The Effect of Histamine on Small Pulmonary Veins in Intact Anesthetized Dog[1] (34411)

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The effects of histamine on the pulmonary circulation have been studied during the past four decades (1–8). The most recent data show that pulmonary vascular resistance increases in response to histamine due to active constriction of the pulmonary veins (6–8). However, most of the studies were either on open-chest dogs or dogs subjected to extensive surgical procedures. Whereas these studies on open-chest animals may provide valuable information, their limitations have been emphasized (9), particularly when attempting to define changes in the intact animal.

Using the transeptal technique described previously (10), we recorded pressures in the atrium and a small pulmonary vein of intact dogs in an effort to observe the behavior of an essentially intact normal pulmonary venous system in response to drugs and vasoactive polypeptides. These studies have necessarily included simultaneous observations of other segments of the circulation to understand better the manner in which the pulmonary veins are integrated in the entire circulation. Thus, the present experiments were designed to study under more normal conditions the responses of small pulmonary veins to histamine and to integrate them with the associated responses of the pulmonary and systemic circulations and the heart.

Material and Methods. The studies were performed on 11 mongrel dogs with average weight of 15.9 kg (range, 15.2–17.3 kg). Each dog was lightly anesthetized with urethane, taped supine to the fluoroscopic table, and the trachea was intubated. A small polyethylene catheter for delivering 100% oxygen (2–3 liters/min) was placed in the endotracheal tube to assure adequate oxygenation. Under fluoroscopic control, cardiac catheters were passed transeptally into a small pulmonary vein and the left atrium as described previously (10). Separate catheters were also passed into the pulmonary artery and the right atrium. Polyethylene tubes were inserted into the femoral artery, the femoral vein, and a small systemic vein. Pressures at all of these sites were simultaneously recorded using Statham strain gauge transducers (P23Db) and a 12-channel recorder.[2] The zero reference point for all pressures was about 7 cm above the top of the fluoroscopic table, *i.e.*, approximately at the midpoint of the right atrium. The electrocardiogram (ECG) was recorded throughout the experiments. The heart and respiratory rates were determined from the ECG and pressure curves of the small pulmonary vein, respectively. Cardiac output and the pulmonary mean transit time were calculated using the dye dilution technique and the Stewart-Hamilton formula (11). A known quantity of indocyanine dye (Cardiogreen) was injected at the junction of the inferior vena cava and the right atrium as blood was being withdrawn simultaneously from the pulmonary artery and the left atrium at a constant rate (24.7 ml/min) through a matched pair of Gilford cuvette densitometers. This technique was described by De Freitas and co-workers (12) and has been used in this laboratory (13).

Pulmonary mean transit time (P_{MTT}) was

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[2] Electronics for Medicine.

TABLE I. Mean Values for 11 Normal Dogs Summarizing Hemodynamic Effects of Histamine Administered Intravenously.[a,b]

						Mean pressure (mm Hg)						Resistance (units)		
	HR	RR	PBV (ml/kg)	CO (ml/min/kg)	SV (ml)	FA	PA	PVS	LA	RA	SVP (leg vein)	TPR	PVR	SR
C	157	37	7.61	171	17.6	143.9	20.1	8.82	3.77	1.00	9.41	6.42	2.01	58.4
1A						111.3[c] 118.3[d]	22.3[d]	10.64[d]	2.86[d]	0.90	9.77			
1	192[d]	55[d]	7.15	185[d]	15.1	118.4[d]	21.1	9.85	2.68[d]	0.60	8.91	6.46	2.45	38.0[d]
2	176	45	7.62	173	15.3	122.3[d]	17.8[d]	9.48	2.65	0.125	8.30	6.79	3.27	53.1
3	152	27	7.49	153	16.2	138.8	16.5[d]	8.14	3.09	0.40	9.45	5.92	2.24	65.4
4	165	29	7.08	165	16.4	138.1	17.9[d]	8.27	2.73	0.80	7.77	6.13	2.32	58.1

[a] HR = heart rate; RR = respiratory rate; PBV = pulmonary blood volume; CO = cardiac output; SV = stroke volume; FA = femoral artery; PA = pulmonary artery; PVS = small pulmonary vein; LA = left atrium; RA = right atrium; SVP = systemic venous pressure; TPR = total pulmonary resistance; PVR = pulmonary venous resistance; SR = systemic vascular resistance.

[b] C = control; 1A = Time at which maximum increase in pulmonary artery pressure occurred; 1 = 2.5 min after the beginning of histamine infusion (i.e., after 500 μg); 2 = 5 min (i.e., after 1 mg); 3 = 5 min after the end of infusion; 4 = 15 min after the end of infusion.

[c] Maximal fall in femoral artery pressure.

[d] p value less than 0.01.

obtained by subtracting the inferior vena cava (IVC) to pulmonary artery (PA) mean transit time from the inferior vena cava to left atrium (LA) mean transit time, *i.e.*,

$$P_{MTT} = (IVC\text{-}LA)_{MTT} - (IVC - PA)_{MTT}.$$

The pulmonary blood volume (PBV) was calculated by multiplying the pulmonary mean transit time by the cardiac output (CO), namely

$$PBV = P_{MTT} \times CO.$$

The experiments were begun when a "steady" state in pressures, heart rate, respiratory rate, and cardiac output was achieved. Histamine phosphate was infused into the femoral vein at a constant rate of 200 μg/min for 5 min, the total amount administered being 1 mg. All pressures were continuously recorded. Cardiac output and the pulmonary blood volume were determined at 2.5 and 5 min during the infusion of histamine and at 5 and 15 min after the infusion was stopped.

Results. The results are summarized in Table I and Figs. 1 and 2. The values given in parentheses in the following sections are averages.

Heart and respiratory rates. The heart rate (HR) increased in 9 of the 11 dogs (from a control of 157 to 192 beats/min) in response to histamine. There was also an increase in respiratory rate (RR) in 10 dogs (from a control of 37 to 55 respirations/min). Near the end of the infusion, both heart and respiratory rates decreased although they remained above the control levels.

Mean cardiovascular blood pressures. Pressure in the small pulmonary veins (PVS). With infusion of histamine an increase in pressure in the small pulmonary vein occurred (from control of 8.82 to 10.64 mm Hg) in association with a simultaneous rise in pulmonary arterial pressure in 10 of the 11 dogs. Interestingly, this rise in pulmonary venous pressure which occurred 15 sec to 1 min after the beginning of the infusion always followed a decline in femoral arterial (FA) pressure. The pulmonary venous pressure remained above the control level as the infusion was continued, although it showed a tendency to decrease. During the recovery phase pulmonary venous pressure tended to return towards the control level.

Pulmonary arterial pressure (PA). Initially with infusion of histamine the pulmonary arterial pressure increased in all dogs (from 20.1 to 22.3 mm Hg). A decrease in PA pressure (to 17.8 mm Hg near the end of

infusion) which followed the initial rise persisted for at least 15 min during the period of recovery.

Femoral arterial pressure (FA). There was a significant decline in systemic arterial pressure in all dogs (from 144 to 111 mm Hg) within 5–30 sec after the start of histamine infusion. During the infusion there was

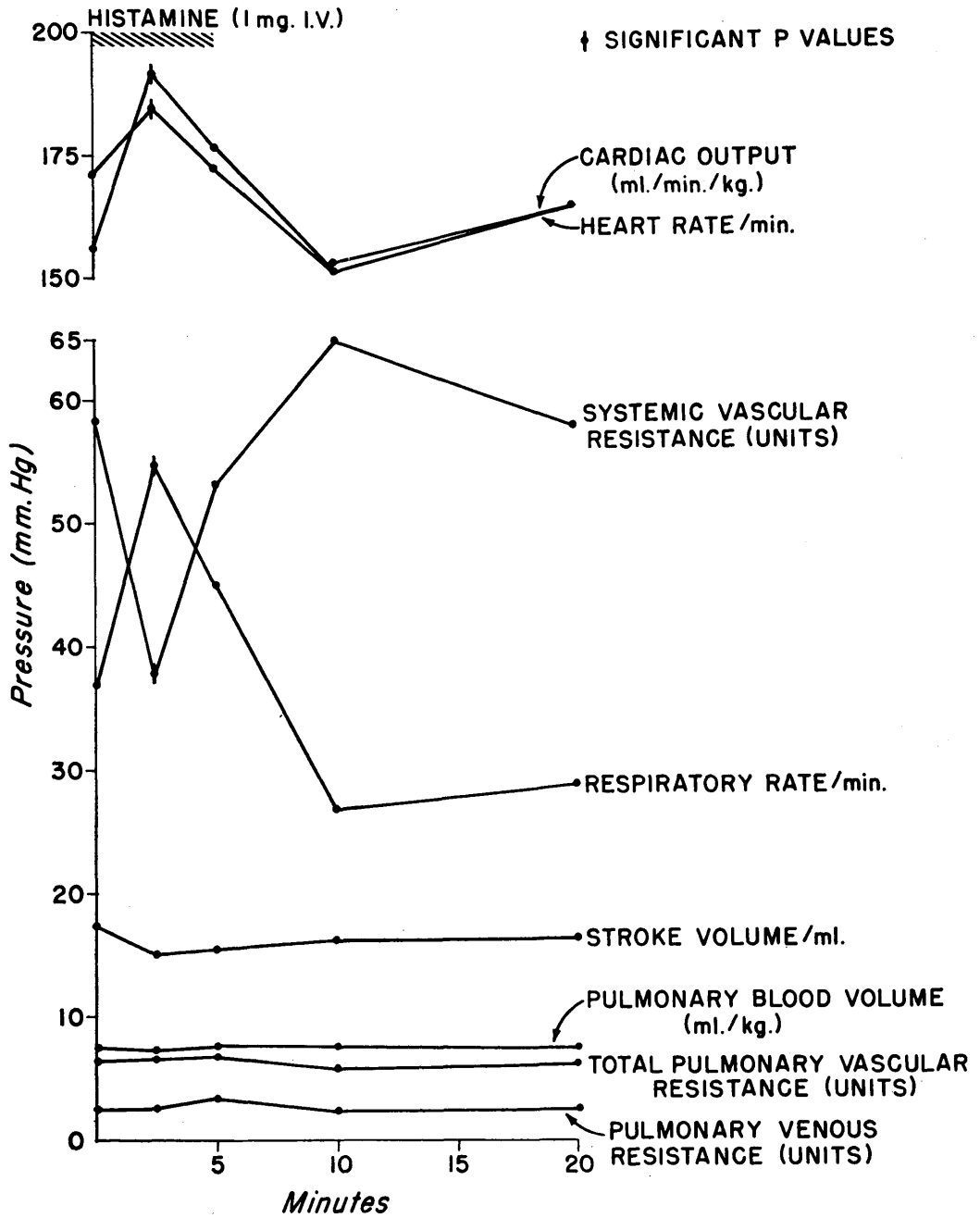

FIG. 1. Influence of histamine on hemodynamic phenomena; the time courses of the mean values of various hemodynamic parameters for 11 dogs that received 1 mg of histamine intravenously in 5 min.

a slight rise following the initial decline, but the pressure remained well below the control level. It returned to near control level 5 min after the end of infusion of histamine.

Left atrial pressure (LA). Initially in response to histamine the left atrial pressure decreased in 6 dogs (from 3.8 to 2.6 mm Hg), remained unchanged in 4 and increased slightly in 1. As the infusion continued, the LA pressure fell below control levels in 9 of

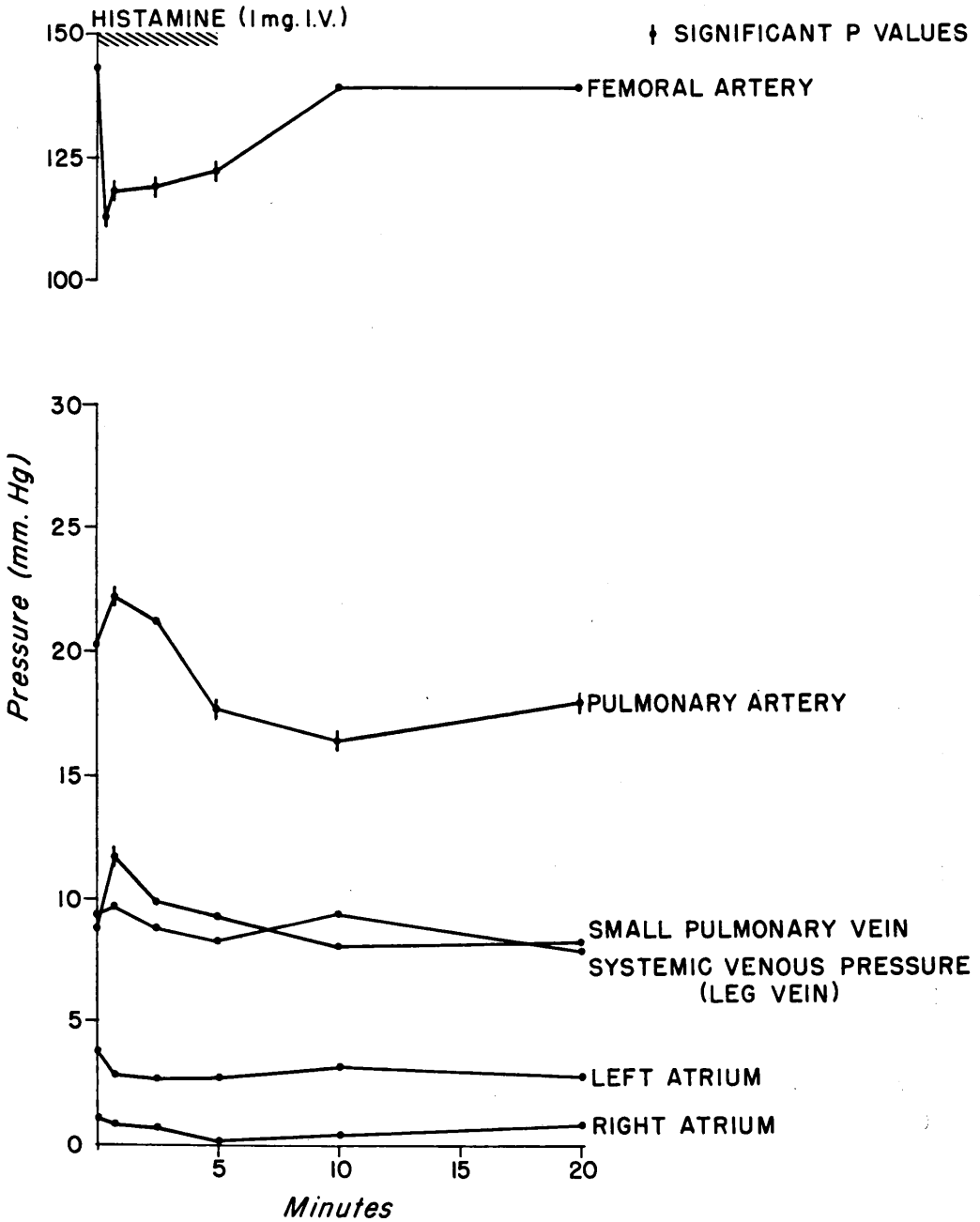

FIG. 2. Influence of histamine on circulatory pressure; the effect of intravenously administered histamine on the mean time courses of pressures in various segments of the cirulation in 11 dogs.

the 11 dogs, was unchanged in 1 and slightly increased in 1.

Right atrial pressure (RA). Right atrial pressure was measured in five dogs. The pressure tended to decrease during infusion of histamine and returned to the control level 15 min after the end of the infusion.

Systemic venous pressure (SVP). The systemic venous pressure increased in 6 dogs, decreased in 4 and remained unchanged in 1 dog. These changes were not statistically significant.

Cardiac output (CO). A significant initial increase in cardiac output (from 171 to 185 ml/min/kg) was observed consistently in response to histamine. The cardiac output declined to control levels near the end of infusion and continued to decrease after the infusion was stopped, but returned to the control levels 15 min later. The increase in cardiac output was mainly due to tachycardia, since the stroke volume (SV) remained somewhat below the control level throughout the administration of histamine.

Pulmonary blood volume (PBV). The changes in pulmonary blood volume were variable. The PBV increased in 4 dogs, decreased in 6, and remained unchanged in 1 dog. The mean changes in PBV during histamine infusion were not statistically significant.

Pulmonary and Systemic Peripheral Vascular Resistances. Initially, there was a significant decrease in systemic peripheral vascular resistance (SR) in response to histamine. The systemic peripheral vascular resistance then returned towards control levels near the end of the infusion. The total pulmonary (TPR) and pulmonary venous (PVR) resistances tended to rise during histamine infusion, but these changes were not significant.

Intrapleural pressures. The intrapleural pressures measured in 3 dogs, decreased slightly in response to histamine. The maximal change was 1 mm Hg.

Discussion. The complexity of the pulmonary vascular responses to infusion of histamine was not only due to differences in behavior of arterial and venous segments of the pulmonary circulation but was also related to variations in the time course of the response of the entire circulatory circuit. Initially, histamine produced an increase in pressure in the small pulmonary veins simultaneously with an increase in pulmonary arterial pressure. At the same time, the left atrial pressure either decreased or did not change. Although there was an initial increase in cardiac output, the stroke volume decreased slightly, and pulmonary blood volume failed to change significantly. These observations indicate an active increase in tone of pulmonary veins due to histamine with or without throttle valve action at the pulmonary vein–left atrial junction (14, 15). Since pulmonary vascular resistance did not consistently increase, "veno-tightening" without "veno-narrowing" must have been responsible for the increase in pressure in the small pulmonary veins. This finding shows that calculated vascular resistances do not necessarily reflect active changes in tone of vessels, *i.e.*, in the state of tension of the smooth muscle within the wall.

As the histamine infusion continued, the pressure in the small pulmonary veins tended to decrease but still remained above control levels, while the pulmonary arterial pressure decreased significantly. The decrease in pulmonary arterial pressure has been attributed by others (2, 16, 17) to a decrease in cardiac output. However, at no time during the infusion of histamine did the cardiac output decrease below control levels, and the stroke volume, after the initial decline, remained unchanged. These observations suggest that the pulmonary veins maintained their tone while relaxation or decrease in tone of the pre-venous segment of the pulmonary circulation was responsible for decrease in pulmonary arterial pressure.

The marked decrease in mean systemic arterial blood pressure associated with only a slight reduction in stroke volume and an increase in cardiac output was due to the well-known systemic arterial dilating properties of histamine (17, 18). Tachycardia could be due to a decrease in baroreceptor activity associated with systemic arterial hypotension (19) as well as to other complex undefined phenomena.

These studies show a difference in the be-

havior of pulmonary veins in comparison with that of systemic veins. Thus, the various venous segments of the circulation do not only behave differently but they may have different chemoreceptor or reflex mechanisms of response to vasoactive chemical agents. These studies also show that observations limited to a single segment of the circulation do not necessarily reflect the behavior of other segments.

Summary. Intravenous infusion of histamine phosphate in intact lightly anesthetized dogs produced a consistent increase in pressure in small pulmonary veins, slight reduction in stroke volume and decrease or lack of change in left atrial pressure. The rise in pulmonary venous pressure was due to an active increase in tone of these veins without change in their caliber, since the pulmonary blood volume did not change significantly.

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