Bronchopulmonary Arterial Shunting without Anatomic Anastomosis in the Dog

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ABSTRACT

The effects of bronchial arterial administration of vasoactive substances on the pulmonary circulation were studied by a new technique for selective catheterization of a bronchial artery in intact dogs. In most experiments, this technique permitted pressor agents to be distributed mainly to one lung with smaller amounts to the other lung. The intercostal arteries were avoided, and in all but 2 of 23 experiments only microscopic quantities of injected India ink could be identified in the distributions of the esophageal and mediastinal branches. These studies indicate that serotonin, angiotensin, histamine, and norepinephrine injected selectively into a bronchial artery increase lobar arterial pressure. Since blood flow was constant and left atrial pressure did not change, the increase in pressure suggests active pulmonary vasoconstriction. Additionally, the responses to bronchial and lobar arterial injections of pressor agents were similar. The contribution of bronchopulmonary shunt flow to pulmonary flow was small, since, under conditions of controlled lobar blood flow, changes in bronchial flow elicited by 65–75-mm Hg changes in bronchial arterial pressure produced little if any change in pressure in the perfused lobar artery or small vein. Bronchoconstriction contributed little to the response to bronchial administration of pressor agents, since responses were similar in the ventilated and the collapsed lobe. Injection of vasoflavin dyes into the bronchial artery showed the close proximity of bronchial and pulmonary arteries and confirmed the bronchial arterial origin of the vasa vasorum of pulmonary arteries. No vasa venorum were identified. Although no direct anatomic bronchial artery–pulmonary artery shunt was identified, ascorbic acid and 5-hydroxydopamine diffused rapidly into intrapulmonary arteries from the bronchial artery. These data suggest that the pulmonary pressor response results from passage of the vasoactive agents from the bronchial artery to the lobar artery through the vasa vasorum and by diffusion. Since no vasa venorum were found, pulmonary venoconstriction probably resulted from pressor agents reaching the veins by way of bronchopulmonary shunt flow. These results suggest a mechanism by which pressor substances present or liberated in the bronchial vascular bed can affect tone in the pulmonary vascular bed.

In his Harvey Lecture of 1936, Daly suggested that humoral substances in the bronchial circulation could affect the pulmonary circulation (1). However, responses reported by Daly’s group were weak and observed only after large doses of epinephrine and histamine had been injected into bronchial arteries (2). These early experiments with the bronchial circulation intact could rarely be controlled, because changes in aortic pressure usually altered pulmonary arterial pressure indirectly by varying bronchopulmonary shunt flow (2). In experiments with arrested bronchial blood flow, Daly et al. (3) found that pulmonary pressor responses to bronchial injections of large doses of these agonists were small and were observed in only half of the experiments. Furthermore, the site of vasoconstriction could not be completely established even in experiments with arrested bronchial blood flow. Since bronchopulmonary shunt vessels enter the pulmonary circulation downstream to arteries, mainly in the veins (4), Daly et al. (3) noted that agonists injected via the arrested bronchial circulation could constrict pulmonary veins and passively increase pulmonary arterial pressure. Moreover, since the bronchial circulation supplies the vasa vasorum of pulmonary vessels, Miller (4) and Daly and Hebb (5) suggested that the pulmonary arterial pressor response could result from the direct effect of the agonists on pulmonary arteries without admixture of bronchial and pulmonary blood at the arterial level. The pulmonary venous constriction that Daly et al. (3) reported could be mediated by agonists in either shunted blood, the rarely described vasa venorum, or both (4).
For the present experiments, we designed a technique for selective catheterization of a bronchial artery supplying one lung or the other in the intact anesthetized dog. The catheterization procedure avoided the intercostal arteries and, in most instances, the mediastinal and esophageal branches of the bronchial artery. With other intact-chest catheterization techniques (6), we were able to pump-perfuse the ipsilateral lung lobe at a controlled flow rate. This intact-chest preparation was used in the present paper to study the effects of bronchial arterial injection of vasoactive substances on the pulmonary circulation. These responses were compared with those produced by lobular arterial injection of the same substances. The contribution of bronchoconstriction was investigated by comparing responses in ventilated and nonventilated lobes. Additionally, the effect of changes in bronchopulmonary shunt flow on the pulmonary vascular bed was examined. The mechanism by which the bronchial arterial route of administration affects the pulmonary vascular bed was further studied with ascorbic acid, 5-hydroxydopamine, 6-hydroxydopamine, and vaso-flavine dye.

Methods

Mongrel dogs, 19-26 kg, were anesthetized with sodium pentobarbital (30 mg/kg, iv) and strapped in the lateral right position to a fluoroscopic table. One end of a 50-cm radiopaque 0.9-mm Teflon catheter was heat molded into a 0.5-1.5-cm U shape and fitted into a standard Cordis visceralcfemoral (Cobra) catheter which had been cut to a length of 35 cm (Fig. 1). The Cobra catheter was passed under fluoroscopic guidance from an external carotid artery into the descending aorta. The right intercostal arteries, from which the bronchial arteries arise (7), were easily identified and entered by rotating the Cobra catheter 10-30° counterclockwise, while Hypaque (sodium diatrizoate 50%, Winthrop Laboratory) was injected. Since the aortic origin of the intercostal arteries bears no relation to vertebral levels or intercostal spaces, exploration of intercostal vessels was always begun 1-2 vertebral levels above the tracheal bifurcation and continued to the level of the diaphragm. Generally, three to five right intercostal arteries were catheterized, and Hypaque was injected. The dorsal bronchial arteries to both lungs were readily identified by opacification readily as they originated at right angles from the more cephalad artery having the most favorably positioned bronchial artery. The acute angle at the end of the Cobra catheter easily passed 0.5-1.0 cm into the intercostal artery so that its lumen lay at the orifice of the bronchial artery. As the specially curved Teflon catheter was extended from the Cobra catheter sheath, the U-shaped end easily traversed the right angle bend into the bronchial artery. The bronchial branches to the esophagus, mediastinum, and the lungs could then be clearly identified by selective opacification with Hypaque. Passing the specially curved Teflon catheter around the bronchial arch to the more distal part of the vessel permitted selective injections into the lobar distribution of the bronchial vessel at a point well downstream to most mediastinal and esophageal branches (7). Injected Hypaque passed selectively to the lung lobe without identifiable spillage into the intercostal, esophageal, or mediastinal branches. Selective opacification readily identified the lung lobe primarily supplied by that bronchial vessel. The Cobra sheath was then gently withdrawn around the smaller Teflon catheter into the aorta, and free bronchial blood flow was demonstrated by the rapid disappearance of injected Hypaque (Fig. 2). Bronchial arterial pressure at the catheter tip was about 80% of aortic pressure. The catheter position was confirmed by opacification with Hypaque periodically during the course of the experiments. In most experiments, the distribution of bronchial flow was also studied at autopsy by injecting India ink through the bronchial arterial catheter. Special care was required to hold the catheter in place with a ligature at autopsy, since bronchial arteries could only be located during mediastinal dissection by identifying the in-situ black Teflon catheter.
Dislodgment was rare since the Teflon catheter generally extended 4-6 cm into the bronchial artery, beyond most of the mediastinal and esophageal branches. When it was required, repositioning was easily accomplished by gently passing the Teflon catheter 2-3 cm further into the bronchial artery under fluoroscopy. Although no pulmonary vascular response to an injection of 1-3 ml of Hypaque was observed, we always waited 5 minutes after such an injection before we continued the experiment. The more cephalad bronchial artery was used in 60% of these studies, but no systematic difference in response was noted between the two bronchial arteries.

After the lung which received most of the branches of the catheterized bronchial artery was identified, the arterial inflow to the major part of the lower lobe of that lung was controlled by techniques described previously (6). A specially designed 20F balloon catheter was passed fluoroscopically from an external jugular vein to the appropriate lobar artery. A Teflon catheter with its tip positioned about 2 cm distal to the balloon was used to measure pressure in the perfused lobar artery. Catheters with side holes were passed fluoroscopically into the aorta and the main pulmonary artery. A radiopaque 8F Teflon catheter was passed transseptally into the left atrium and inserted retrograde into the vein from the perfused lobe. A specially prepared 0.9-mm radiopaque catheter with an end hole and two side holes was passed through the larger transseptal catheter and wedged retrograde into a randomly selected small vein in the perfused lobe. The larger transseptal catheter was then withdrawn around the wedged catheter to the left atrium near the venoatrial junction and fixed in position. The smaller wedged catheter was withdrawn until the pressure abruptly fell and then withdrawn an additional 2-3 cm to ensure against wedging. During withdrawal, pulsatile pressure in the small catheter clearly changed from an arterial to an atrial contour, and free flow of injected Hypaque around the catheter tip into the vein and the left atrium was confirmed. Postmortem studies showed that these veins were 2.5-3.0 mm in diameter. The smaller catheter was fixed in place with a Cope adaptor, and both catheters were secured in the jugular vein by compressing hemostats. All vascular pressures were measured with Statham P23D transducers, zeroed at the mid–right atrial level, and mean pressures were recorded on an oscilloscopic recorder (Electronics for Medicine model DR-12). After all of the catheters had been positioned and sodium heparin (500 units/kg, iv) had been administered, the balloon on the perfusion catheter was distended with Hypaque so that flow from the main pulmonary artery to that lobar artery was occluded. Pressures in the occluded lobar artery and the small vein fell to the level of pressure in the left atrium. The vascularly isolated lobe was then perfused by a Sarns roller pump (model 3500) with blood withdrawn from a catheter in the right atrium. In these experiments, an extra length of pump tubing primed with low-molecular weight dextran was used to obtain a pump circuit time of 4.5-8.0 minutes at flow rates of 350-425 ml/min. When necessary, an extracorporeal heating unit was used to maintain the perfusate at body temperature. The flow rate was adjusted so that lobar arterial pressure approximated that in the main pulmonary artery and was not changed throughout the experiment.

A Carlens endobronchial divider (no. 39) was inserted through a tracheostomy and positioned fluoroscopically. The balloon cuffs were carefully distended with Hypaque under direct observation to ensure a proper fit. The divider was periodically checked for leaks by immersing the tubing from one or the other side in water while the contralateral side was inflated. The catheter positions, lung expansion, and the positions of the diaphragms were also monitored fluoroscopically during positive-pressure inflation at 30 cm H₂O and were confirmed at autopsy. Pressure in the pleural space was measured through a Harvard pleural tap introduced without pneumothorax. The lungs were ventilated separately with a dual-cylinder Harvard respirator, the left lower lobe at a stroke volume of 150-175 ml and the right lung at a stroke volume of 250-300 ml at a rate of 25-30 cycles/min. Translobar airway pressure was measured with a Statham differential transducer (PMS9) bridged between the ventilated ipsilateral lobar bronchus and the pleural space. Peak differential airway pressures ranged from 8 to 15 cm H₂O. The lungs were inflated to 30 cm H₂O at 15-20-minute intervals to prevent atelectasis. Spontaneous respiratory movements were abolished with succinylcholine (0.5-2 mg, given slowly, iv).

The data from these experiments were evaluated by methods described by Snedecor for paired and group comparison (8). Values were expressed as means ± se, and significance was taken as P < 0.05. Drugs used were norepinephrine (L-norepinephrine hydrochloride, Sigma), serotonin creatinine sulfate (Sandoz), histamine...
Results

DISTRIBUTION OF THE BRONCHIAL ARTERIES AND THEIR RELATION TO THE INTRAPULMONARY VESSELS

The gross anatomic distribution of the catheterized cephalad bronchial artery was investigated in 14 dogs by injecting 4–8 ml of India ink into the artery and electrically fibrillating the heart 5–10 seconds later with a bipolar electrode catheter. Injection of the ink into this bronchial artery always intensely blackened the entire right bronchial mucosa, the tracheal bifurcation, and the adjacent 2–3 cm of trachea. In 6 dogs, the left bronchial mucosa was also discolored to various extents. In 4 of these dogs gray discoloration was confined to the proximal part of the left bronchial mucosa, but in 2 the entire left lung was blackened. No gross evidence of India ink was seen in the left lung in the other 8 dogs, although, in all, small scattered amounts could be seen in microscopic sections. Selective injection of India ink into the more caudal bronchial artery was made in 9 other dogs. In each of these dogs, the bronchial mucosa in the left lung was blackened; however, the lower lobe was more intensely darkened. In 2 of these dogs the tracheal bifurcation and the proximal part of the right bronchial mucosa were also equally blackened, but in the other 7 the tracheal bifurcation was only grayed to various extents and the right bronchial mucosa was minimally discolored (Fig. 3). Microscopic sections revealed various amounts of India ink in the right bronchial mucosa in all cases. However, in 2 of 23 experiments minimum discoloration of the esophagus adjacent to the tracheal bifurcation was observed. In sections of esophagus taken from 2 dogs without discoloration, only rare scattered particles of India ink were observed with the microscope. Discoloration of the intercostal muscles with India ink was not seen in these studies.

LOBAR RESPONSES TO SELECTIVE INJECTIONS IN THE BRONCHIAL ARTERY AND THE LOBAR ARTERY

The anatomy of the bronchial arterial tree as well as the selectivity of the catheterization procedure sometimes differed within the group of dogs studied. Despite these possible differences, the effects of bronchial arterial injections of vasoactive agents on pressure in the perfused lobar artery and vein were studied and compared with responses obtained when these agents were injected into the lobar artery. In each of six dogs, injections into the bronchial artery of serotonin, histamine, norepinephrine, and angiotensin were made in a random sequence in doses of 3, 10, and 30 μg. The increases in pressure in the lobar artery and the small vein.
were significantly greater with lobar arterial injections than they were with bronchial arterial injections of serotonin and larger doses of norepinephrine (Fig. 4), but they were similar with angiotensin and histamine (Fig. 5). Changes in aortic pressure produced by selective bronchial arterial injection of the 30μg dose of these agonists were as follows: serotonin 124 ± 7 mm Hg (control) to 109 ± 7 mm Hg (P < 0.05), norepinephrine 121 ± 6 mm Hg (control) to 168 ± 9 mm Hg (P < 0.05), angiotensin 116 ± 7 mm Hg (control) to 168 ± 8 mm Hg (P < 0.05), and histamine 105 ± 3 mm Hg (control) to 78 ± 8 mm Hg (P < 0.05). However, with each of the four agents, the lobar vascular response from the two injection sites was qualitatively similar in that serotonin and norepinephrine increased pressure more in the lobar artery, histamine increased pressure more in the small vein, and angiotensin increased pressure only in the lobar artery. Pressure in the left atrium was unchanged by these agents. Similar segmental lobar vascular responses have been documented with lobar arterial injection of these agonists in experiments using the intact-chest perfusion technique (9, 10), the open-chest perfusion technique (3, 11-16), microscopic study of rapidly frozen lung (17), and isolated vascular smooth muscle strips (18).

CONTRIBUTION OF BRONCHOCONSTRICTION TO LOBAR VASCULAR RESPONSES TO BRONCHIAL ARTERY ADMINISTRATION OF PRESSOR AGENTS

Vasoactive hormones selectively injected into the bronchial artery increased lobar arterial pressure, but some also increased peak translobar airway pressure. The possibility that bronchoconstriction might have contributed passively to the increase in lobar arterial pressure was evaluated by injecting agents selectively into the bronchial artery while the lobe was ventilated by positive pressure and while the bronchus was occluded. Three of these dogs, selected randomly, were first ventilated with oxygen for 20-30 minutes before a control injection of pressor hormones was made. A Dotter-Lukas 8F balloon catheter was then passed fluoroscopically into the bronchus of the perfused lobe, and the balloon was distended to occlude the bronchus for 20 minutes. Bronchial gas was withdrawn with a syringe. Translobar airway pressure was measured between the occluded bronchus through the Dotter-Lukas catheter end hole and the pleural space with a Statham differential transducer. The pressor responses were again determined with the selective injection of these agonists, and the responses were compared in the respiring and the nonrespiring lobe. In the other half of the dogs, the initial injections were made while the bronchus was occluded and then after the bronchial balloon catheter had been removed and the reinflated lobe ventilated with oxygen for 10-15 minutes.

Injection of serotonin (50μg) and histamine (30μg) into the bronchial artery increased both lobar arterial and translobar airway pressure during positive-pressure ventilation. However, similar increases in lobar arterial pressure occurred with the bronchus occluded. Furthermore, the increase in airway pressure during ventilation was not always

**FIGURE 4**

Comparison of increases in pressure in the lobar artery and small vein produced by injection of serotonin and norepinephrine into the bronchial artery and the lobar artery. The increases in vascular pressure produced by lobar arterial administration of serotonin and larger doses of norepinephrine were significantly greater than the responses produced by bronchial arterial administration of these agents. An asterisk indicates a significant difference (P < 0.05) between the injection sites.
Comparison of responses to angiotensin and histamine when they were injected into the bronchial artery and the lobar artery. The response to histamine injected at the two sites was similar (except for the increase in venous pressure with the 3-μg dose). Pressor responses to angiotensin injected at the two sites were also similar. Injection of these substances into the bronchial or lobar artery did not increase pressure significantly in the small vein. An asterisk indicates a significant difference (P < 0.05) between the injection sites.

Measurement of pressure in the small vein was omitted in these experiments, since the position of the catheter in the small vein might have been altered by collapse of the lobe. However, in three other experiments with serotonin (50 ng) and two with histamine (30 μg), pressure in the lobar small vein was measured before and immediately after ventilation in the ipsilateral perfused lobe was stopped without inserting a bronchial occluding balloon catheter. In these experiments, similar increases in pressure occurred in the lobar small vein as well as in the lobar artery with ventilation and with arrested ventilation. With serotonin, the pressure in the small vein increased 3, 4, and 4 mm Hg with positive-pressure ventilation and 3, 4, and 4 mm Hg after ventilation was arrested. With histamine, the pressure in the small vein increased 4 and 3 mm Hg with ventilation and 4 and 3 mm Hg after ventilation was arrested. Previous studies have also indicated that bronchoconstriction contributes little to pulmonary vascular responses to vasoactive agents injected into a perfused lobar artery (9, 11, 19–23).

**Figure 5**

Increases in lobar arterial pressure and peak translobar airway pressure elicited by selective bronchial arterial injection of hormones while the lobe was ventilated by positive pressure and while ventilation to the lobe was arrested by airway occlusion. During positive-pressure ventilation, peak translobar airway pressure was increased significantly by serotonin and histamine but not by norepinephrine and angiotensin. However, lobar arterial responses were similar in the ventilated and the nonventilated lobe. Peak translobar airway pressure was not significantly increased by the hormones when ventilation was arrested. An asterisk indicates that pressure was increased significantly. V indicates the ventilated lobe whereas O indicates that the lobar bronchus was occluded.

**Figure 6**

Increases in lobar arterial pressure and peak translobar airway pressure elicited by selective bronchial arterial injection of hormones while the lobe was ventilated by positive pressure and while ventilation to the lobe was arrested by airway occlusion. During positive-pressure ventilation, peak translobar airway pressure was increased significantly by serotonin and histamine but not by norepinephrine and angiotensin. However, lobar arterial responses were similar in the ventilated and the nonventilated lobe. Peak translobar airway pressure was not significantly increased by the hormones when ventilation was arrested. An asterisk indicates that pressure was increased significantly. V indicates the ventilated lobe whereas O indicates that the lobar bronchus was occluded.

**Effect of Changes in Bronchial Arterial Pressure on Pressure in the Perfused Lobar Artery**

In 13 dogs, changes in thoracic aortic pressure were produced by distending an intra-aortic balloon and by injecting norepinephrine and angiotensin into the aorta. In these dogs, blood flow in the artery to the right (7 dogs) or left (6 dogs) lower lobe was maintained constant with the balloon.
perfusion catheter technique described in the Methods, but selective catheterization of a bronchial artery was omitted. An 8F Dotter-Lukas double-lumen balloon catheter (U.S. Catheter and Instrument Co.) was passed fluoroscopically from the femoral artery retrograde until the balloon was just proximal (upstream) to the intercostal arteries. Aortic pressure was monitored both proximal and distal to the balloon. Fluoroscopic monitoring confirmed that the large, fairly rigid catheter prevented distal migration of the balloon during distention with Hypaque in 12 of 13 dogs. In the other dog in which distal migration occurred, the catheter was reinserted from a carotid artery and held manually during balloon distention. In these dogs, changes in aortic pressure were produced by distending the balloon carefully to avoid changes in pressure in the left atrium. Mean pressure in the aorta upstream to the balloon increased from $135 \pm 6$ mm Hg to a peak value of $197 \pm 7$ mm Hg during a 0.5-3-minute period of balloon distention, and pressure in the section of the aorta from which the bronchial arteries originated fell to $29 \pm 4$ mm Hg. In 10 dogs, pressure in the perfused lobar artery and small vein was unchanged (Fig. 7). In 3 dogs, pressure in the small vein decreased for 8-10 seconds and then returned to the control value, but the fall never exceeded 1.0 mm Hg. Lobar pressures were unaffected by collapsing the balloon. The balloon was then moved under fluoroscopic guidance to the level of the diaphragm so that the origin of the bronchial arteries was upstream from the balloon. Under these conditions, balloon distention increased thoracic aortic pressure from $128 \pm 4$ mm Hg to a peak value of $171 \pm 9$ mm Hg. The increase in bronchial arterial pressure did not affect lobar arterial and venous pressure in the 10 dogs in which these pressures were unchanged by decreasing bronchial arterial pressure. In the 3 other dogs, pressure in the small vein decreased for 8-10 seconds before returning to the control level. However, lobar arterial pressure was unchanged. Left atrial pressure was also unchanged by intra-aortic balloon distention.

In four dogs norepinephrine (10 $\mu$g) was injected into the aorta below the diaphragm, and in five other dogs angiotensin (30 $\mu$g) was injected. In these nine dogs, the pressor hormones increased aortic pressure from $130 \pm 7$ mm Hg to a peak value of $205 \pm 8$ mm Hg. In seven of these dogs, no change in lobar arterial or venous pressure occurred. In the other two dogs, in which aortic pressure rose 67 mm Hg with norepinephrine and 86 mm Hg with angiotensin, pressure in the lobar small vein rose less than 1.0 mm Hg for 6-12 seconds and then returned to the control level. Pressure in the lobar artery and the left atrium was, however, unchanged.

**RELATION OF SMALL BRONCHIAL ARTERIES TO LOBAR ARTERIES**

Since the mechanism by which bronchial arterial administration of pressor hormones affects the
pulmonary circulation is unclear, additional experiments were done to detect substances injected into the bronchial arteries in intrapulmonary arteries and veins. The relation of the bronchial artery to the lobar vessels was studied in three intact anesthetized dogs with vasoflavine, a nontoxic fluorescent dye which has a strong affinity for the endothelium of blood vessels but which diffuses poorly (24). Selective injection of 4–6 ml of the vasoflavine solution was made into the catheterized bronchial artery; at thoracotomy 20–30 seconds later, portions of the ipsilateral lower lobe were rapidly removed and frozen in liquid nitrogen. Photomicrographs of sections under ultraviolet illumination revealed intense yellow fluorescence throughout the bronchial mucosa and the peribronchial connective tissue. Bronchial arteries and the vasa vasorum in the wall of lobar arteries as small as 300 \mu m exhibited intense yellow fluorescence, but no vasoflavine dye was seen in the lumen of the lobar arteries (Fig. 8). The close proximity of smaller bronchial and lobar arteries with minimum adventitial separation was also evident (Fig. 9). Vasa venorum were not seen in the lobar veins, but a less intense greenish fluorescence characteristic of vasoflavine diluted with blood was evident in the lumen of these vessels. This finding suggests that the dye reached the veins via a bronchopulmonary shunt and not through the vasa venorum. The lobar veins, unlike the lobar arteries, were not located immediately adjacent to the bronchial arteries.

**DIFFUSION FROM THE BRONCHIAL CIRCULATION TO THE LOBAR ARTERY**

Ascorbic acid was used in six dogs to detect diffusion of physiological substances across the bronchial arterial wall to the lobar artery. The cephalad bronchial artery was studied in four dogs and the caudal in two dogs. Platinum electrode catheters (4F) were positioned fluoroscopically in the wedged position in the ipsilateral lobar artery and in the main pulmonary artery. Catheterization and vascular isolation of the lobe were omitted in these dogs. The low-impedance d-c input circuit connected to the Electronics-for-Medicine recorder was used for detection of the ascorbic acid signal at the platinum electrode. Freshly dissolved ascorbic acid (10–30 mg in 0.1–0.3 ml of saline) was injected into the bronchial arterial catheter (0.5–0.8 ml volume), and the catheter was rapidly flushed with 5.0 ml of saline. In each experiment, the ascorbic acid was detected by the wedged catheter within 1–3 seconds after injection but was not detected by the catheter in the main pulmonary artery (Fig. 10). In three of the four experiments with the cephalad bronchial artery, the wedged catheter was changed from the ipsilateral lobar arterial wedge position to the contralateral
Photomicrograph of a small lobar artery, bronchial arteries, and a small bronchus obtained after vasoflazine dye had been injected into the selected bronchial artery. The intensely staining particles are in the vasa vasorum in the lower edge of the lobar artery. Intense fluorescence was also seen in the bronchial mucosa and the small bronchial arteries. The proximity of the small bronchial and lobar arteries is apparent. Bar in the lower right corner of the top section is 100 μ. A. and a. = artery.

lower lobe wedge position; the ascorbic acid injection was then repeated. A prompt signal from the contralateral wedge position was detected in only one of these dogs. A prompt signal was not detected in the contralateral lung with two injections into the caudal bronchial artery. India ink injection in this group revealed extensive bilateral mucosal blackening only in the one cephalad bronchial
arterial experiment with rapid ascorbic acid signals appearing bilaterally. The other dogs had almost complete lateralization of the India ink. The wedged catheters were in lobar arteries approximately 2-2.5 mm in diameter.

**SELECTIVE INJECTION OF 5-HYDROXYDOPAMINE AND 6-HYDROXYDOPAMINE**

These agents, which liberate norepinephrine from adrenergic nerve terminals, were selectively injected into the bronchial artery to evaluate the vascular response of the ipsilateral perfused lobe. The long extracorporeal pump tubing delayed the blood withdrawn from the right atrium from reaching the lobar artery for 6.0-6.5 minutes in these dogs. Selective bronchial arterial injection of 3.0 mg of 6-hydroxydopamine in six dogs significantly increased mean pressure in the perfused lobar artery from 18.2 ± 1.0 mm Hg to 22.2 ± 0.8 mm Hg and pressure in the small vein from 10.4 ± 0.57 mm Hg to 12.4 ± 0.4 mm Hg. Aortic pressure increased significantly from 117 ± 9 mm Hg to 153 ± 16 mm Hg. Pressures began to rise about 30-40 seconds after the bronchial arterial administration of the drug and reached a plateau in 2.5-3.5 minutes. Pressures gradually returned to the control value. Left atrial and translobar airway pressures were unchanged. A similar rapid response to 6-hydroxydopamine in the sinus node artery has been reported (25). The possibility of a direct pulmonary vasoconstrictor effect of 6-hydroxydopamine was investigated in three of these dogs by repeating the injection of 3.0 mg of the drug into the bronchial artery 1.5-2.5 hours after the initial injections. In these three dogs, lobar arterial pressures were unchanged by the second injection of 6-hydroxydopamine.

In six other dogs, similar increases in lobar arterial and venous pressure were elicited by bronchial arterial administration of 2-3 mg of 5-hydroxydopamine, an agent which is taken up and liberates norepinephrine without destroying nerve terminals. Lobar arterial pressure rose from 16.6 ± 0.9 mm Hg to 20.8 ± 1.0 mm Hg, and venous pressure increased from 9.2 ± 0.5 mm Hg to 11.1 ± 0.6 mm Hg. Aortic pressure increased from 121 ± 9 mm Hg to 158 ± 16 mm Hg. Portions of the perfused lung lobe were obtained for electron microscopic study in another dog in which a similar selective bronchial arterial injection of 3 mg of 5-hydroxydopamine had been made. Five minutes after injection, the lobe was fixed in situ by changing the perfusate from blood to 3% glutaraldehyde in Millonig’s phosphate buffer. The thorax was then opened, and tissue blocks containing intralobar vessels were removed for electron microscopy. Many adrenergic varicosities in the wall of intralobar arteries were found to contain many vesicles with expanded dense cores, suggesting that 5-hydroxydopamine was taken up by these adrenergic terminals (Fig. 11). Similar vesicles with enlarged cores were found in adrenergic varicosities in lobar veins, bronchial arteries, and bronchial airway smooth muscle. In control dogs not receiving 5-hydroxydopamine, vesicles of adrenergic varicosities contained very little dense-core material (Fig. 12). Similar findings from the cat iris and the rat vas deferens have been reported (26).
FIGURE 11

Electron micrograph of an intralobar artery after injection of 5-hydroxydopamine into a bronchial artery. Adrenergic varicosities in the wall of the intralobar artery were found to contain many vesicles filled with electron-dense material, suggesting that the 5-hydroxydopamine was taken up into these vesicles. Similar vesicles were found in the adrenergic terminals in bronchial smooth muscle, bronchial arteries, and pulmonary veins. The bar in the lower right corner is 1μ. A indicates adrenergic varicosity, and SM is smooth muscle.

FIGURE 12

Electron micrograph of an intralobar artery in a control dog that did not receive a 5-hydroxydopamine injection, showing vesicles of adrenergic varicosities containing very little dense-core material. The bar in the lower right corner is 1μ. A indicates adrenergic varicosity, and SM is smooth muscle.
Discussion

Studies of the bronchial circulation in open-chest dogs require extensive surgery for cannulation of vessels (1, 21, 27-30). Previous methods of selective bronchial arterial administration of vasoactive hormones generally include esophageal and mediastinal branches and, to some degree, the intercostal artery (31). The present study describes a simple intact-chest technique for investigating the effects of selective bronchial arterial injection of vasoactive substances on the pulmonary circulation. Cephalad or caudad dorsal bronchial arteries were rapidly and selectively catheterized with small Teflon catheters, excluding the intercostal arteries and, in most instances, the esophageal and mediastinal branches. In 80% of the dogs, the catheter tip was positioned so that contrast material passed selectively to one lung or the other. At autopsy, India ink was distributed in the same manner. Lateralization of the injected material into the bronchial artery might still have been incomplete, since microscopic sections of the contralateral bronchial mucosa generally revealed small numbers of ink particles. Alternatively, small particles in the contralateral lobe might have come, in part, from recirculation by way of the left heart, aorta, and bronchial circulation. In the other dogs, ink injected into the bronchial artery was largely distributed to both lungs. Albeit, this technique differs from earlier methods for selective bronchial arterial catheterization in that it prevents overflow of the injected substance into intercostal arteries and, in most instances, avoids overflow into esophageal and mediastinal vessels (2, 27-31).

These studies in intact dogs indicate that vasoactive hormones selectively injected into the bronchial artery increase pressure in the perfused lobe. Since blood flow to the lobe was held constant and left atrial pressure was unchanged, the increase in lobar arterial pressure reflects an increase in vascular resistance in the lung. The observation that increases in lobar arterial pressure in response to pressor hormones injected into the bronchial artery were similar whereas responses to serotonin and norepinephrine were somewhat smaller when they were injected into the bronchial artery as opposed to the lobar artery, the relative concentration of agonist arriving at the site of action may be different. The reason for the difference in concentration is that even though the same dose of agonist was injected into bronchial and lobar arteries, the rate of blood flow in the two vessels differed by several orders of magnitude. Hence, the concentration of drug at the site of action and the period of time spent at the “receptor” may have differed greatly. In addition, it is known that changes in pressure in the aorta, pulmonary artery, and right or left atrium can affect the distribution of bronchial blood flow (30). Therefore, comparison of responses obtained by the two routes of administration is difficult. Previous reports of experiments in intact dogs have been directed toward defining the site of action of these agents when they are infused or injected into the pulmonary vascular bed (9-16). Those data suggested that angiotensin constricts vessels upstream to the small veins, presumably small arteries, that histamine constricts predominantly veins, and that norepinephrine and serotonin constrict both vascular segments. The present data are consistent with these interpretations and extend the earlier findings by showing that bronchial arterial administration of these hormones causes a similar pattern of response in the pulmonary vascular bed.

The magnitude of the lobar pressor response to bronchial arterial injection in our intact dogs differed from that found in previous studies by Alcock et al. (2) in dogs subjected to thoracotomy. In two of these previous experiments in which the bronchial circulation was intact, selective injection of large doses of epinephrine into the bronchial circulation caused a small increase in pulmonary arterial pressure, but large doses of histamine had no effect (2). Administration of similar doses of these agents into the pulmonary artery produced large increases in pressure (2). With bronchial flow arrested, selective bronchial arterial injection of 0.5-1.0 mg of these agents was required to obtain 1.0-1.5-mm Hg increases in pulmonary arterial pressure, but much larger pulmonary pressor responses were elicited by injection of about 10% of that dose into the pulmonary artery (3). Furthermore, bronchial injection of these substances produced pressor responses in only half the experiments (3). The greater response to bronchial arterial administration of much smaller doses of agon-
ists in the present study compared with the minimum response to much larger doses in earlier studies was probably due in part to more selective administration of these agents. Additionally, surgical trauma to the lung and vessels was avoided, lobar vessels were not cannulated, and blood flow was within the physiological range. Most other studies of vasoactive agents in the bronchial circulation have been confined to the effects of these agonists on the airways or to effects on bronchial blood flow and distribution of bronchial blood flow (3, 27-31).

Changes in bronchopulmonary shunt flow resulting from alterations in aortic pressure probably did not contribute to responses observed in the present experiments. Moreover, the present studies with controlled blood flow in dogs with their chests intact indicate that changes in the aortic pressure of 65-75 mm Hg produced by intra-aortic balloon distention or intra-aortic injection of vasoconstrictor agents have little if any effect on lobar arterial pressure. Additionally, pressure in the small vein was altered in only 3 of 13 dogs, and in these dogs the changes were less than 1.0 mm Hg and persisted for less than 12 seconds. The small inconsistent pressure changes might have been due to changes in bronchopulmonary shunt flow, since shunted blood drains into the small pulmonary veins (2). However, earlier studies indicated that sharp rises in aortic pressure and thus bronchial perfusion pressure produce a complex spectrum of changes in pulmonary arterial pressure (2). The response was usually pressor but occasionally depressor or, more rarely, biphasic; in only 2 of 26 experiments was pressure unchanged (2). These alterations in pulmonary arterial pressure were generally considered to be passively mediated by variations in bronchopulmonary shunt flow induced by changes in aortic pressure (2). Active mediation of pulmonary pressor responses to vasoactive agents injected into bronchial vessels in those experiments could only be detected when bronchial blood flow was surgically occluded or in infrequent preparations in which pulmonary pressure was found to be unaffected by changes in aortic pressure (2, 3). The reason for the absence of larger consistent changes in lobar arterial pressure in intact dogs in the present experiments may largely be due, as Daly and Hebb (5) inferred, to the greater ratio of pulmonary to bronchial blood flow which could obscure responses to small changes in shunt flow.

Lobar arterial responses to bronchial arterial administration of pressor agents are unlikely to be mediated passively by increases in pulmonary venous pressure, since angiotensin increased pressure in the lobar artery without changing pressure in the small vein. Additionally, arterial pressor responses to serotonin and norepinephrine are most likely due to active constriction of small arteries for the most part, since the increase in lobar arterial pressure was greater than the increase in venous pressure and the pressure gradient between the two segments increased. The site of action and the relative contribution of passive factors to similar responses to pulmonary arterial administration of vasoactive substances have been reported previously (11-17, 23, 32).

The route by which vasoactive substances injected into the bronchial artery reach the pulmonary vessels is not established. However, vasoflavine dyes injected in intact dogs demonstrated that bronchial arteries supply the vasa vasorum of the pulmonary arteries as small as 300 μ and showed the close proximity of the bronchial and lobar arteries. Furthermore, the data indicate that ascorbic acid and 5-hydroxydopamine readily pass from the bronchial artery to the pulmonary arterial wall even though no anatomic shunts could be found in intact-chest experiments with vasoflavine dyes or in earlier postmortem injection studies (4). The present data suggest that the active vasoconstriction results from passage of pressor hormones from the bronchial artery to the lobar artery through the vasa vasorum. In addition, the close proximity may suggest that some direct passage from vessel to vessel may also occur. Since no vasa venorum were found, pulmonary venoconstriction probably resulted from vasoactive substances reaching pulmonary veins by way of bronchopulmonary flow after injection into the bronchial artery. The present data indicate that catecholamines and agents which release norepinephrine from adrenergic terminals as well as other vasoactive substances in or liberated in the bronchial circulation may actively constrict lobar vessels (33). These data suggest that the increase in pulmonary vascular resistance in response to sympathetic nerve stimulation may be mediated in part by release of transmitter from nerve terminals in the bronchial vascular bed (34). Moreover, the data suggest a mechanism for the pulmonary vasoconstrictor response to other vasoactive substances in the bronchial circulation (29).

References


Circulation Research, Vol. 37, September 1975
Bronchopulmonary arterial shunting without anatomic anastomosis in the dog.
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doi: 10.1161/01.RES.37.3.285

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