Differential Reactivity in the Pulmonary Circulation

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ABSTRACT A new method for relating regional intravascular resistance to pulmonary arterial, capillary, and venous pressure and volume was used to evaluate local differences of reactivity in the pulmonary blood vessels in the isolated lung lobe of the dog.

Intravascular infusion of isoproterenol caused active dilatation of pulmonary arteries and veins. Capillary conductance (1/resistance) and volume increased, possibly as a result of the opening of previously closed capillaries. Serotonin infusion caused active constriction of both the pulmonary arteries and veins. A low dose of serotonin (1.5 μg/min per kg) caused predominant constriction of whichever vessels were upstream (arteries during forward perfusion, veins during reverse perfusion). A high dose of serotonin (4.5–5.0 μg/min per kg) caused constriction of both upstream and downstream vessels. Metabolic inactivation of serotonin by the lung is suggested as an explanation for these observations. Histamine infusion caused predominant venous constriction whether veins were upstream or downstream. Capillary volume and conductance decreased during forward and reverse perfusion, perhaps as a result of pericapillary edema formation. Large arterial vessels constricted slightly, whereas small arterial vessels appeared to be passively dilated.

INTRODUCTION

Measurements of pulmonary arterial, capillary, and venous responses to stimuli that affect the pulmonary circulation have been limited by technical difficulties inherent in the determination of intravascular pressure at points throughout the pulmonary vascular bed. In the preceding paper (1), we described a method for determining the longitudinal distribution of vascular resistance in the lung. This method, based on a principle described by Piiper (2), provides a way of determining pressure and resistance to blood flow throughout the pulmonary vascular bed without requiring direct pressure measurements from multiple points within the lung vessels.

The present study was undertaken to determine if the methods described could be used to measure the differential reactivity of the pulmonary arteries, capillaries, and veins. Measurements of lobar pulmonary artery or vein volume, total lobar blood volume, and the volume to the midpoint of lobar vascular resistance were made in the dog isolated lung lobe before and during infusion of isoproterenol, serotonin, or histamine into the vascular inflow of the lobe. Measurements made during a control period and during drug infusion were compared, and arterial, capillary, and venous responses to the drugs were analyzed.

METHODS

The details of the methods used and the principles involved in this study are described in the preceding paper (1).

In seven dogs weighing 10–14 kg, the left basal lobe was removed, placed in an airtight Plexiglas box, and perfused at constant flow with blood drawn from a heparinized donor dog. The blood, warmed to 37°C, flowed through the lung into a constant pressure reservoir which was set to maintain downstream vascular pressure at about 10 cm H_2O, and was drained from this reservoir by gravity back into the donor dog. The isolated lobe was ventilated with room air by a positive pressure respirator with a con-

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stant stroke volume set to produce transpulmonary pressures of 8–10 cm H_2O at peak inspiration. End expiratory pressure was kept constant at 3–5 cm H_2O.

Lobar pulmonary artery volume was measured during forward perfusion, and lobar pulmonary vein volume was measured during reverse perfusion by the ether plethysmograph technique (3). Total lobar blood volume was measured by the Stewart-Hamilton dye dilution technique (4).

The volume to the midpoint of pulmonary vascular resistance and the longitudinal distribution of pulmonary vascular resistance were calculated from the decrease in perfusion pressure with time produced by the passage of a bolus of low viscosity fluid (2 ml of saline solution) through the pulmonary vessels. According to Poiseuille's law, during steady laminar flow a sudden decrease in the viscosity of the fluid perfusing the lobe will cause a decrease in perfusion pressure proportional to the resistance of the vessels through which the low viscosity fluid is passing. The volume (time × flow) to the midpoint of the perfusion pressure vs. time curve minus an appropriate apparatus dead space gives the volume to the midpoint of lobar vascular resistance, i.e., the point in volume from which 50% of vascular resistance is upstream and 50% of vascular resistance is downstream. The longitudinal distribution of vascular resistance in the lobe was determined by analyzing the saline-induced pressure curve at 2-ml intervals. The details of the methods and accuracy and reproducibility of the results are described in the preceding paper (1).

The ischemic time from removal of the lobe to the beginning of perfusion was never longer than 30 min. All measurements were made in duplicate before and during constant infusion of either isoproterenol, serotonin, or histamine into the vascular inflow of the lobe. Initial control measurements were not made until perfusion pressure was stable, usually 15–20 min after perfusion had begun. Drug infusion usually lasted 20–30 min. Control measurements after drug infusion was stopped were made only after perfusion pressure had been constant for 5 min (usually 10–20 min after drug infusion had been discontinued). The sequence of drug infusion varied and is listed in Tables I and II. The results were not dependent on the order in which the drugs were given. The average oxygen pressure (P_{O_2}) of blood perfusing the lobe was 70 mm Hg. The average carbon dioxide pressure (P_{CO_2}) was 38 mm Hg, and the average pH was 7.30. Measurements were made during short periods of apnea at an end expiratory pressure of 3–5 cm H_2O after a prior inflation of the lobe to 20–25 cm H_2O. Since downstream pressure exceeded alveolar pressure during the measurements, nonsluice conditions were present in the lobe (5).

Total vascular resistance was calculated by substracting downstream pressure from inflow pressure, multiplying by 980 to convert to dynes per square centimeter and dividing by flow in milliliter per second. Arterial resistance and combined capillary and venous resistance were calculated during forward perfusion, whereas venous resistance and combined capillary and arterial resistance were calculated during reverse perfusion. This method was used because capillary volume was not measured separately, and because the calculation of vascular resistance became less accurate the farther downstream the saline bolus moved (1).

The per cent of resistance in a vascular segment was calculated by dividing the sum of resistances calculated at 2-ml intervals in the vessel by the sum of 2-ml resistances for the whole lobe. Conductance, the reciprocal of resistance, was calculated for each vascular segment by dividing flow (milliliters per second) by the pressure drop across that vascular segment (dynes per square centimeter). Mean distending pressure (transmural pressure) for a vascular segment was determined by multiplying the total pressure drop across the lobe by the per cent of resistance in the vascular segment, dividing by two, and subtracting this result from the upstream pressure (centimeters of water) in the segment. Resistivity, defined as resistance in dynes·second·centimeter^{-5} per milliliter, was calculated as described in the preceding paper (1).

RESULTS

A summary of the results of drug infusion is presented in Table I (forward perfusion) and Table II (reverse perfusion). Typical saline-induced pressure curves before and during drug infusion are shown in Fig. 1. The per cent changes mentioned below are mean changes for each drug, since the changes with each drug were consistent in all experiments.

The mean difference between the per cent of total resistance in a specific vascular segment determined from duplicate saline injection curves was 3% with a standard deviation of ± 2% and standard error of ± 1%. The mean difference between duplicate determinations of conductance was 0.0005 dyne^{-1}·sec^{-1}·cm^5 (SD ± 0.0005) which was 8.9% of the mean conductance measurement, 0.0056 dyne^{-1}·sec^{-1}·cm^5. The mean difference between duplicate determinations of total lobar blood volume was 1.4 ml (SD ± 0.7 ml) which was 6.0% of the mean lobar blood volume. The mean difference between duplicate determinations of pulmonary artery or pulmonary vein volume was 0.2 ml (SD ± 0.2 ml) which was 3.6% of mean artery and vein volume.

Isoproterenol. During forward perfusion isoproterenol (1.0 μg/min per kg) caused a 17% decrease in vascular resistance, i.e., perfusion pressure decreased while flow remained constant. The midpoint of vascular resistance moved downstream away from the pulmonary artery signifying a relative decrease in arterial resistance. Mean arterial distending pressure decreased 7%, but arterial volume (+ 10%) and conductance

TABLE I

Forward Perfusion

Dog	Resistance	Vmp	Resistance PA	Vpa	$\bar{P}$pa	Gpa	Vpc+pv	$\bar{P}$pc+pv	Gpc+pv
	dynes·sec·cm^{-5}	*ml*	*% total*	*ml*	*cm H$_2$O*	*dyne^{-1}·sec^{-1}·cm^5*	*ml*	*cm H$_2$O*	*dyne^{-1}·sec^{-1}·cm^5*
Control									
B (3)	6730	3.4	58	4.2	16.8	0.00026	13.0	11.3	0.00036
C (1)	3340	5.7	40	4.9	18.0	0.00075	20.4	13.0	0.00050
D (1)	3340	6.1	51	6.5	17.6	0.00059	22.0	12.4	0.00061
Mean	4470	5.1	50	5.2	17.5	0.00053	18.5	12.2	0.00049
Isoproterenol, *1.0 μg/min per kg*									
B (4)	5200	3.6	59	4.7	15.1	0.00035	14.0	10.9	0.00043
C (2)	3000	6.7	36	5.3	17.4	0.00092	24.3	12.8	0.00053
D (2)	3000	8.0	48	7.1	16.8	0.00069	24.3	12.3	0.00065
Mean	3733	6.1	48	5.7	16.4	0.00065	20.9	12.0	0.00054
% Change	−17%	+20%	−4%	+10%	−7%	+23%	+13%	−2%	+10%
Control									
B (1)	6150	5.6	48	5.4	16.6	0.00034	14.2	11.6	0.00032
C (3)	3670	4.5	50	4.5	18.2	0.00055	21.0	12.8	0.00055
D (3)	3500	5.7	60	6.3	17.3	0.00048	18.9	12.1	0.00072
E (1)	4260	5.8	54	6.5	21.7	0.00042	27.5	13.7	0.00049
Mean	4395	5.4	52	5.7	18.5	0.00045	20.4	12.6	0.00052
Serotonin, *1.5 μg/min per kg*									
B (2)	9750	1.6	77	4.2	19.4	0.00013	14.0	11.4	0.00043
C (4)	5660	2.3	57	3.3	22.2	0.00032	20.8	13.6	0.00041
D (4)	4510	1.8	69	5.4	18.9	0.00032	18.1	12.1	0.00072
E (2)	6600	3.9	63	5.2	28.5	0.00024	27.0	14.2	0.00041
Mean	6630	2.4	67	4.5	22.3	0.00025	20.0	12.8	0.00049
% Change	+51%	−56%	+23%	−21%	+21%	−45%	−2%	+2%	−6%
Serotonin, *5.0 μg/min per kg*									
E (3)	10,950	2.7	63	4.3	37.4	0.00015	22.3	17.4	0.00025
Control									
C (5)	4160	3.4	50	4.4	18.9	0.00048	20.2	12.6	0.00049
D (5)	4500	8.6	44	6.6	20.5	0.00050	18.4	13.7	0.00040
F (1)	7350	3.0	65	5.0	23.5	0.00021	16.5	13.5	0.00039
Mean	5337	5.0	53	5.3	21.0	0.00040	18.4	13.3	0.00043
Histamine, *3.0 μg/min per kg*									
C (6)	5175	6.1	40	4.5	21.9	0.00049	17.8	14.2	0.00032
D (6)	5990	10.5	33	6.6	25.0	0.00050	14.5	16.0	0.00025
F (2)	8820	5.0	51	5.0	28.0	0.00023	14.0	16.0	0.00023
Mean	6662	7.2	41	5.4	25.0	0.00041	15.4	15.4	0.00027
% Change	+23%	+44%	−23%	+2%	+19%	+3%	−16%	+16%	−37%

V, volume; $\bar{P}$, mean distending pressure; G, conductance; Vmp, volume to the midpoint of vascular resistance. pa, pc, and pv refer to pulmonary artery, pulmonary capillary, and pulmonary vein respectively. Numbers in parentheses next to letters identifying dog refer to the sequence of experiments.

(+ 23%) increased. The mean distending pressure of the capillaries and veins decreased slightly, yet capillary and vein volume and conductance increased 13 and 10% respectively. Resistance per milliliter or resistivity, calculated at 2-ml volume intervals (Fig. 2), decreased throughout the vascular bed. Although the decrease was most marked in the pulmonary arteries, there was no great change in the longitudinal distribution of vascular resistance.

During reverse perfusion isoproterenol (1.0 μg/min per kg) caused an 11% decrease in vascular resistance. The resistance midpoint did not change. Mean venous distending pressure decreased slightly, whereas venous volume (+ 15%) and conductance (+ 14%) increased. Combined capillary and artery distending pressure decreased slightly (− 4%), but capillary and artery volume increased 16%, and conductance increased 11%. Resistivity decreased throughout the pulmonary vascular bed (Fig. 2).

Serotonin. During forward perfusion, 1.5 μg/min per kg of serotonin (low dose) caused a 51% increase in vascular resistance. The midpoint of

vascular resistance moved forward into the pulmonary artery signifying a relative increase in arterial resistance. Mean arterial distending pressure increased 21%, but arterial volume decreased 21%, and arterial conductance decreased 44%. The changes in the capillaries and veins were too small to be regarded as significant. Resistivity (Fig. 2) increased markedly in both the large and small pulmonary arteries but remained unchanged in the capillaries and veins. The arteries accounted for 52% of total vascular resistance before and 67% of vascular resistance during serotonin infusion.

In one experiment infusion of 5.0 μg/min per kg of serotonin (high dose) caused a further increase in vascular resistance, an additional increase in pulmonary arterial distending pressure, and a decrease in pulmonary arterial volume and conductance. High dose serotonin also caused an increase in capillary and vein distending pressure (+ 23%) and a decrease in combined capillary and vein volume (− 17%) and conductance (− 39%). The additional increase in vascular resistance produced by the higher dose of serotonin was fairly evenly distributed between upstream and downstream vessels.

During reverse perfusion a low dose of serotonin caused a 22% increase in vascular resistance.

TABLE II

Reverse Perfusion

Dog	Resistance	Vmp	Resistance PV	Vpv	$\bar{P}$pv	Gpv	Vpc+pa	$\bar{P}$pc+pa	Gpc+pa
	dynes·sec·cm⁻⁵	*ml*	*% total*	*ml*	*cm H₂O*	*dyne⁻¹·sec⁻¹·cm⁵*	*ml*	*cm H₂O*	*dyne⁻¹·sec⁻¹·cm⁵*
Control									
G (6)	3220	13.9	28	6.8	18.0	0.00111	14.6	13.0	0.00043
H (1)	3860	11.7	20	5.5	20.4	0.00130	14.2	15.2	0.00032
Mean	3540	12.8	24	6.2	19.2	0.00121	14.4	14.1	0.00038
Isoproterenol, *1.0 μg/min per kg*									
G (7)	3060	13.4	26	7.7	17.2	0.00124	16.9	12.4	0.00045
H (2)	3300	12.2	20	6.4	19.1	0.00151	16.5	14.6	0.00038
Mean	3150	12.8	23	7.1	18.2	0.00138	16.7	13.5	0.00042
% Change	−11%	0	−4%	+15%	−5%	+14%	+16%	−4%	+11%
Control									
G (3)	3220	13.5	22	7.1	18.4	0.00142	14.3	13.1	0.00040
H (3)	3650	12.8	21	5.5	20.0	0.00129	16.1	14.9	0.00035
Mean	3435	13.4	22	6.3	19.2	0.00136	15.2	14.0	0.00038
Serotonin, *1.5 μg/min per kg*									
G (4)	4510	12.2	26	5.4	21.7	0.00085	17.6	14.7	0.00029
H (4)	4400	10.1	31	4.9	21.2	0.00074	17.2	15.2	0.00033
Mean	4455	11.2	29	5.2	21.5	0.00080	17.4	15.0	0.00031
% Change	+30%	−16%	+32%	−18%	+12%	−41%	+15%	+7%	−18%
Serotonin, *4.5 μg/min per kg*									
G (5)	6300	12.8	21	5.3	27.0	0.00077	13.6	17.5	0.00021
H (5)	6240	10.8	33	4.8	25.2	0.00049	13.4	16.7	0.00024
Mean	6270	11.8	27	5.1	26.1	0.00063	13.5	17.1	0.00023
% Change	+83%	−12%	+23%	−21%	+36%	−54%	−11%	+22%	−40%
Control									
G (1)	3050	13.7	20	6.7	18.0	0.00163	16.7	13.1	0.00041
H (6)	3300	15.2	20	6.1	19.1	0.00151	17.1	14.6	0.00038
Mean	3175	14.5	20	6.4	18.6	0.00157	16.9	13.9	0.00040
Histamine, *3.0 μg/min per kg*									
G (2)	3220	11.8	26	6.0	18.2	0.00119	15.0	12.7	0.00042
H (7)	3850	12.8	36	4.5	19.6	0.00072	13.3	14.9	0.00041
Mean	3535	12.3	31	5.3	18.7	0.00096	14.2	13.8	0.00042
% Change	+11%	−15%	+55%	−17%	+1%	−39%	−16%	−7%	+3%

V, volume; $\bar{P}$, mean distending pressure; G, conductance; Vmp, volume to the midpoint of vascular resistance. pa, pc, and pv refer to pulmonary artery, pulmonary capillary, and pulmonary vein respectively. Numbers in parentheses next to letters identifying dog refer to the sequence of experiments.

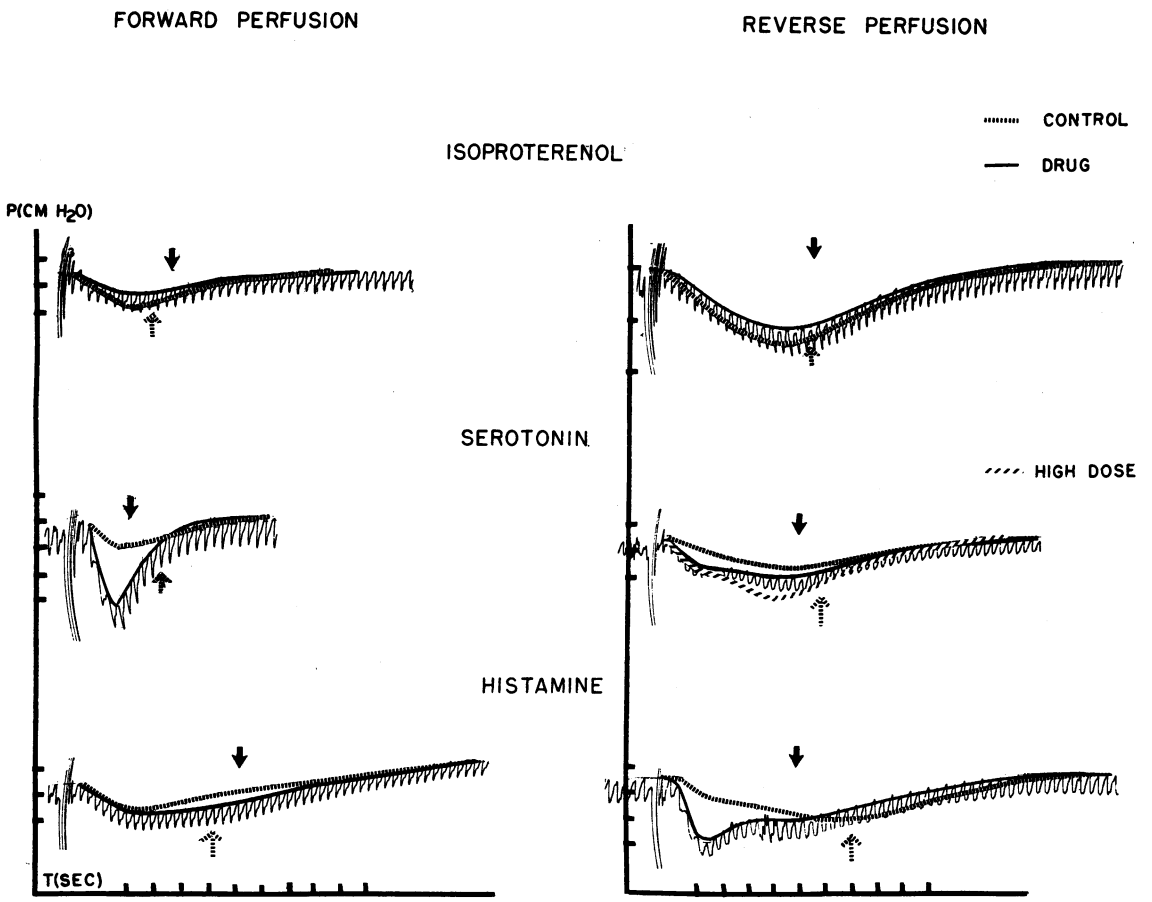

FIGURE 1 Saline bolus-induced pressure curves. Control and drug infusion saline bolus-induced pressure curves are from selected forward and reverse perfusion experiments. Control curves are traced by the interrupted line. Drug infusion curves are reproduced and traced by the solid line. The arrows mark control (interrupted) and drug infusion (solid) midpoint of vasclar resistance.

The resistance midpoint moved upstream toward the veins signifying a relative increase in venous resistance. Mean venous distending pressure increased 12%, but pulmonary vein volume decreased 18%, and conductance decreased 32%. Mean capillary and artery distending pressure increased slightly, 7%, and volume increased 15%, but capillary and artery conductance decreased 18%. Resistivity (Fig. 2) increased markedly in the pulmonary veins and also increased slightly in downstream vessels. Venous resistance increased from 22 to 29% of total vascular resistance.

A high dose of serotonin caused a larger increase in total vascular resistance, a further increase in venous distending pressure and a further decrease in venous volume and conductance. Capillary and artery distending pressure rose 22%, whereas volume decreased 11%, and conductance decreased 40%. Resistivity increased slightly in the veins but markedly in the downstream vessels, probably in the arteries.

The changes produced by serotonin were probably not caused by platelet aggregation, since the blood perfusing the lung was heparinized, and heparin prevents the platelet aggregation produced by serotonin (6).

Histamine. During forward perfusion 3.0 μg/min per kg of histamine caused a 23% increase in vascular resistance. Mean pulmonary artery distending pressure increased 19%, but pulmonary artery volume did not change. Arterial conductance did not change. Capillary and vein distending pressure increased, whereas volume decreased 16%, and conductance decreased 37%. The re-

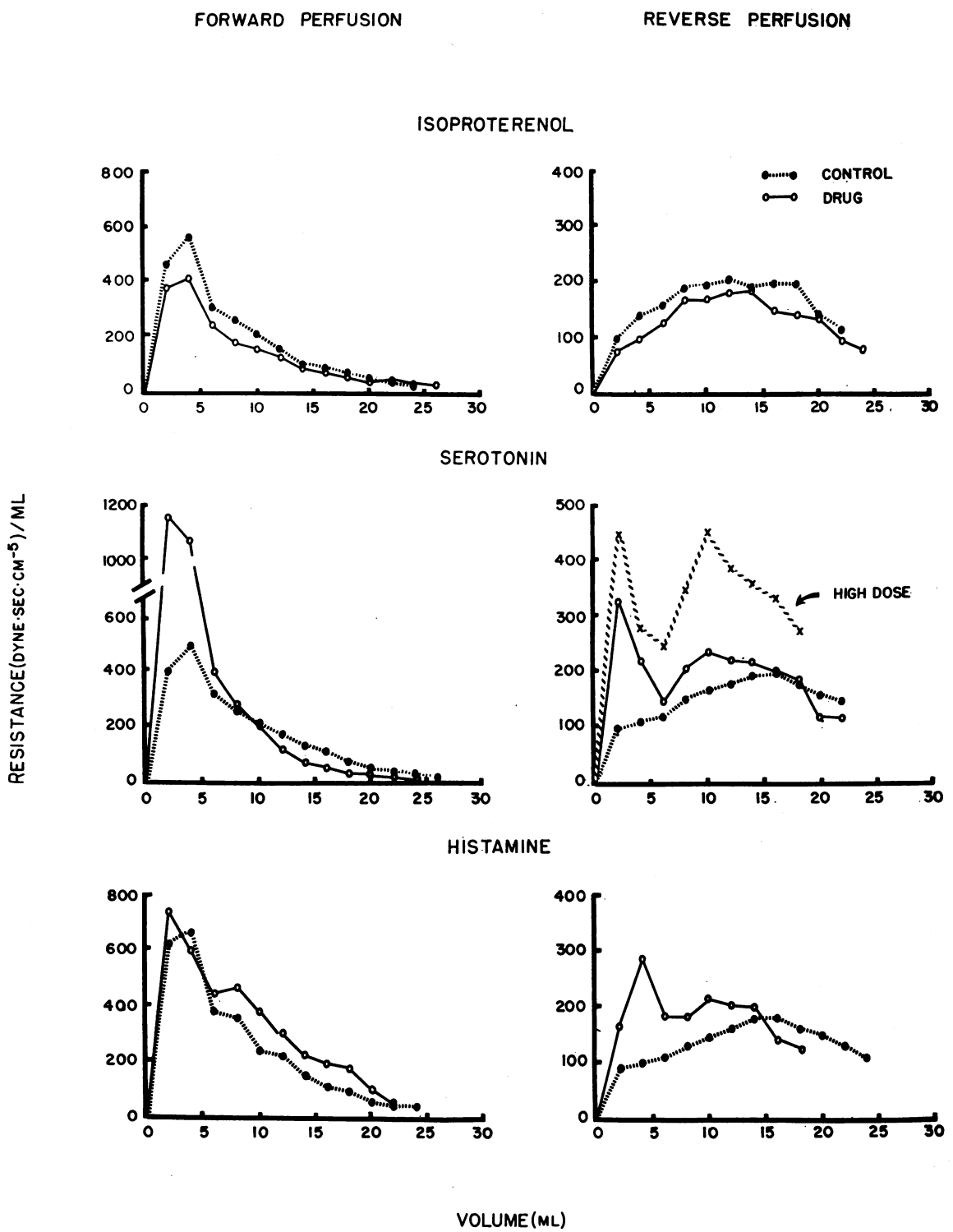

FIGURE 2 Resistivity before and during drug infusion. Resistance per milliliter (resistivity) is calculated at 2-ml volume intervals before (interrupted line) and during (solid line) infusion of isoproterenol, serotonin, and histamine in forward and reverse perfusion experiments. Results are means of all experiments.

sistance midpoint moved toward the veins signifying a relative increase in downstream resistance. Resistivity (Fig. 2) was virtually unchanged in the pulmonary artery but increased throughout the downstream vessels.

During reverse perfusion histamine increased vascular resistance, and the resistance midpoint moved upstream toward the veins. Venous distending pressure increased 1%, but venous volume decreased 17%, and venous conductance decreased 39%. Capillary and artery distending pressure decreased 7%, but combined capillary and artery volume decreased 16%, and conductance increased 3%. Resistivity (Fig. 2) increased markedly in the veins and to a lesser extent in the early downstream vessels. Venous resistance increased from 20% to 31% of lobar vascular resistance.

Transpulmonary pressure (bronchial pressure − plethysmograph pressure) for a given inspired volume was unchanged during isoproterenol and serotonin infusion. During histamine infusion transpulmonary pressure rose about 20%. There was no gross evidence of air-trapping, and since all measurements were made at an end expiratory pressure of 3–5 cm H_2O, bronchoconstriction should not have affected the results.

There were no significant changes in Po_2, Pco_2, or pH of the blood flowing into the lobe during infusion of any of the drugs. The amount of ether evolved did not change during drug infusion which suggests that gross pulmonary edema did not occur (3).

DISCUSSION

The resistance to blood flow through a vessel is dependent on the tensions that develop in the vessel wall and on the pressure distending the vessel. Wall tension may change as a result of nervous stimulation and alterations in the composition of inflow blood or alveolar gas. Vascular distending pressure is dependent on the rate of blood flow and on downstream ("left atrial") pressure. In the present experiments blood and alveolar gas tensions were held constant, and nervous connections were severed. Blood flow and "left atrial" pressure were constant. Therefore, the alterations in vascular resistance measured resulted from changes in vascular tone induced by the drugs and changes in vascular distending pressure, both dependently associated.

Shifts in the midpoint of vascular resistance give a general picture of the predominant changes in vascular resistance that occurred after drug infusion. Changes in arterial and downstream volume and venous and downstream volume provide further information about individual vascular responses. But only by calculating resistance and pressure throughout the pulmonary blood vessels and relating intravascular distending pressure to the individual vascular volumes could an accurate analysis of vessel response be made.

Isoproterenol. Isoproterenol caused active vasodilation in all of the pulmonary vessels without altering the longitudinal distribution of vascular resistance. Resistivity decreased throughout the pulmonary vascular bed during both forward and reverse perfusion. During forward perfusion arterial distending pressure deceased, but arterial volume and conductance increased. This phenomenon can only be explained by active arterial vasodilation. A similar pattern was present in downstream (combined capillary and venous) vessels. During reverse perfusion venous distending pressure decreased, whereas venous volume and conductance increased. This is the picture of active vasodilation. The capillary and arterial vessels responded in the same fashion.

The increase in arterial and venous conductance can be explained by relaxation of vascular smooth muscle, but the explanation for the apparent increase in capillary conductance is not clear. If the capillaries reacted in a purely passive fashion, capillary volume and conductance should have decreased because of the lower downstream distending pressure in the veins (forward perfusion) or the arteries (reverse perfusion). The absence of contractile cells around the capillaries or smooth muscle in the capillary walls makes it unlikely that the individual capillaries could contract or dilate actively (7). The apparent active dilation of the capillary bed might be explained by the opening of capillary vessels distal to arterioles (forward perfusion) or venules (reverse perfusion) which dilated in response to isoproterenol. This type of response is supported by the studies of Wearn, Ernstone, Bromer, Barr, German, and Zschiesche (8) who observed intermittence of blood flow in the pulmonary capillaries as a result of vasomotor changes in the arterioles.

These results indicate that both arteries and

veins are capable of constriction in the isolated lobe preparation. Since isoproterenol decreased resistance in arteries and veins but did not markedly alter the longitudinal distribution of vascular resistance in the lobe, it appears that mechanical factors such as vascular distending pressure rather than vasomotor tone are the most important determinants of the resistance to blood flow in the isolated lung.

Most investigators have found that isoproterenol causes vasodilation in the pulmonary circulation (8, 9). We are unaware, however, of any other studies of the specific pulmonary vessels affected by isoproterenol.

Serotonin. Serotonin caused active constriction of both the pulmonary arteries and veins. During forward perfusion pulmonary artery volume and conductance decreased despite an increase in distending pressure. Both large and small arteries must have constricted because there were large changes in conductance (predominantly attributable to small arteries) and volume (predominantly attributable to large arteries). There was little or no measurable change in the remainder of the vascular bed. A high dose of serotonin caused additional arterial vasoconstriction and a definite decrease in downstream conductance and volume.

During reverse perfusion a low dose of serotonin caused generalized vasoconstriction in the pulmonary veins. There was a slight increase in downstream resistivity and decrease in capillary and artery conductance presumably as a result of arterial constriction. Capillary and artery volume inceased probably as a result of capillary distention caused by constriction of the arterial vessels. A high dose of serotonin caused further venous constriction and rather marked downstream vasoconstriction. The increase in capillary resistivity and large capillary and artery volume change may have resulted from closure of capillaries distal to markedly constricted small veins, a mechanism operating in the opposite direction of that proposed with isoproterenol infusion.

Low doses of serotonin caused active constriction of whichever vessels were upstream, arteries or veins. High doses produced significant constriction of downstream vessels as well. These findings suggest that the environment of the downstream vessels altered the threshold of response to serotonin, or that the concentration of the serotonin in the downstream vessels was less than that in the upstream vessels. The latter possibility is supported by the work of Gaddum, Hebb, Silver and Swan (10) who showed that 20% of injected serotonin can be metabolized in one passage through the isolated lung. Recently Davies and Wang (11) found similar rapid inactivation of serotonin in the intact lung. It is possible that pulmonary metabolism of other drugs may alter downstream vascular responses. Eiseman, Bryant, and Waltuch (12) have shown that norepinephrine, acetylcholine, and serotonin, but not histamine, are metabolized in the isolated lung.

Although it is generally agreed that serotonin causes pulmonary vasoconstriction (8, 13), there is no consensus about which vessels in the lung serotonin affects. Several studies have shown venous constriction (14, 15), whereas others have found predominant arterial constriction (16, 17). Our findings help explain many of the seemingly conflicting results in the literature.

Histamine. Histamine caused predominantly active venous constriction, but changes also occurred in capillary and arterial vessels. During forward perfusion the major response to histamine was in the downsteam vessels. Resistivity increased throughout the capillary and venous vessels, and capillary and venous conductance and volume decreased. The increased intravascular distending pressure transmitted to the lobar arteries caused no change in arterial conductance or volume. If the arteries had responded in a purely passive fashion arterial volume should have increased 10–15% (18). The lack of volume change suggests that there may have been a slight increase in arterial tone which countered the increased distending pressure.

The increased capillary resistivity cannot be explained by closing of capillaries distal to constricted upstream arterial vessels, since these vessels constricted only slightly. Histamine produces an increase in capillary permeability in systemic vessels, probably as a direct action on the capillary wall (19, 20). Such an increase in pulmonary capillary permeability could lead to interstitial fluid accumulation in the pericapillary spaces with compression of the capillary vessels and decrease in capillary volume and conductance.

Reverse perfusion experiments support the above hypothesis. Active venous constriction of

both large and small vessels predominated. Capillary resistivity increased, possibly as a result of pericapillary edema. Total capillary and artery conductance increased slightly. This increase could be explained by large artery constriction producing an increase in small artery distending pressure with a passive increase in small artery volume and conductance.

There is rather general agreement that histamine causes predominant pulmonary venous constriction (8, 21), but associated arterial constriction has been found by some investigators (13). The effect of histamine on the pulmonary capillary vessels has not previously been investigated.

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