produced in the absence of serum and could be neutralized by the addition of serum. Conversely, the second type of toxin designated Z required the presence of serum for its production and was not neutralized by the addition of fresh serum. Since bacterial plaques are formed only in the presence of serum, toxin Z is indirectly implicated as the causative factor responsible for plaques in HeLa monolayers.

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## The Influence of Phenoxybenzamine (Dibenzyline) on the Pulmonary Veins of Intact Anesthetized Dogs* (33865)

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The pulmonary veins of intact dogs have been shown to be active in hemodynamic responses to acute changes in the circulating blood volume (1), immersion hyperthermia and hypothermia (2), and administration of histamine (3). The effects of phenoxybenzamine, a potent alpha-adrenergic blocking agent, on the systemic circulation are well known (4–6), whereas its effects on the pulmonary circulation, especially the veins, have received little attention. Studies were undertaken to observe the pulmonary venous response to phenoxybenzamine infusion in intact dogs anesthetized with urethane.

*Material and Methods.* Eleven adult mongrel dogs weighing 14.8–18.2 kg (mean, 16.5 kg) were lightly anesthized with urethane (1.5 g/kg). After intubation with an endotracheal tube, a mixture of 100% oxygen with room air was given at the rate of 2.5–3 liters/min to prevent the animal from becoming anoxic. Final oxygen concentration of the gas mixture at these flow rates probably ranged between 35 and 55% (7).

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Under fluoroscopic control, cardiac catheters were passed transeptally into a small pulmonary vein (i.d., 0.51 min; o.d., 0.91 mm) and left atrium (i.d., 1.5 mm; o.d., 2.8 mm) as described previously (1, 2). Separate catheters (i.d., 1.2 mm; o.d., 2.2 mm) were positioned in the main pulmonary artery just beyond the pulmonary valve and at the junction of the inferior vena cava and the right atrium. Polyethylene tubes were inserted into the right femoral artery, right femoral vein, and percutaneously into a small vein in the left hind leg. It has been shown (10) that the catheters in the pulmonary veins do not obstruct venous flow sufficiently to interfere with the experiment.

All catheters were connected by polyethylene tubing to strain gauge transducers[1] and mean pressures were recorded simultaneously on a multichannel oscillographic recorder.[2] Zero levels were determined 7–9 cm above the top of the fluoroscopic table.

Cardiac output and pulmonary blood volume were measured by the dye-dilution technique, using the Stewart–Hamilton formula (8). A known quantity of indocyanine dye

[1] Statham P23Db strain gauge transducers.

[2] Electronics for Medicine recorder.

(Cardio-green) was injected at the junction of the right atrium and inferior vena cava and blood was withdrawn simultaneously at a constant rate (24.7 ml/min) through a matched pair of cuvette densitometers[3] from the catheters placed in the pulmonary artery and left atrium as previously described (1, 2).

Pulmonary and systemic vascular resistances were calculated according to usual hemodynamic formulas.

Experiments were begun when a "steady" state was reached in relation to cardiovascular pressures, cardiac output, and heart rate. Phenoxybenzamine[4] was then infused into the right femoral vein at a rate of 0.33 mg/min over a 30-min period (total dose, 10 mg). Mean pressures were recorded simultaneously and continuously from the sites mentioned above. Cardiac output and pulmonary blood volume were determined 5, 10, 15, 20, and 30 min after the start of the infusion and 15 and 30 min after the end of the infusion.

*Results.* The results are summarized in Table I and Fig. 1. There was a consistent, significant decrease in pressure in the small pulmonary veins in response to phenoxybenzamine infusion. The pressure remained below control levels throughout both the infusion and postinfusion periods. There was no significant change in pulmonary blood volume during the infusion, however. Figure 1 summarizes the relationship between the pressure in a small pulmonary vein and the pulmonary blood volume for the 11 dogs. The pulmonary arterial pressure and total pulmonary vascular resistance decreased significantly in response to phenoxybenzamine. There was also a significant decrease in left atrial pressure.

Heart rate increased initially in all dogs, but near the end of the infusion it tended to return to control levels. An initial increase in cardiac output also occurred in response to phenoxybenzamine but was mainly due to tachycardia since the stroke volume consis-

TABLE I. Mean Values for 11 Normal Dogs Infused with Phenoxybenzamine.[b]

| Time[a] (min) | Heart rate/min | Cardiac output (ml/min) | Stroke vol (ml) | PBV (ml/kg) | Mean pressure (mm Hg) | | | | | | Resistance (units) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | FA | PA | PVS | LA | RA | LVS | PVS —LA | TPR | PVR | SR |
| Control | 147 | 173 | 19.7 | 10.0 | 151 | 16.7 | 8.8 | 3.1 | 0.8 | 10.8 | 5.8 | 4.75 | 1.99 | 52.6 |
| 5 | 167[c] | 183 | 18.7 | 9.8 | 140[c] | 16.2 | 8.8 | 2.6[c] | 1.0 | 10.8 | 6.2 | 4.49 | 2.05 | 46.2[c] |
| 10 | 172[c] | 190[c] | 17.7 | 10.2 | 127[c] | 15.1 | 8.2 | 2.0[c] | 0.8 | 9.6 | 6.2 | 4.23[c] | 2.00 | 41.1[c] |
| 15 | 154 | 159 | 17.0[c] | 10.6 | 116[c] | 12.7[c] | 6.6[c] | 2.0[c] | 0.6 | 9.2[c] | 4.6[c] | 4.02 | 1.72 | 43.6[c] |
| 20 | 167[c] | 166 | 16.3[c] | 10.6 | 101[c] | 13.3[c] | 8.0[c] | 1.6[c] | 0.7 | 9.1[c] | 6.4 | 4.31 | 2.36[c] | 37.3[c] |
| 30 | 153 | 159 | 17.0[c] | 10.3 | 88[c] | 11.6[c] | 7.2[c] | 1.6[c] | 0.6 | 8.1[c] | 5.6 | 3.83[c] | 2.14 | 33.7[c] |
| 45 | 153 | 129[c] | 14.0[c] | 9.5 | 73[c] | 10.4[c] | 6.0[c] | 1.2[c] | (—)0.3[c] | 7.3[c] | 5.0 | 4.33 | 2.26 | 34.4[c] |
| 60 | 142 | 129[c] | 15.3[c] | 11.0[c] | 73[c] | 9.6[c] | 5.9[c] | 0.7[c] | (—)0.7[c] | 6.1[c] | 5.2 | 4.20 | 2.45[c] | 34.4[c] |

[a] Infusion period = first 30 min.

[b] PBV = pulmonary blood volume; FA = femoral artery; PVS = small pulmonary vein; LA = left atrium; RA = right atrium; PVS—LA = small pulmonary vein—left atrial pressure gradient; LVS = small leg vein; TPR = total pulmonary vascular resistance; PVR = pulmonary venous resistance; and SR = systemic vascular resistance.

[c] $p < 0.01$.

[3] Gilford densitometer.

[4] Supplied as Dibenzyline by Ciba Pharmaceutical Company, Summit, New Jersey.

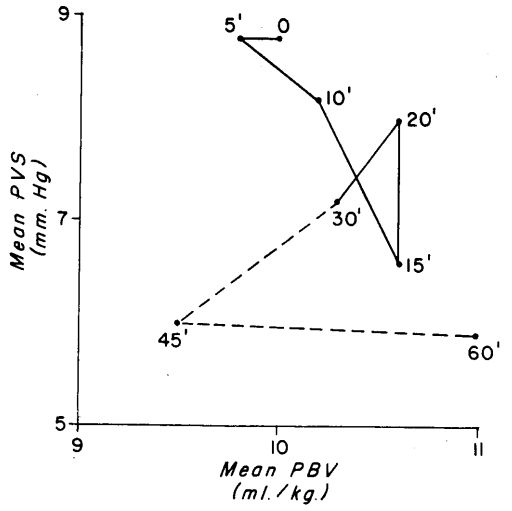


FIG. 1. The influence of phenoxybenzamine on the time course of pressure in a small pulmonary vein and on pulmonary blood volume in the intact anesthetized dog [mean values for 11 dogs; (—), during phenoxybenzamine infusion; ( - - ) after infusion].

tently decreased over the same time interval. During the latter half of the infusion, the cardiac output decreased despite tachycardia. In all dogs there was a progressive and significant decrease in systemic arterial pressure and systemic vascular resistance with a decrease in systemic venous pressure. The phenoxybenzamine did not change right atrial pressure significantly.

*Discussion.* Phenoxybenzamine has been known to decrease tone of the systemic vasculature, including that of the systemic veins, by blocking the alpha-adrenergic receptors. The present study shows that the drug decreases tone in the pulmonary arteries and veins as well. Active reduction in pulmonary venous tone is indicated by the finding of a simultaneous decrease in pressure in the small pulmonary vein with either an increase or no change in pulmonary blood volume. A simultaneous reduction in pulmonary arterial tone is also reflected by the decrease in pulmonary arterial pressure and total pulmonary vascular resistance.

It has been suggested that phenoxybenzamine causes a shift of blood from the pulmonary to the systemic vascular bed due to a greater reduction in tone in the latter (9). However, no significant changes in pulmonary blood volume were observed in our study.

The presence of alpha receptors in the pulmonary veins was suggested by our previous findings of the venoconstrictive effects of norepinephrine on the pulmonary veins of the intact anesthetized dog (10). Since phenoxybenzamine blocks alpha receptors, our data further show that alpha receptors exist in the pulmonary veins of dogs.

*Summary.* The effect of phenoxybenzamine on the pulmonary veins of intact dogs was studied. The drug decreased tone in the small pulmonary veins, thus supporting the presence of alpha receptor sites in these vessels.

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