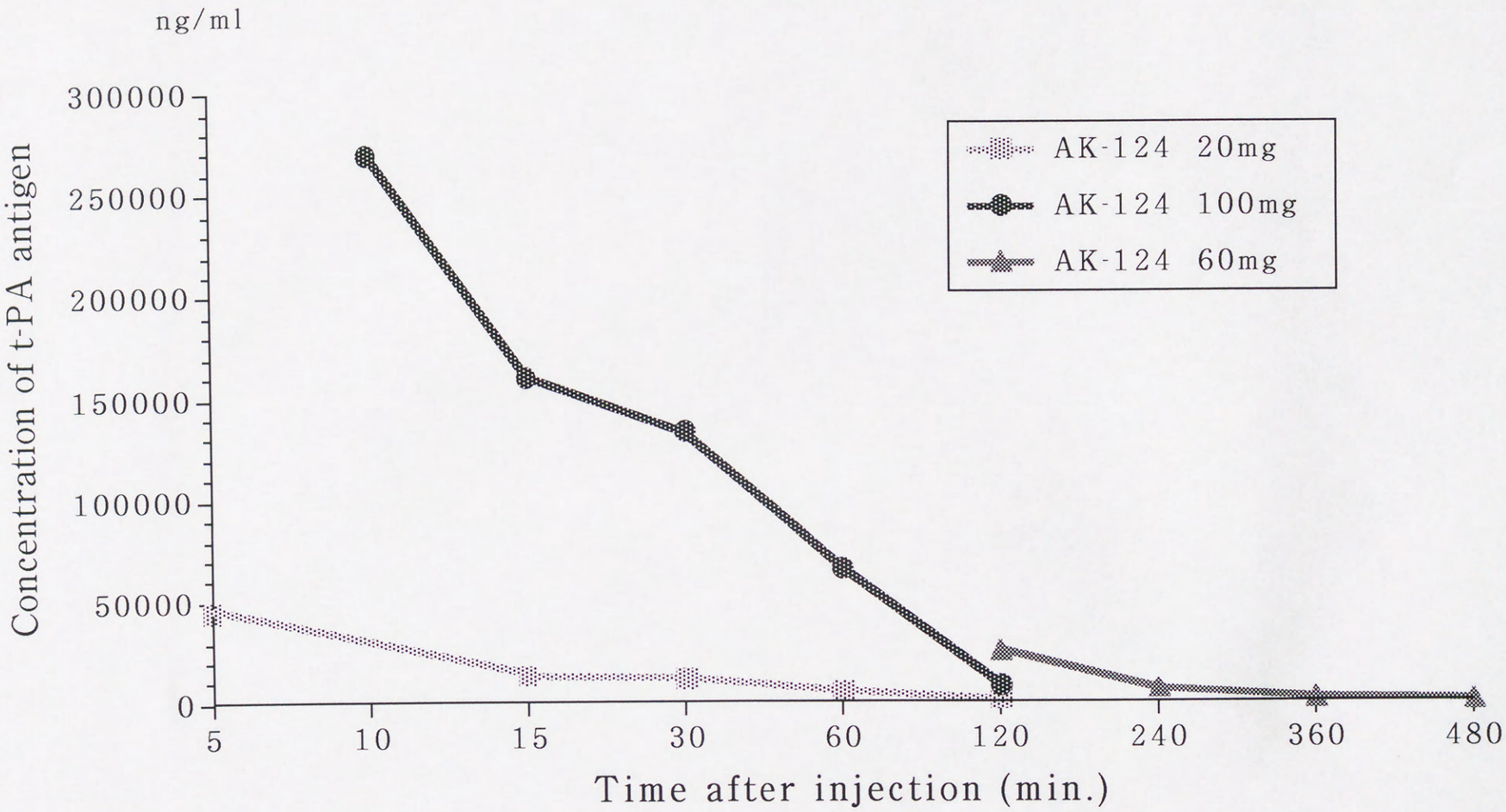


Fig.11 Serial concentration changes of the cisternal tissue plasminogen activator (t-PA) after the cisternal injection of 20mg, 100mg and 60mg dose of t-PA (AK-124) in canines.

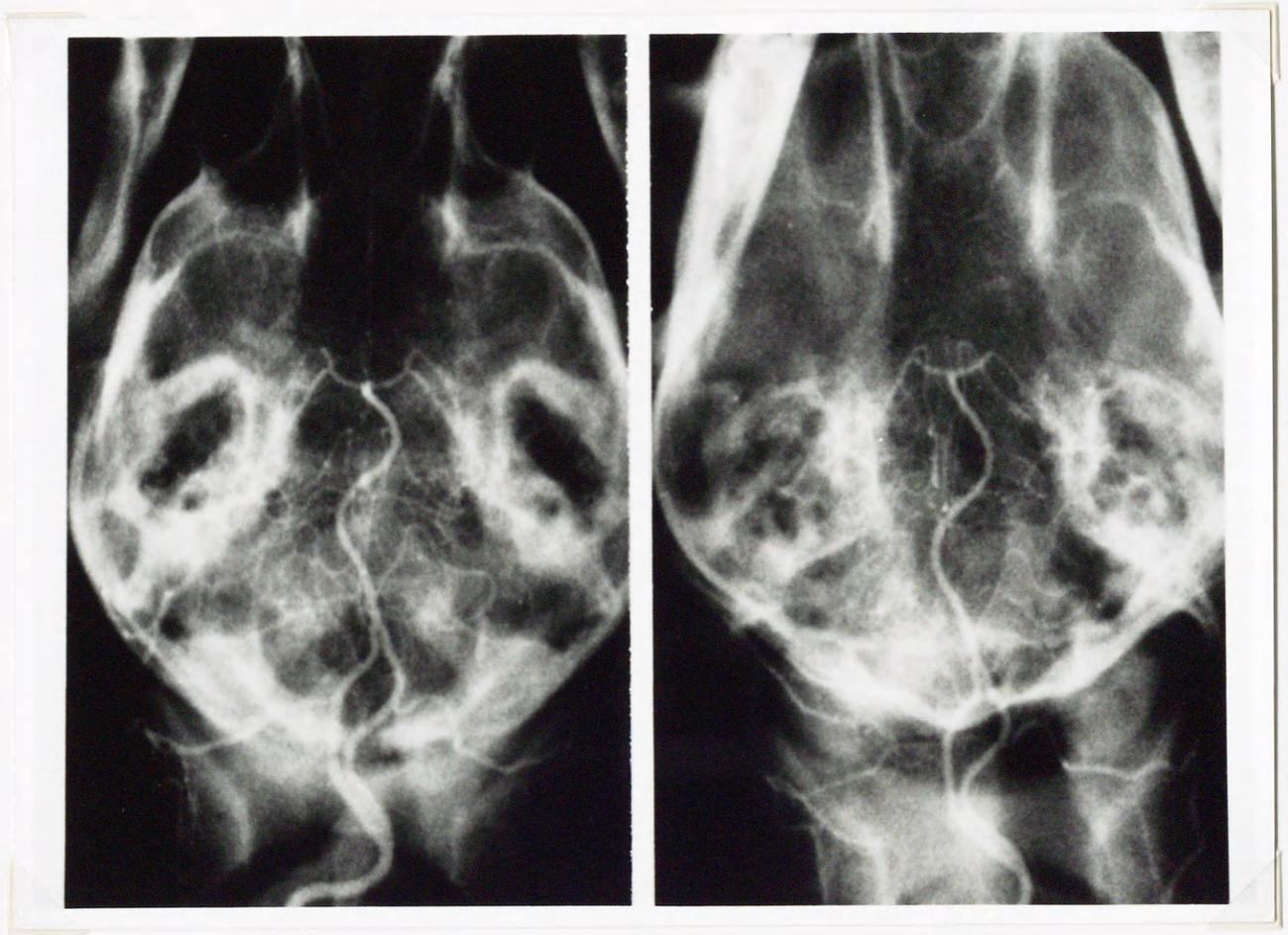


Fig. 12 Vertebral angiograms in a) t-PA Group

Left : on Day 0, Right : on Day 7

Percent reduction of intraluminal diameter of this basilar artery was 10.0%.

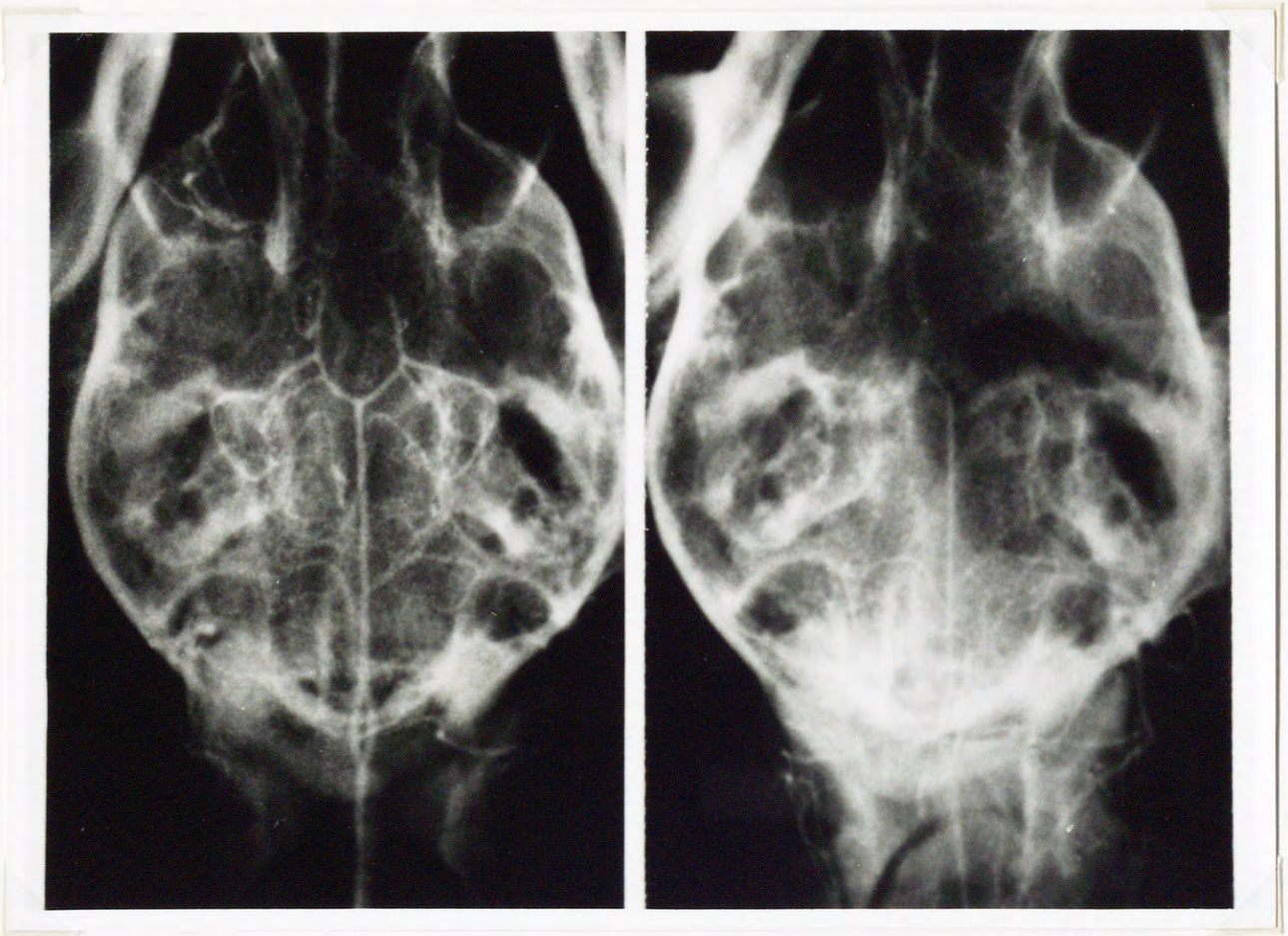


Fig. 13 Vertebral angiograms in b) t-PA MC Group

Left : on Day 0, Right : on Day 7

Percent reduction of intraluminal diameter of this basilar artery was 18.9%.

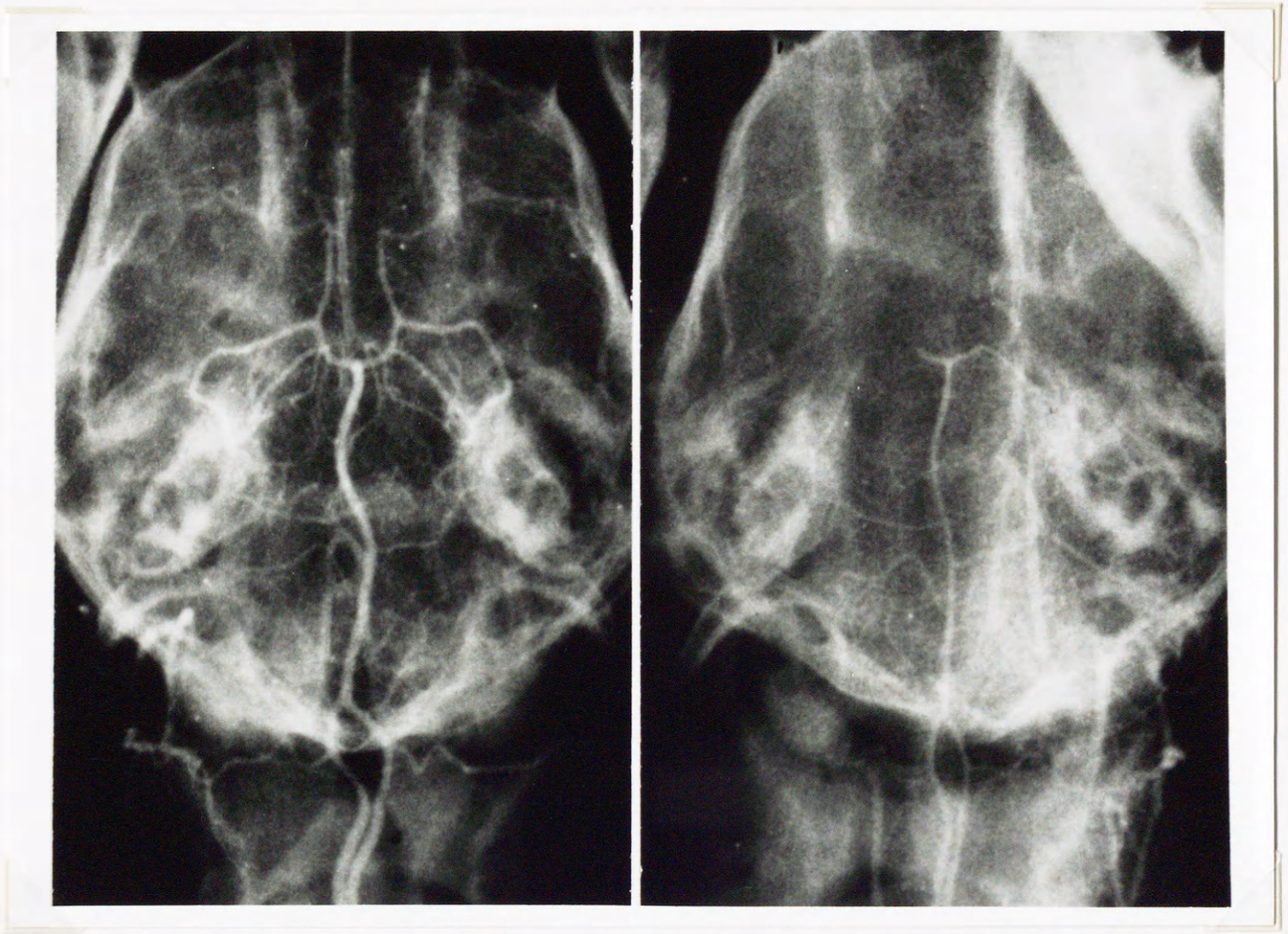


Fig. 14 Vertebral angiograms in c) PLGA MC Group

Left : on Day 0, Right : on Day 7

Percent reduction of intraluminal diameter of this basilar artery was 44.7%.

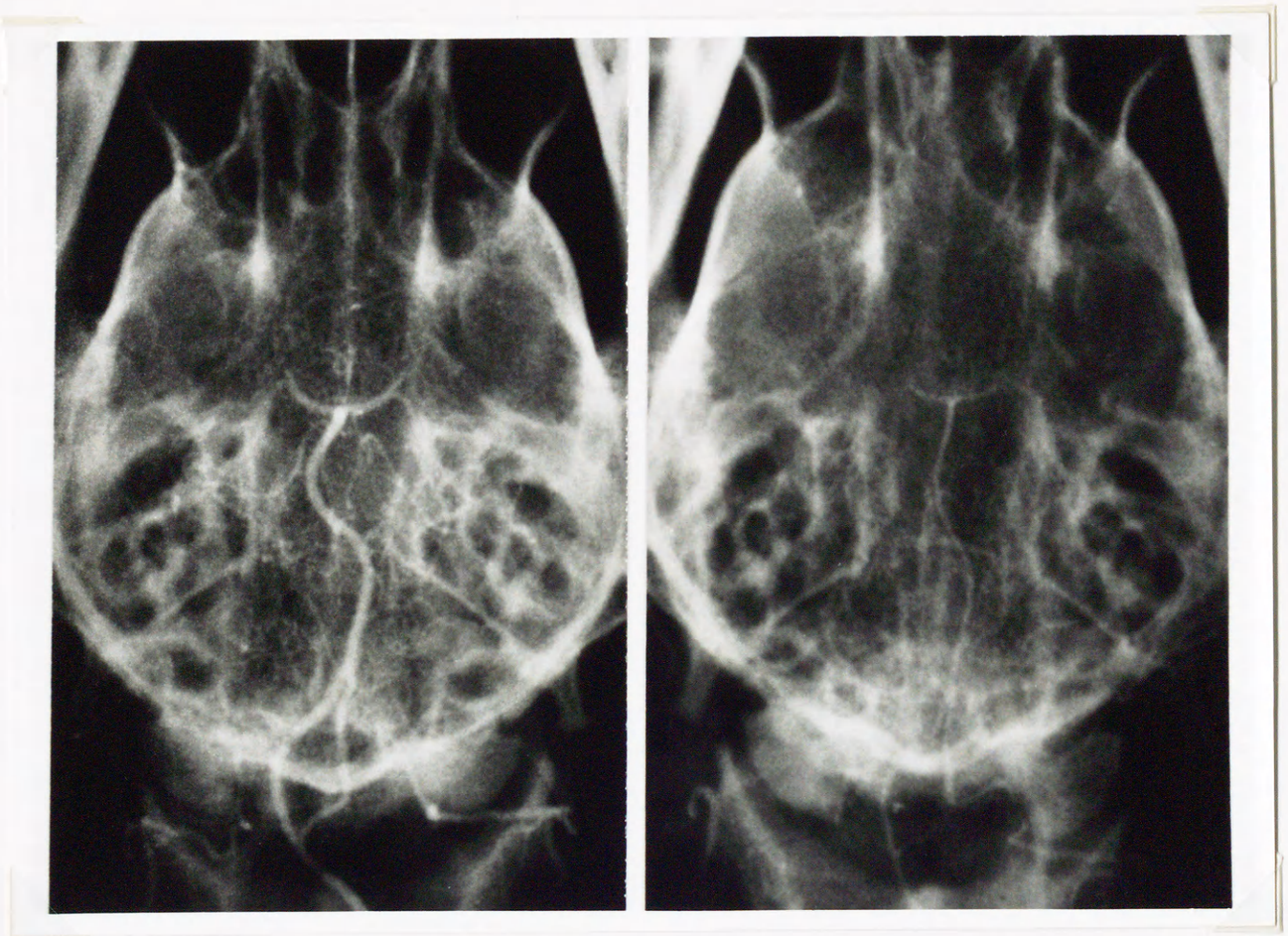


Fig. 15 Vertebral angiograms in d) control Group

Left : on Day 0, Right : on Day 7

Percent reduction of intraluminal diameter of this basilar artery was 44.2%.

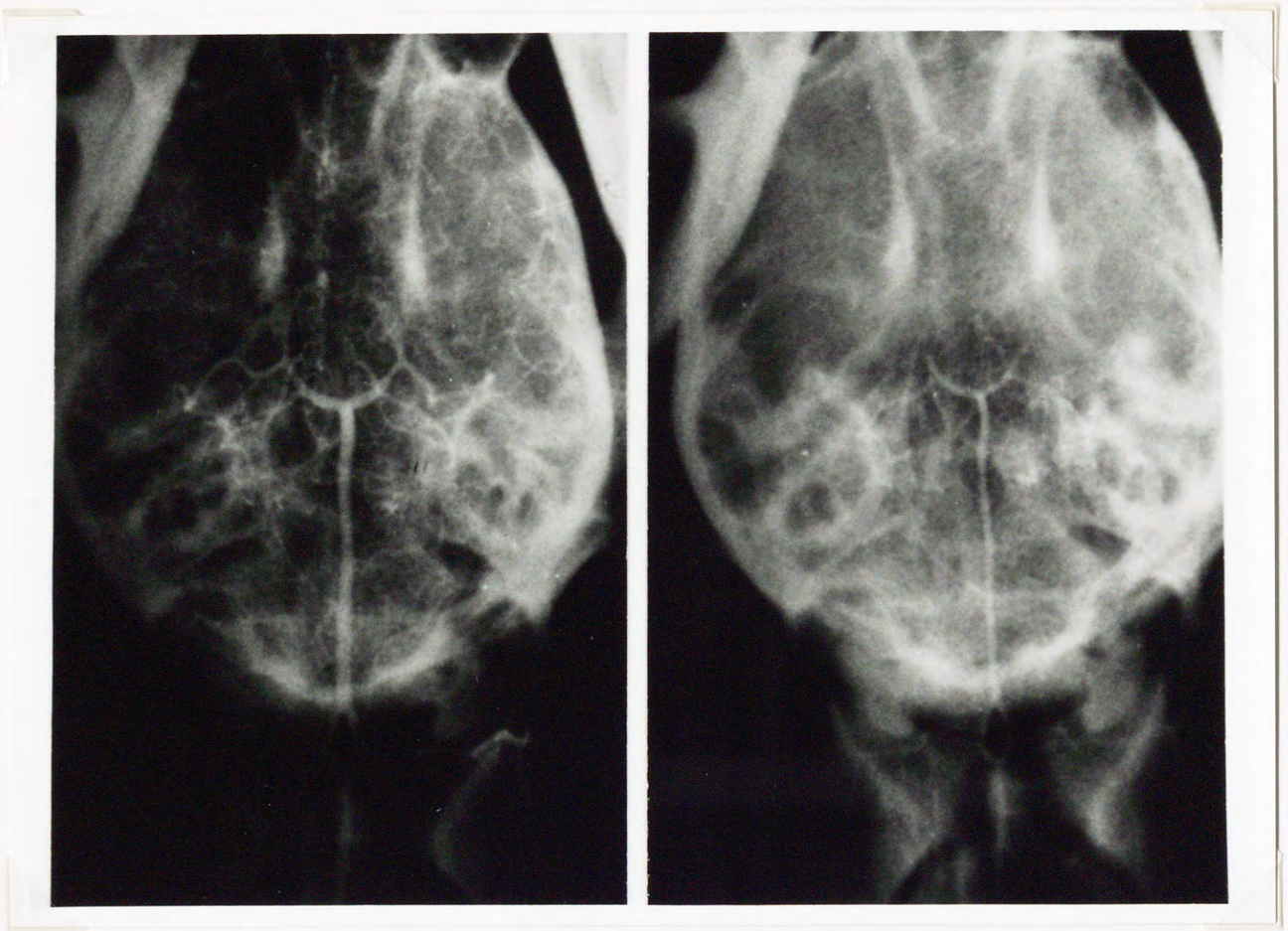


Fig. 16 Vertebral angiograms in e) S.A.H. Group

Left : on Day 0, Right : on Day 7

Percent reduction of intraluminal diameter of this basilar artery was 42.1 %.

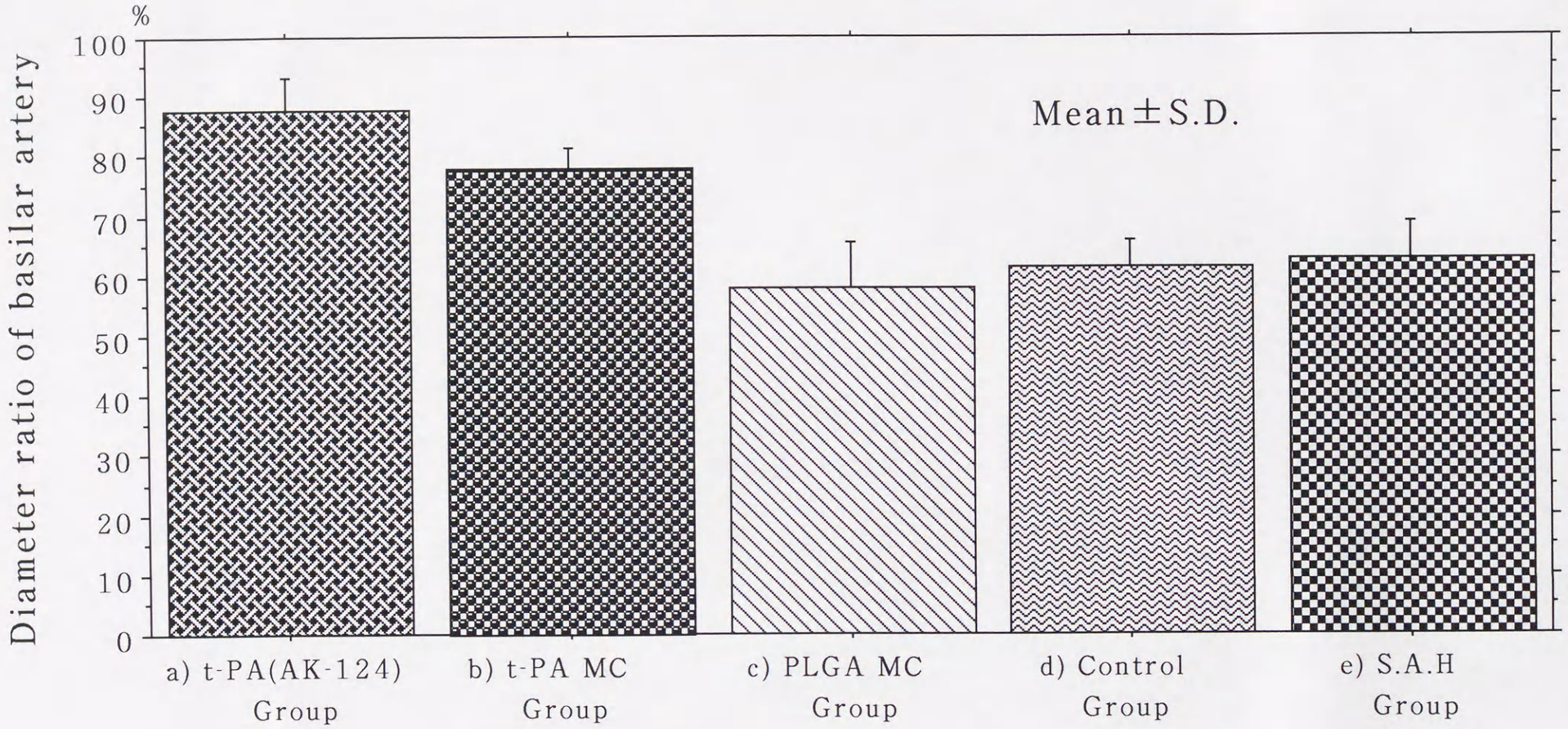


Fig. 17 Diameter ratio of basilar artery

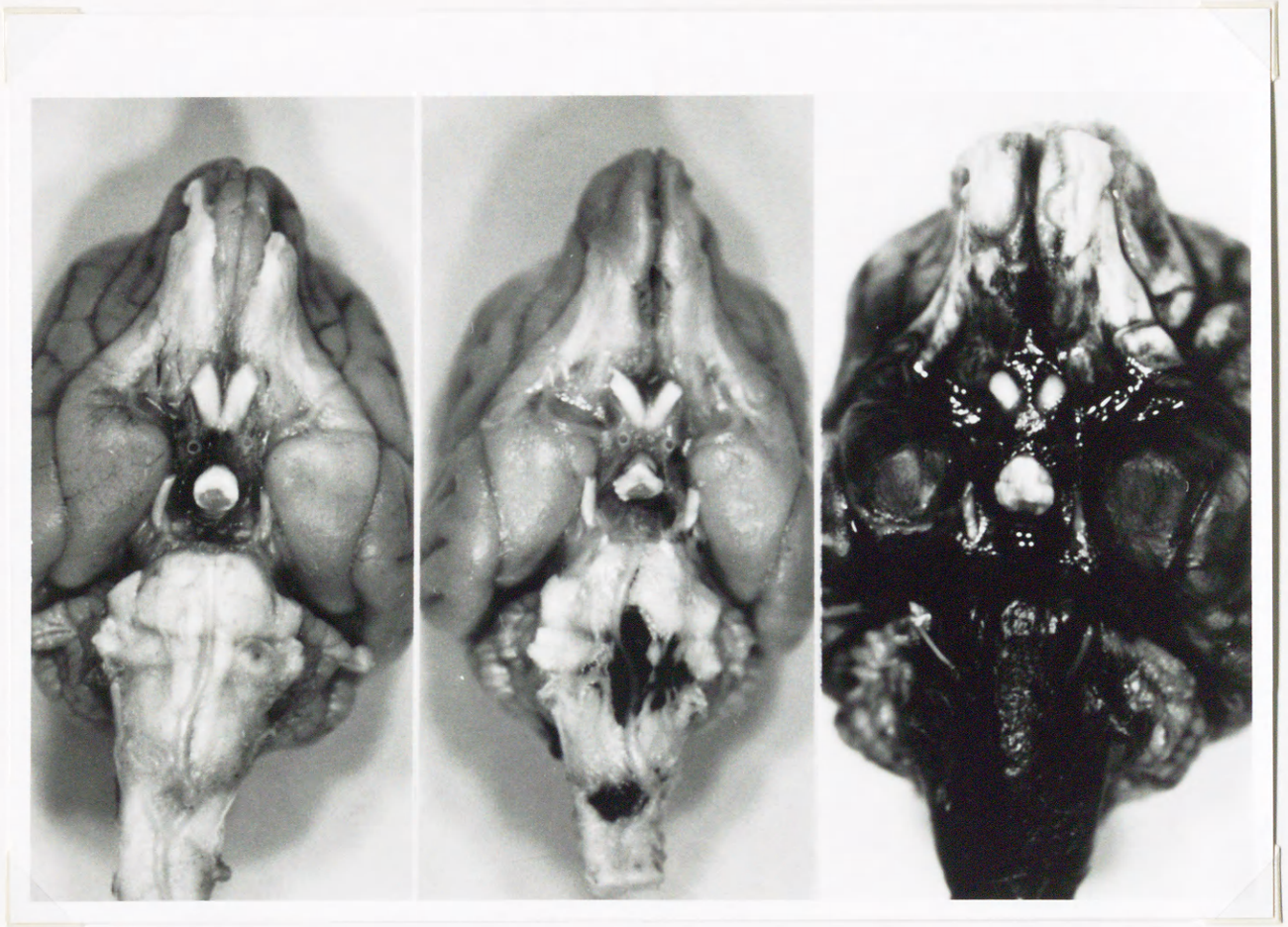


Fig.18 Perfused canine brains taken on DAY 7 in 3 groups
Left : a) t-PA Group, Center : b) t-PA MC Group, Right : e) SAH Group
In SAH Group residual subarachnoid clot was observed,
whereas in other Group less clot was visible.

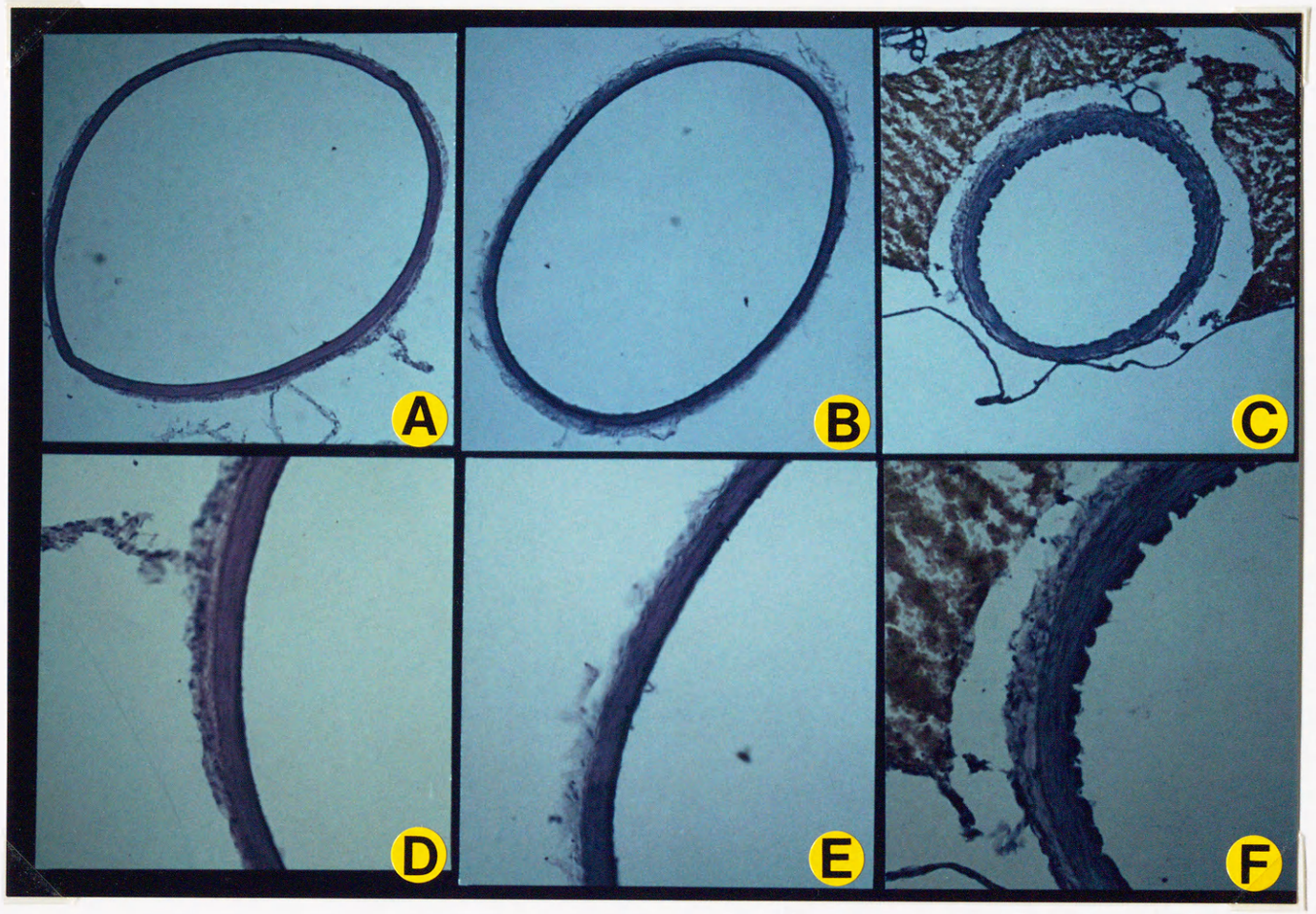


Fig. 19 Light micrographs of the canine basilar artery in 3 groups
A,D : a) t-PA Group, B,E : b) t-PA MC Group, C,F : e) SAH Group
Intimal corrugation and thickened smooth muscle layer are observed only in SAH group, but not in other Groups. (H&E, upper :×40, lower :×100.)

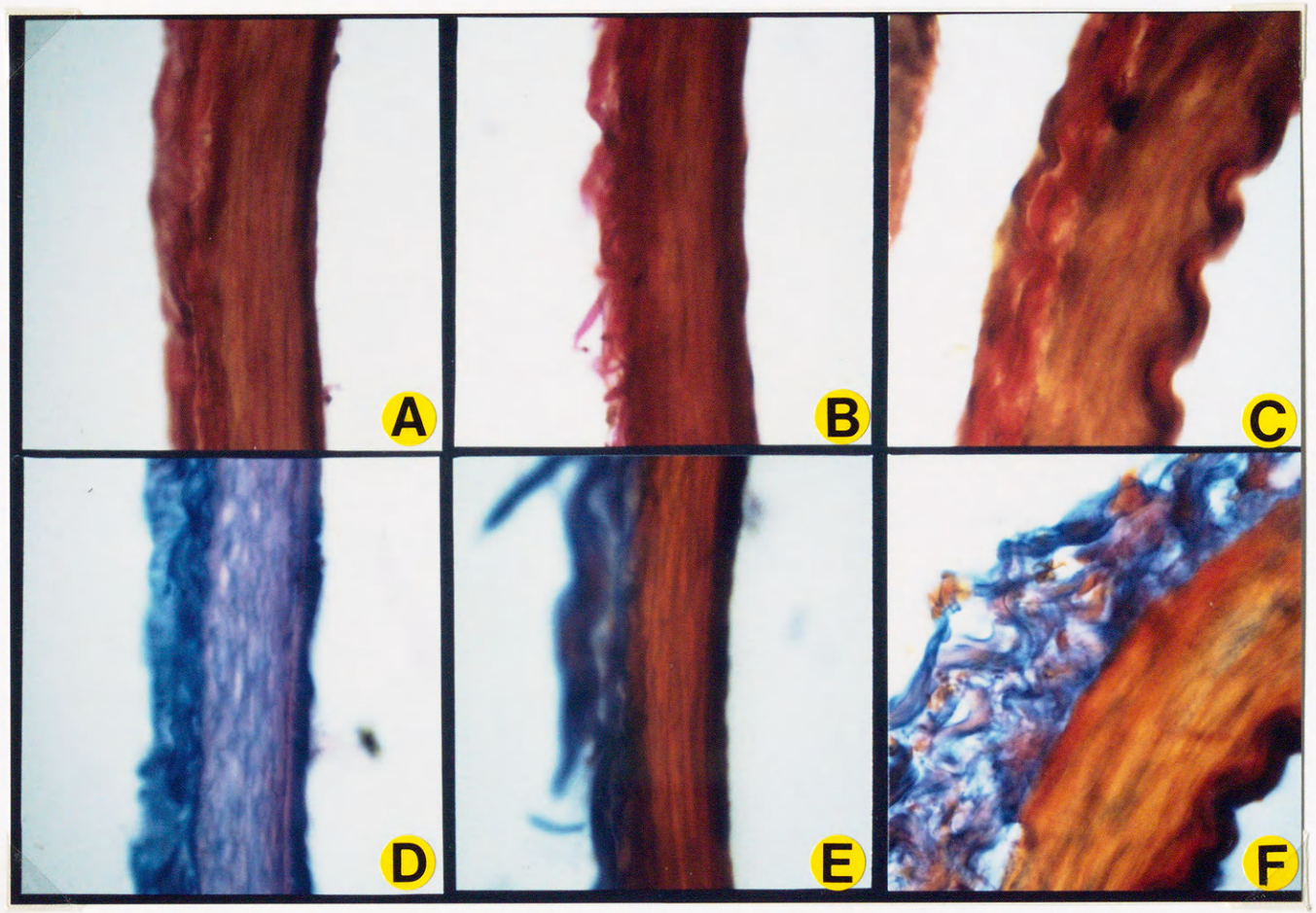


Fig. 20 Light micrographs of the canine basilar artery in 3 groups
A,D : a) t-PA Group, B,E : b) t-PA MC Group, C,F : e) S.A.H. Group.
Intimal corrugation and the thickened smooth muscle layer and adventitia are observed only in SAH group, but not in other Groups. (upper : Elastica van Gieson, lower : Azan. × 400)

copoly (lactic/glycolic acid)

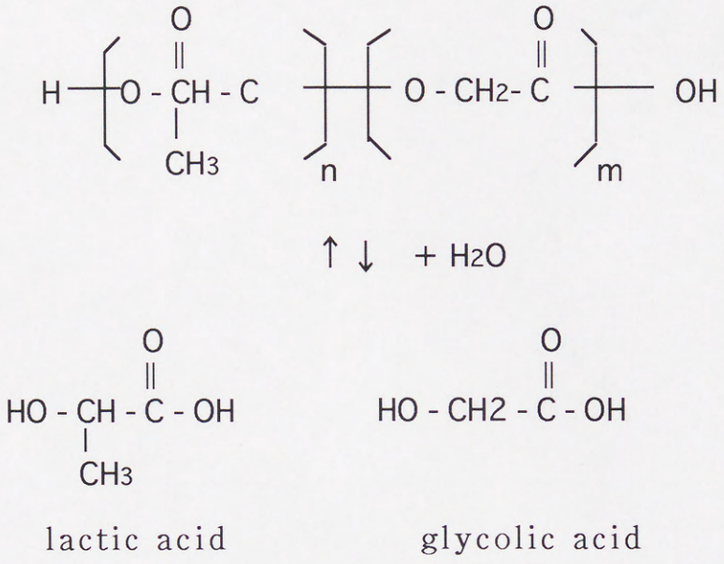


Fig. 21 Hydrolysis of copoly (lactic/glycolic acid)

Table 1 Summary of liquefaction ratio of hematoma from canine arterial blood

	Mean ± S.D. (%)	Liquefaction ratio 1	Liquefaction ratio 2	Liquefaction ratio 3	Liquefaction ratio 4	Liquefaction ratio 5	Liquefaction ratio 6
a) Continuous injection of t-PA Group	80.6 ± 12.4	97.4	66.3	93.9	72.8	78.9	74.3
b) Fractionated injection of t-PA Group	75.5 ± 11.9	87.1	54.8	87.1	73.1	76.5	74.2
c) Bolus injection of t-PA Group	71.9 ± 6.5	74.0	69.7	83.9	66.1	70.1	67.3
d) Control Group	24.1 ± 2.1	26.1	22.6	24.6	26.7	21.3	23.3
e) Incubate Group	19.3 ± 2.1	21.9	19.9	17.4	21.5	16.8	18.3

Table 2 Summary of liquefaction ratio of hematoma from human venous blood

	Mean ± S.D. (%)	Liquefaction ratio 1	Liquefaction ratio 2	Liquefaction ratio 3	Liquefaction ratio 4	Liquefaction ratio 5
a) Continuous injection of t-PA Group	81.0 ± 3.1	79.0	79.9	86.5	79.2	80.6
b) Fractionated injection of t-PA Group	77.9 ± 1.3	76.2	78.6	79.6	77.1	77.9
c) Bolus injection of t-PA Group	74.8 ± 6.3	75.3	64.0	79.9	77.8	77.2
d) Control Group	24.0 ± 1.2	22.9	25.4	23.1	25.2	23.4
e) Incubate Group	21.2 ± 1.1	22.9	21.8	20.4	20.6	20.5

Table 3

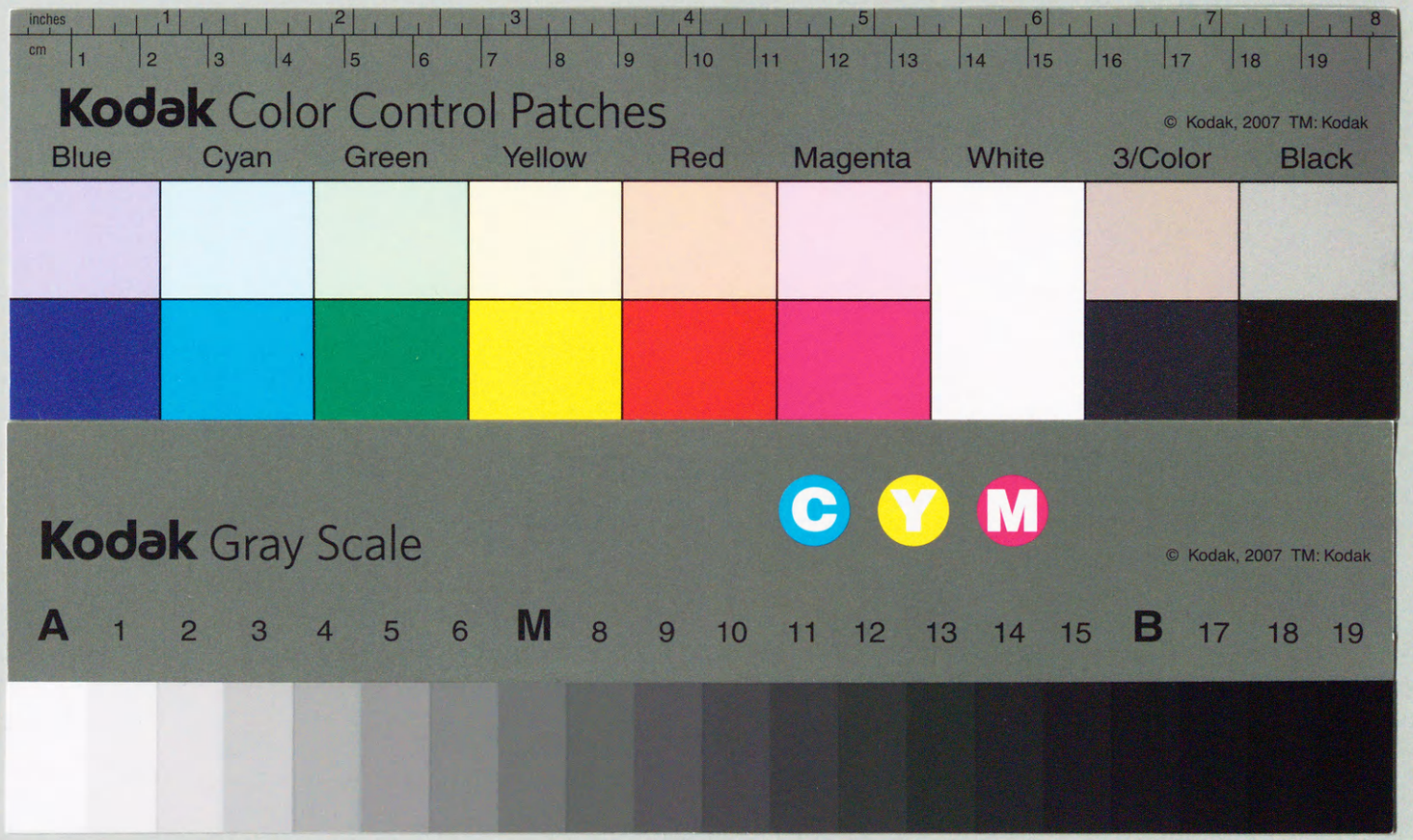
Experimental summary of 26 dogs in Two-hemorrhage Canine Model

Dog No.	Groups	B.W. (kg)	Diameter of basilar artery on DAY 0 angiography (mm)	Diameter of basilar artery on DAY 7 angiography (mm)	Diameter ratio (%)
1	a	7.5	1.10	1.03	93.6
2	a	6.6	1.00	0.90	90.0
3	a	6.2	1.00	0.87	87.0
4	a	7.7	1.23	1.10	89.4
5	a	7.4	1.27	1.00	78.7
6	b	6.0	1.07	0.87	81.3
7	b	5.5	0.90	0.70	77.8
8	b	5.4	0.90	0.73	81.1
9	b	8.0	1.37	1.03	75.2
10	b	6.3	1.13	0.83	73.5
11	c	7.2	1.03	0.50	48.5
12	c	7.0	1.03	0.57	55.3
13	c	6.3	1.13	0.63	55.8
14	c	5.2	0.93	0.63	67.7
15	c	7.4	1.23	0.77	62.6
16	d	7.7	1.30	0.80	61.5
17	d	8.0	1.37	0.93	67.9
18	d	6.0	1.03	0.63	61.2
19	d	7.0	1.27	0.77	60.6
20	d	7.1	1.20	0.67	55.8
21	e	7.7	1.33	0.77	57.9
22	e	6.0	0.93	0.60	64.5
23	e	7.4	1.20	0.80	66.7
24	e	7.0	1.20	0.87	72.5
25	e	6.7	1.17	0.67	57.3
26	e	7.6	1.33	0.77	57.9

Table 4 Diameter ratio of basilar artery

	Mean (%)	Standard Deviation	Number	Minimum	Maximum
a) t-PA (AK-124) Group	87.7	5.6	5	78.7	93.6
b) t-PA MC* Group	77.8	3.5	5	73.5	81.3
c) PLGA MC* Group	58.0	7.4	5	48.5	67.7
d) Control Group	61.4	4.3	5	55.8	67.9
e) S.A.H. Group	62.8	6.2	6	57.3	72.5

MC* = microcapsule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