THE EFFECTS OF PHARMACOLOGIC AGENTS ON THE PULMONARY CIRCULATION IN THE DOG. STUDIES ON EPINEPHRINE, NOR-EPINEPHRINE, 5-HYDROXYTRYPTAMINE, ACETYLCHOLINE, HISTAMINE AND AMINOPHYLLINE [1]

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Despite a large body of literature dealing with the subject of drug-induced pulmonary vasomotor activity, there are divergent opinions as to the significance of such effects. While most investigators agree that the tone of the pulmonary vessels can be changed by drugs, the physiologic importance of such changes has been challenged.

Some of the existing disagreement is probably due to the technical problems of measuring the principal variables in pulmonary hemodynamics, namely the effective pulmonary artery and left atrial pressures, cardiac output and transpulmonary pressure (*i.e.*, the pressure difference between the alveolar and the pleural surfaces of the lung). Further confusion arises from lack of appreciation of the influence of these variables on pulmonary vascular resistance. It is clear from the studies of Edwards (1) and others (2, 3) that these factors have to be rigidly controlled if one is to differentiate direct effects of drugs on the lung vessels from secondary mechanical effects.

In the present study, control of the flow and pressures in the pulmonary circulation in the living dog was accomplished by replacing the right ventricle with a pump and perfusing each lung separately. Blood flow to each lung was measured continuously (2). Drugs were administered into the pulmonary artery of one lung, while the other lung served as a control.

METHOD

Sixteen dogs weighing between 14 and 29 kg. were anesthetized with either morphine (1.6 mg. per kg.), chloralose and urethane (67 and 670 mg. per kg.) or Nembutal® (34 mg. per kg.) as initial doses.

The animals were tracheotomized and a tracheal divider cannula was inserted. The lungs were ventilated separately by a pair of Starling pumps which gave constant-volume strokes. The chest was opened by sagittal sternotomy and the end-expiratory pressure was adjusted to 5 cm. H_2O in order to limit lung collapse.

The right ventricle was then replaced by a pump circuit and the pulmonary arteries cannulated as described in a previous communication (2). The procedure involved insertion into right atrium and ventricle of an outflow tube which drained systemic venous blood into a reservoir. From there the blood was pumped through flowmeters into the lungs via a pair of cannulae tied into the main pulmonary artery and the left pulmonary artery, respectively. This procedure was performed without interruption of the circulation. Donor blood and dextran [4] were used for priming the extracorporeal circuit. Mepesulfate [5] was used as an anticoagulant.

Flow to each lung was measured with a Shipley-Wilson rotameter. Pressures in both pulmonary arteries beyond the cannulae, in the left atrium, and in the femoral artery were measured with electromanometers. The left and right airway pressures were measured in some experiments with inductance manometers. All values were continuously recorded on an oscillograph. Vascular pressures and flows were expressed as mean values (electrically integrated).

Drug injections and infusions usually were administered into the right and left pulmonary inflow tubes. Administration at a point proximal to the rotameters ensured adequate mixing. All drugs were administered at a fixed pump output (constant total pulmonary flow). In most experiments no attempt was made to prevent recirculation of the drug. This was done because, while the lung receiving the drug obtained a relatively undiluted concentration, any recirculating diluted drug would affect both lungs to an equal degree. Further, the reservoir-pump system ensured more dilution and longer circulation time than would occur in the uncannulated animal.

Unilateral vasomotor activity in this preparation was

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[4] Expandex, generously supplied through Commercial Solvents Corp., Dr. J. Martin.

[5] Mepesulfate, generously supplied through Hoffman-La Roche, Inc., Dr. E. Severinghaus.

denoted by a redistribution of the blood flow to the two lungs. When this flow redistribution was marked, there was a noticeable deviation from each other of the two pulmonary artery pressures (measured beyond the cannulae). This pressure deviation was caused by the apparatus resistances interposed between the pump and the two pulmonary arteries. A consequence of this artificial pressure deviation was that the actual flow redistribution was somewhat less than would have occurred if the pressures had remained equal. At a blood flow of 0.5 to 1.5 L. per min. through each lung the resistances of the right and left flowmeter cannula systems were 8 to 10 cm. H_2O per L. per min. and 9.5 to 12.5 cm. H_2O per L. per min., respectively.

RESULTS

Epinephrine and nor-epinephrine [6]

Epinephrine (Suprarenin® Bitartrate, Winthrop-Stearns), was rapidly injected into one lung 32 times in 9 experimental preparations. In thirty instances, the injection was followed by a redistribution of the blood flow, the flow decreasing in the test lung. This denoted vasoconstriction. The flows started to change within 6 seconds after the injection, reached their maximum redistribution within one-half minute and returned to control levels within 2 to 3 minutes. The dosage ranged from 0.17 to 6.3 gamma per kg. body weight with an average of 2.3 gamma per kg. The unilateral flow decrease amounted to 4 to 15 per cent (average, 8.6 per cent). For reasons stated above, the flow redistribution is somewhat less than would occur in the absence of the flow metering system. The effect of a given dose was usually more marked on the left because the concentration obtained was higher in the smaller lung. Failure to produce vasoconstriction occurred in two instances and was apparently due to inadequate dosage (2 runs, 0.32 and 0.44 gamma per kg.), for larger doses produced vasoconstriction in the same animals. In different animals there was a marked variability in response.

The effects of epinephrine on pulmonary arterial, left atrial, and femoral arterial pressures and on flow distributions are shown in Table I. In spite of the pulmonary vasoconstriction, the pulmonary artery pressure fell in 13 instances in which left atrial pressure also decreased. Femoral artery pressure rose in 31 of 32 runs. Control femoral artery pressures varied between 70 and 140 mm. Hg.

Airway pressure was unchanged by epinephrine in 5 dogs in which it was measured.

Nor-epinephrine (Levophed® Bitartrate, Winthrop-Stearns) was administered to 4 animals on 24 occasions. In 22 instances there was a decrease in blood flow in the lung receiving the drug, denoting pulmonary vasoconstriction. The dosage varied from 0.17 to 6.3 gamma per kg. body weight (average, 2.2 gamma per kg.). The per cent decrease of unilateral flow ranged from 3 to 16 with an average of 7.3 per cent. In two instances (in one dog) pulmonary vasoconstric-

TABLE I

Effect of epinephrine, injected into one lung, on the blood flow and arterial pressure (PA) of the same lung and on pressures in left atrium (LA) and femoral artery (FA) in 9 dogs—Dose range 0.17 to 6.3 gamma per kg. body weight—The total blood flow was held constant

		Number of observations	Change	
			Range	Mean
Unilat. flow	No change	2		
	Fall	30	4–15%	8.6%
PA cm. H_2O	Rise	17	0.2–3.2	1.5
	No change	1		
	Fall	14	0.3–3.7	1.4
LA cm. H_2O	Rise	5	0.7–3.8	1.3
	No change	2		
	Fall	25	0.2–7.2	2.3
FA	Rise	31	3–86%	30%
	Fall	1		24%

TABLE II

Effect of nor-epinephrine, injected into one lung, on the blood flow and arterial pressure (PA) in the same lung and on pressures in left atrium (LA) and femoral artery (FA) in 4 dogs—Dose range 0.17 to 6.3 gamma per kg. body weight —The total blood flow was held constant

		Number of observations	Change	
			Range	Mean
Unilat. flow	No change	2		
	Fall	22	3–16%	7.3%
PA cm. H_2O	Rise	11	0.4–2.6	1.7
	No change	1		
	Fall	12	0.3–1.4	0.6
LA cm. H_2O	Rise	3	0.5–1.5	1.1
	Fall	21	0.6–6.0	2.8
FA	Rise	24	6–90%	44%

[6] Dosage expressed in epinephrine and nor-epinephrine base.

TABLE III

Effect of serotonin infusion into one lung—Total blood flow kept constant—Both PA pressures equal

Dog No.	Side	No. of steps	Duration (*min.*) per step	Dose *gamma/kg./min.*	Max. % decr. of unilateral flow
55	Lt.	1	4	20	45
55	Rt.	1	2.5	20	29
63	Rt.	5	2	12–33.6	55
63	Lt.	3	2.5	12–33.6	79
63	Rt.	3	3	12–19.2	47
63	Rt.	3	2	12–33.6	43

tion failed to occur after 0.5 gamma per kg.; in this experiment vasoconstriction was produced by larger doses. The response was rapid. There was also a marked variation of responsiveness in different animals.

As with epinephrine administration, the pulmonary artery pressure tended to follow left atrial pressure change (Table II). In 10 instances in which left atrial pressure fell, pulmonary arterial pressure also decreased in spite of the pulmonary vasoconstriction. Femoral artery pressure rose by an average of 44 per cent (range, 6 to 90 per cent) from control values of 70 to 122 mm. Hg.

5-Hydroxytryptamine

5-Hydroxytryptamine (Serotonin Creatinin Sulfate—Sandoz)[7] was administered into one pulmonary artery in 5 dogs. There were 2 injections (2.3 and 4.5 gamma per kg. body weight) and 11 infusions (2.3 to 33.6 gamma per kg. body weight per min.). In five of the infusions the dosage was increased in steps.

All doses resulted in marked pulmonary vasoconstriction in the lung receiving the drug, denoted by large redistribution of blood flow and a marked rise in both pulmonary artery pressures. There was also a noticeable discrepancy between the right and left pulmonary artery pressures, as explained under methods. In 2 animals the pulmonary artery pressures were made equal at the height of the response by constricting the respective pulmonary inflow tubes; the resulting decrease in blood flow on the side receiving the infusion is shown in Table III. One of these experiments is illustrated in Figure 1.

[7] Dosage expressed as Serotinin creatinin sulfate.

The onset of pulmonary vasoconstriction occurred within a few seconds at any given dose. The duration of action after stopping the infusions varied between 5 and 15 minutes, depending on the dosage and the duration of infusion. Pulmonary artery pressures increased in all runs, irrespective of coincident changes in left atrial pressure. Left atrial pressure followed directionally the changes in femoral artery pressure.

Mean femoral artery pressure did not behave in a consistent pattern. It usually was unchanged unless very high doses were administered when it showed large fluctuations around the control value. No bronchoconstriction was produced in these experiments.

Acetylcholine and Histamine

Acetylcholine, given as an aerosol into one lung, produced an increase in airway pressure. Since

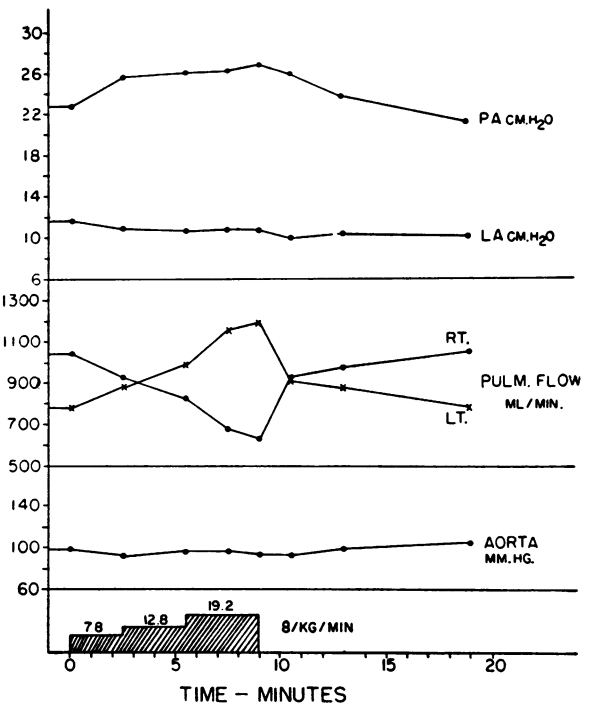

FIG. 1. EXP. NO. 63. BODY WEIGHT 21 KG. EFFECT OF 5-HYDROXYTRYPTAMINE, INFUSED INTO THE RIGHT PULMONARY ARTERY, ON PULMONARY VASCULAR PRESSURES (PA AND LA), LEFT AND RIGHT LUNG BLOOD FLOW AND AORTIC PRESSURE

Total pulmonary blood flow was held constant. Vasoconstriction in the treated lung is denoted by the altered flow distribution. The pressures in the two pulmonary arteries were made equal by constriction of the left inflow tubing.

the lung was ventilated by a constant-volume pump, this was presumably due to bronchoconstriction. The increase of airway pressure resulted in a decrease of blood flow through the lung under study with a corresponding increase in flow on the other side. In these experiments the inspiratory airway pressure rose 4 to 10 cm. H_2O and the flow in the tested lung decreased 10 to 20 per cent.

Acetylcholine and histamine also produced a rise in airway pressure when administered into the pulmonary artery. Experiments were therefore performed in which drugs were given to the collapsed or air-free lung. A lung was made air free by ventilating the dog with pure oxygen and then allowing the gas to be absorbed from the collapsed lung. Induced bronchoconstriction then had no effect on intra-alveolar pressure.

Acetylcholine was injected into the artery of the non-ventilated lung of 6 animals in 11 instances. The dose range (3 to 9.1 gamma per kg. body weight) was sufficient to reduce systemic blood pressure by 40 to 80 per cent. In two animals pulmonary vasoconstriction occurred; in one animal there was vasoconstriction followed by prolonged vasodilation, and in two there was vasodilation only. There was no effect in one animal. The vasomotor changes always were of small magnitude. The pulmonary artery pressure usually rose at first together with left atrial pressure and fell subsequently as left atrial pressure decreased. These pressure changes occurred whether there was pulmonary vasomotor reaction or not. See Figure 2.

Histamine was administered into the artery of the non-ventilated lung of 4 animals in 8 instances. There were 6 infusions (3 to 11 gamma per kg. body weight per min.) and 2 injections (4.3 to 20 gamma per kg.). Femoral artery pressure was reduced substantially in each run. Pulmonary vasoconstriction of small magnitude was observed in 3 animals. The changes in pulmonary artery pressure again reflected the changes in left atrial pressure.

Aminophylline

Aminophylline was injected in doses ranging from 2.2 to 24 mg. per kg. body weight to 5 animals in 8 instances. Pulmonary vasodilation was produced in 3 instances in 2 animals (dosage, 2.4 to 2.9 mg. per kg. body weight, unilateral increase of flow, 7 to 14 per cent). In each run, systemic blood pressure and left atrial pressure were reduced substantially. Pulmonary artery pressure fell concomitantly with left atrial pressure.

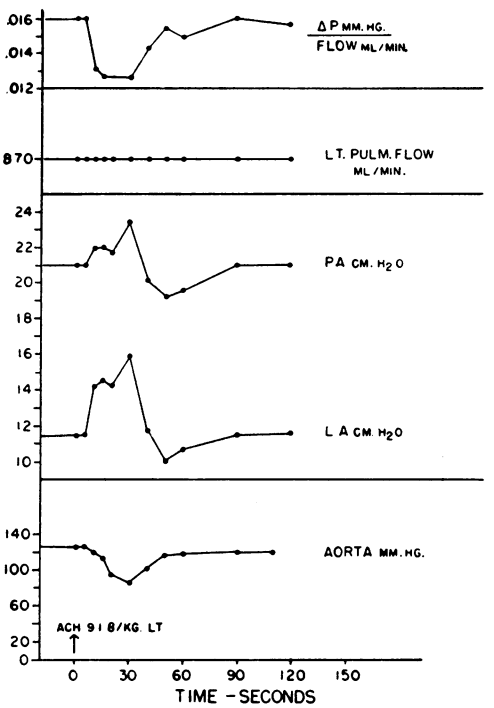

FIG. 2. EXP. NO. 64. BODY WEIGHT 22 KG. EFFECT OF ACETYLCHOLINE, INJECTED INTO LEFT PULMONARY ARTERY

Total pulmonary flow was held constant; there was no change of left pulmonary flow, indicating no pulmonary vasomotion. Note the changes in pulmonary vascular pressures (PA and LA) and left pulmonary vascular resistance in spite of the absence of pulmonary vasomotion and flow change.

DISCUSSION

Sharpey Schafer and Lim (4) and Friedberg, Katz, and Steinitz (5) have drawn attention to the complex factors which determine the response of the lesser circulation to drugs. In addition to direct effects on the tone of the pulmonary vessels, there are secondary mechanical changes of pulmonary vascular geometry and resistance due to changes in cardiac output, left atrial pressure, and transpulmonary pressure. The qualitative and quantitative effects of these factors on pulmonary vascular resistance have been studied separately (2, 3, 6).

The preparation used for these experiments facilitates the evaluation of pulmonary vasomotor tone changes. The drug is injected into one lung while the other lung is used as the control. Redistribution of flow is used as the criterion for vasomotor activity instead of changes in pulmonary arterial pressure and resistance. Alterations of vascular resistance due to changes of pulmonary vasomotor tone can be differentiated from changes of resistance due to left atrial pressure variation, since the latter pressure influences both pulmonary vascular beds. Alterations of pulmonary vascular resistance due to changes in transpulmonary pressure can be avoided. A comparison of pulmonary and peripheral vascular effects is also possible.

Vasomotor changes

Epinephrine and nor-epinephrine were found to have a consistent but moderate vasoconstrictor effect. A comparison of the pulmonary and systemic actions of these drugs gives an indication of the probable physiologic importance of their pulmonary vasomotor effects. Whereas the femoral artery pressure responses to both drugs were marked, the changes in pulmonary arterial pressure were of only the same magnitude as those of the left atrial pressure. The blood flow redistribution in the two lungs was relatively small even with the large doses used. A marked cardiac inotropic effect is produced by less than 1 gamma per kg. of these drugs (7). It is concluded that the action of these drugs on pulmonary vascular tone is of small magnitude and of minor hemodynamic importance. Results in agreement with these were obtained by Edwards (1) and Rose, Freis, Hufnagel, and Massullo (8) in experiments in which flow and pulmonary venous pressures were controlled.

On the other hand, serotonin is a potent pulmonary vasoconstrictor agent, as is suggested by other studies (9, 10). The systemic circulation was affected only when large doses of serotonin were infused, or when serotonin was administered intra-arterially. Marked pulmonary vasoconstriction with, indeed, systemic vasodilation was found also by Rudolph and Paul (11). The prominent pulmonary effect of serotonin is of interest in view of the fact that it is liberated when intravascular clotting occurs and thus may play a role in the vascular response to pulmonary embolism.

The lack of consistent pulmonary vasodilation with drugs like acetylcholine and Aminophylline may be due to the fact that the "control" tone of the pulmonary vascular bed was low. Apparently these drugs may cause a marked vasodilation in patients with increased pulmonary vascular tone (12, 13).

Changes in pulmonary vascular resistance due to changes in left atrial pressure

Left atrial pressure (left ventricular filling pressure) may be altered by drugs in two ways in this preparation in which the ventricular output is kept constant. A positive inotropic drug will lower the left atrial pressure; a negative inotropic drug will raise it. On the other hand, systemic vasomotor action of a drug will alter the work load of the left ventricle and thereby influence the left atrial pressure (14). When a drug has, for instance, a positive inotropic effect and a peripheral vasoconstrictor effect, the directional change in left atrial pressure will depend on the balance of these two factors; this often varies with the dose of the drug.

The predominance of inotropic effects or peripheral effects of a substance cannot be predicted quantitatively and therefore left atrial pressure must be measured simultaneously with pulmonary artery pressure in order to differentiate passive mechanical changes from active vasomotor changes. In the intact circulation, the significance of any recorded pulmonary artery pressure change may be further obscured by simultaneous changes of cardiac output. These facts make the results of a large number of previous investigations difficult or impossible to interpret.

It is important to recall that when left atrial pressure is raised, at a constant flow, pulmonary artery pressure does not rise proportionately (Figure 2). Equal rises in both pressures occur only at high degrees of pulmonary vascular distension, when resistance does not decrease any further (2, 3). For this reason the measurement of the pressure drop from the pulmonary artery to the left atrium alone (15) is not sufficient for assessing active pulmonary vasomotion.

Pulmonary vascular resistance, *i.e.*, the pressure drop from the pulmonary artery to the left atrium

divided by flow rate is inversely related to the fourth power of the radii of all vessels contributing to resistance. It has been shown that in the highly distensible pulmonary vascular bed small changes of the distending pressures (both the pulmonary arterial and left atrial pressures) can produce large changes in resistance (2, 3). When left atrial pressure rises or flow increases, resistance falls.

The changes in pulmonary resistance produced by substances which affect predominantly the heart and systemic circulation frequently reflect the mechanical behavior of the lung vessels rather than active pulmonary vasomotion (Figure 2). On the other hand, the pulmonary resistance changes induced by serotonin, for example, are due to active pulmonary vasomotion rather than indirect mechanical effects.

Effect of airway pressure

The caliber of vessels which contribute to pulmonary vascular resistance is affected by changes in transpulmonary pressure, *i.e.*, the pressure difference between the alveolar and pleural surfaces of the lung. When flow is kept constant, resistance to flow rises when the lung is inflated (6). It is thought that the capillaries are compressed by inflation of the lung.

In these experiments, histamine and acetylcholine both increased transpulmonary pressure by way of bronchoconstriction and when this was marked, resistance to flow increased. Similar conclusions could be drawn from the findings of Field and Drinker (16), von Euler (17) and Müller, Salomon, and Zuelzer (18). When the effects of bronchoconstriction on the transpulmonary pressure had been abolished by collapsing the lung, a consistent vasoconstrictor response to these drugs could not be demonstrated. It is necessary, therefore, to consider a possible change in transpulmonary pressure when pulmonary vasomotion is being investigated.

SUMMARY

1. A preparation was used which permitted the differentiation of active pulmonary vasomotor responses from secondary mechanical changes in the lung vessels. Unilateral pharmacologically induced pulmonary vasomotion was studied with a number of drugs.

2. Epinephrine, nor-epinephrine and 5-hydroxytryptamine produced consistent pulmonary vasoconstriction. Of the drugs studied, 5-hydroxytryptamine had the most marked pulmonary vasomotor effect.

3. Acetylcholine and histamine increased transpulmonary pressure. When this effect was prevented, inconsistent pulmonary vasomotor effects of small magnitude were found.

4. Aminophylline produced pulmonary vasodilation in some animals while it had no effect in others.

5. The prerequisites for the assessment of active pulmonary vasomotor changes in the lungs have been discussed.

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