Effects of Drugs on the Pulmonary Circulation and Ventilation as Reflected by Changes in the Arterial Oxygen Saturation

By Albert H. Niden, M.D., Benjamin Burrows, M.D., and William R. Barclay, M.D.

Numerous investigators have demonstrated arteriovenous communications normally present in both human and animal lungs. Arteriovenous shunts have also been implicated in such pathologic states as primary and secondary polycythemia, sickle cell anemia, and patent ductus arteriosus. The dynamic behavior of these anastomoses has been discussed in a previous report suggesting that these channels open following pulmonary embolization. Recently, Garcia Ramos and Rudomin produced changes with drugs and nerve stimulation in the peripheral arterial oxygen saturation in experimental animals. In their experiments, the oxygen percent saturation of arterial blood (SaO₂) of the dog was measured with a cuvette oximeter, while the blood oxygen saturation of the rabbit was monitored with an ear oximeter. Results were similar in both dogs and rabbits; epinephrine or direct sympathetic nerve stimulation produced a fall in SaO₂ and acetylcholine or vagal stimulation resulting in an increase in SaO₂. These same investigators attempted to control cardiac output in some experiments with direct ventricular stimulation. Although no data are presented, results were said to be the same whether ventilation was controlled, total ventilation varied, or the animals ventilated with 100 per cent oxygen. Garcia Ramos and Rudomin thus concluded that there was a "double vascular system" in the lung (i.e., arteriovenous shunts) under nervous control. Initial studies of the present investigation confirmed that administration of various drugs changed SaO₂. There are several possible mechanisms by which such changes might occur. These include: (1) changes in ventilation (both volume and distribution); (2) changes in the diffusion of oxygen from the alveolus to the blood; (3) changes in perfusion, either over-all, local, or both; (4) opening or closing of arteriovenous anastomoses; (5) artefacts in the response of the oximeter photocells, either due to acute changes in the blood, blood hematocrit, or in the flow of blood.

To elucidate the mechanisms of the arterial oxygen saturation changes noted and to determine the role, if any, of arteriovenous shunting, experiments were designed in which each of the factors mentioned above could be assessed independently.

Methods

Twenty-four experiments were conducted on mongrel dogs varying in weight from 10 to 22 Kg. Morphine sulfate (2 mg./Kg.) and chloralose (70 to 100 mg./Kg.) were the anesthetics usually used. (Pentobarbital, 25 to 35 mg./Kg., was used in a few experiments without a difference in response.) Mepesulfate* (35 to 50 mg./Kg.) was used for anticoagulation. The trachea was cannulated routinely. The perfusion pump was primed with whole blood or gelatin. When necessary, artificial respiration was maintained at +5 to +15 cm. H₂O with a Harvard constant volume respirator, and intratracheal pressure was measured with a Statham strain gage transducer. Spontaneous respiration was monitored with a pneumograph. Pressures in a carotid artery, pulmonary

*Generously supplied by Dr. M. J. Schiffrin, of Hoffmann-LaRoche, Inc.
†Generously supplied by Dr. James Dugger, Upjohn Company.
artery, and in the perfused pulmonary artery were measured with Statham strain gage transducers after insertion of appropriate catheters into the carotid artery, into the pulmonary artery via right heart catheterization, or into the perfused pulmonary artery through a glass cannula, respectively. All pressures were recorded on a Grass polygraph. Peripheral arterial blood oxygen concentration saturation was measured continuously from 1 femoral artery with a Wood-type cuvette oximeter and recorded on an Esterline Angus recorder. Both single and double scale readings were obtained. In the isolated lung experiments, mixed venous blood was obtained from the right atrium of a donor dog. This blood was perfused at a constant rate by a Dale-Schuster pump through the experimental lung via a glass cannula tied into the main pulmonary artery. After collection of the left atrial outflow into a reservoir, the blood was returned to the donor dog via the femoral artery (fig. 1B). A portion of the left atrial outflow was continuously diverted through a cuvette oximeter before being collected in the reservoir. In the innervated (intact) lung perfusions, a plastic cannula was tied into the right atrium of the experimental dog. From this, mixed venous blood was freely collected into a reservoir and perfused at a constant rate by a Dale-Schuster pump through a plastic cannula tied into the main pulmonary artery (fig. 1A). The pulmonary artery cannula was inserted through a trocar placed into the right ventricle. All drugs were injected into the femoral vein (intact animal) or pulmonary artery (perfused lung).

**Results**

**Intact Dog**

In the intact animal, L-epinephrine (5μg./Kg.), acetylcholine (5μg./Kg.), histamine (5μg./Kg.), aminophylline (5mg./Kg.), and serotonin (5μg./Kg.) produced acute, transient, and significant changes in the arterial oxygen saturation when injected intravenously. Epinephrine (table 1, fig. 2A) produced an average fall in SaO₂ of 5 per cent in 6 dogs. A total of 16 responses ranged between −1 and −12 per cent. A diphasic response was rarely observed. Of the drugs tested (vide infra), epinephrine was most consistent and effective in producing a decrease in the peripheral arterial oxygen saturation. Frequently, associated with the fall in SaO₂ was an initial period of respiratory depression, occasionally apnea, often followed by a brief period of respiratory stimulation (fig. 3). However respiratory depression was not essential to the observed changes in SaO₂ (fig. 2A). Epinephrine also produced an increase in both the carotid artery and pulmonary artery blood pressures.

Histamine caused a decrease in SaO₂ averaging 2.9 per cent (table 1, fig. 4A). Nine injections in 6 dogs resulted in changes ranging between −9.5 and +1 per cent. Respira-
A. B. C.

Figure 2

Effect of l-epinephrine on the peripheral arterial oxygen per cent saturation of the intact dog, 90 µg. of l-epinephrine injected intravenously: A. Typical response in an intact dog breathing spontaneously. B. Same dog while over-all ventilation was constant with artificial respiration. C. Same preparation used on dog breathing 25 per cent oxygen with total ventilation constant. For this and subsequent figures (unless otherwise noted): PAP = pulmonary artery blood pressure; Resp. = respiration; ITP = intratracheal pressure; O2% Sat. = peripheral arterial oxygen per cent saturation. All time intervals are 15 seconds apart. All drugs injected at the arrow.

tory depression with occasional apnea closely paralleled the observed SaO2 changes. Pulmonary artery blood pressure responses were variable, usually showing a slight rise, but occasionally revealing a fall or a diphase reaction. Systemic hypotension was consistently observed.

Acetylcholine injections resulted in an average fall in SaO2 of 1.3 per cent (table 1, fig. 52%). Eight of 10 responses were between —1.5 and —5 per cent. There was 1 reaction of +3 per cent and, on 1 occasion, no response in SaO2 to acetylcholine. Respiratory depression (with occasional apnea) and systemic hypotension were fairly consistently observed following the administration of acetylcholine. The response of the pulmonary artery blood pressure was variable and quite similar to that of histamine.

Aminophylline, of the drugs tested, was the least consistent in its effect on the SaO2 of the intact animal (table 1, fig. 4B). The number of experiments (6) was admittedly small, with an average decrease in SaO2 of 1.3 per cent. These included 1 reaction of +1 per cent and 1 instance of no response. Aminophylline usually produced a slight fall in the pulmonary artery blood pressure. Its effect on both the systemic blood pressure and respiration was quite variable. The carotid blood pressure response was frequently diphasic, while respiration was either depressed or mildly stimulated. Rarely a diphase respiratory response (depression followed by stimulation) was associated with a diphase SaO2 response paralleling the respiration.

Serotonin, in contrast to the above drugs, produced an average increase in SaO2 of 2.1 per cent in 3 dogs (table 1, fig. 5A). These included 5 responses of +3 per cent, 1 of +2 per cent, and 1 of —2 per cent. Mild to marked respiratory stimulation was observed, often with an initial very brief period of apnea. The apnea was more pronounced in the 1 instance, where a fall in peripheral arterial blood oxygen saturation was noted. The injection of serotonin resulted in an increase in pulmonary artery blood pressure, while the systemic artery blood pressure was quite variable, frequently being diphasic in response.

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Vagotomy in 2 dogs did not alter the subsequent response of the arterial blood oxygen saturation to the drugs tested. The magnitude of the change in $\text{SaO}_2$ was confirmed by periodic double scale cuvette oximeter readings. Artefacts in the response of the oximeter photocells were ruled out by isolated controlled studies on the cuvette oximeter. Blood was perfused through the cuvette oximeter at controlled rates by the Dale-Schuster pump. Neither the injection of drugs in experimental concentrations, nor altering the flow over a wide range (1.0 to 50 ml./min.) had any discernible effect on the oxygen per cent saturation as measured by the cuvette oximeter. In 1 experiment (intact dog) arterial blood samples were collected before and during a drug response. The blood was analyzed in duplicate for oxygen content, oxygen capacity, and oxygen saturation. Simultaneous cuvette oximeter reading revealed a fall in oxygen per cent saturation from 91 to 87 per cent (−4 per cent), as compared to 90.5 to 86.5 per cent (−4 per cent) by Van Slyke determinations.

No acute change in hematocrit of the blood was noted following drug injection.

**Role of Ventilation**

By keeping the volume of ventilation constant with artificial respiration, the effect on arterial oxygen saturation was reduced but not eliminated, even with the chest widely opened (fig. 2B, fig. 6). In 10 dogs, 19 injections of serotonin produced an average increase in $\text{SaO}_2$ of 1.6 per cent; the effect varied between no response (3 instances) and +4.5 per cent. In 14 dogs, l-epinephrine, acetylcholine, histamine and aminophylline (total 112 injections) caused an average fall in $\text{SaO}_2$ of 2.0 per cent. These included 1 response each of +2.5 per cent (histamine), +4.5 per cent (histamine), and +3.5 per cent (aminophylline), 6 instances without significant response, and 103 reactions ranging between −1 and −13.5 per cent. The $\text{SaO}_2$ changes to the individual drugs are presented in table 1.

Decreasing over-all ventilation, by reducing...
Table 1

Summary of Results

<table>
<thead>
<tr>
<th>Drug</th>
<th>Intact</th>
<th>Controlled ventilation intact and open chest</th>
<th>Perfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>-5% ± 3.7%</td>
<td>-0.7% ± 2.8%</td>
<td>-1.5% ± 1.5%</td>
</tr>
<tr>
<td>6 dogs</td>
<td>n=16</td>
<td>14 dogs</td>
<td>n=66</td>
</tr>
<tr>
<td>Histamine</td>
<td>-2.9% ± 3.4%</td>
<td>-1.7% ± 2.6%</td>
<td>-1.4% ± 1.1%</td>
</tr>
<tr>
<td>6 dogs</td>
<td>n=9</td>
<td>11 dogs</td>
<td>n=16</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>-1.3% ± 3.7%</td>
<td>-1.6% ± 1.5%</td>
<td>-2.0% ± 2.5%</td>
</tr>
<tr>
<td>6 dogs</td>
<td>n=10</td>
<td>9 dogs</td>
<td>n=16</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>-1.3% ± 3.5%</td>
<td>-1.8% ± 2.0%</td>
<td>-1.8% ± 1.7%</td>
</tr>
<tr>
<td>5 dogs</td>
<td>n=6</td>
<td>8 dogs</td>
<td>n=14</td>
</tr>
<tr>
<td>Serotonin</td>
<td>+2.1% ± 1.7%</td>
<td>+1.6% ± 1.2%</td>
<td>+1.0% ± 1.5%</td>
</tr>
<tr>
<td>3 dogs</td>
<td>n=7</td>
<td>10 dogs</td>
<td>n=10</td>
</tr>
</tbody>
</table>

n = total number of experiments in each category.

the tidal volume and/or the rate of the artificial respirator, exaggerated the subsequent response to the drugs (fig. 7). This maneuver enhanced the increase in oxygen per cent saturation seen with serotonin, as well as the fall in saturation noted with the other drugs.

With ventilation controlled, epinephrine and aminophylline produced a decrease, while histamine, acetylcholine, and serotonin produced an increase in intratracheal pressure.

Effect of Inspired Oxygen Concentration

Although further reduced, the effect was not eliminated by the administration of 25 or 30 per cent oxygen (fig. 2C). On the other hand, 100 per cent oxygen completely abolished the effect in all the preparations studied, including the perfusion experiments to be described next.

Role of Blood Flow

The possible significance of changes in overall pulmonary blood flow on the peripheral arterial saturation was next studied. Changes in blood flow were controlled by acute, rapid bleeding and transfusing of blood, sudden oc-
elusion of the left main pulmonary artery with a ligature, and increasing or decreasing rate of lung perfusion in the "isolated" as well as "intact" lung. With ventilation maintained constant by artificial respiration, maneuvers increasing pulmonary blood flow caused a decrease in arterial oxygen saturation, whereas those decreasing pulmonary blood flow caused an increase in arterial oxygen saturation. By occlusion of the left main pulmonary artery and increasing the blood flow to the right lung, the subsequent response to all of the drugs tested was exaggerated (fig. 8).

From the above observations, it was apparent that blood flow changes might be a significant factor in the saturation changes noted with drugs. For this reason, 6 isolated lung and 2 innervated lung perfusions were conducted to control blood flow. When both overall ventilation and overall perfusion were kept constant, l-epinephrine, acetylcholine, histamine, and aminophylline still produced a significant fall in oxygen saturation, averaging 1.6 per cent in a total of 58 injections (table 1, fig. 9). These included 1 response of +1 per cent, 12 instances where there was no response, and 45 reactions demonstrating a decrease in \( \text{SaO}_2 \) to as much as \(-8.5\) per cent (1 occasion). The response to serotonin under these conditions was decreased to the range of questionable validity. However, a slight rise in saturation was noted in 11 out of 13 tests, with an average increase in \( \text{SaO}_2 \) of 1.0 per cent (table 1).

With over-all pulmonary blood flow main-
DRUGS ON PULMONARY CIRCULATION

Figure 8

Effect of occlusion of pulmonary artery on subsequent injection of l-epinephrine. Left. One hundred μg. of l-epinephrine were injected into a dog with chest widely opened and ventilation maintained constant. Right. Same dog as on left, with occlusion of the left pulmonary artery. Ventilation altered after occlusion in order to obtain a control SaO₂ identical with the control in the left illustration. At the arrow, 100 μg. of l-epinephrine were injected intravenously.

Discussion

Epinephrine, histamine, acetylcholine, and aminophylline produce an acute transient fall in SaO₂, while serotonin produces a rise. Maintaining over-all ventilation and perfusion at a constant level reduces but does not eliminate the effect. The response is not abolished by the inhalation of 25 or 30 per cent oxygen but is completely eliminated by the administration of 100 per cent oxygen. Thus, the change in arterial oxygen per cent saturation observed with drugs cannot be completely explained by a change in any single parameter studied.

Contrary to the report of Garcia Ramos and Rudomin, the major drug effect appears to be one of changes in over-all ventilation. However, the persistence of the phenomena with artificial ventilation indicates that other factors must have played a role. That the effect was not eliminated with 25 or 30 per cent oxygen suggests that a diffusion defect secondary to marked changes in the capillary bed, alveolar-capillary membrane and/or blood was not the sole explanation.

The degree of desaturation noted while breathing air was such that an anatomic shunt, if present, may have been masked by the administration of 100 per cent oxygen. This might result from the amount of oxygen dissolved in plasma at this high arterial oxygen blood tension (pO₂). Therefore, an anatomic shunt is not excluded by the elimination of the response with 100 per cent oxygen. Thus, on breathing 100 per cent oxygen, direct measurements of pO₂ would be necessary to demonstrate small anatomic shunts due to the relative insensitivity of SaO₂ changes at this range of the oxygen dissociation curve.

The alterations in arterial oxygen saturation noted with changes in blood flow while over-all ventilation was kept constant, confirms the theoretical considerations of Rahn. To our knowledge, this has not previously been demonstrated experimentally. Because of the apparent importance of perfusion changes in
blood oxygenation, it was felt necessary to keep blood flow as well as ventilation constant. In this way, local shunting could be distinguished from changes in the overall ventilation/perfusion ratio. The results indicated that the drugs also produce a significant degree of local shunting. Decreasing the ventilation or increasing blood flow exaggerates the subsequent response to the drugs. As would be expected, by lowering SaO\(_2\) into a steeper portion of the oxygen dissociation curve, these maneuvers would increase the sensitivity of SaO\(_2\) measurements to alterations in ventilation/perfusion ratios from whatever mechanism. This would also explain the findings of Fritts et al.,\(^\text{13}\) who noted a fall in SaO\(_2\) following the intravenous injection of acetylcholine in normal patients breathing 12 per cent oxygen. No change in SaO\(_2\) occurred with acetylcholine in the same individuals breathing room air.

All the drugs tested produce significant bronchomotor as well as vasmotor tone changes which might result in local variations in ventilation out of proportion to perfusion, or vice versa. Although over-all pulmonary ventilation may be controlled by artificial respiration and total lung perfusion maintained constant by perfusion studies, these local phenomena cannot be controlled nor predicted.

This persistence of significant changes in arterial oxygen saturation from drugs while both total ventilation and perfusion were controlled (perfusion studies) indicates either physiologic shunting, i.e., local changes in ventilation/perfusion ratios, or anatomic shunting, i.e., dynamic changes in anatomic arteriovenous communications. It is impossible to separate these phenomena by the techniques used. Although acetylcholine, histamine, epinephrine, and aminophylline each have different actions on the lung, they all produce a similar effect on blood oxygenation. These drugs are known to result in significant ventilatory and circulatory changes in the lung (table 2). Therefore, the results obtained when both over-all ventilation and perfusion were controlled might be readily explained by a local change in the ventilation/perfusion ratios.

However, for the following reasons, we feel that anatomic shunting may also play a role. First, these channels are known to be present morphologically, although their functional

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**Table 2**

<table>
<thead>
<tr>
<th>Drug</th>
<th>CBP</th>
<th>Resp.</th>
<th>ITP</th>
<th>P.A.P.</th>
<th>Perf. P.A.P.</th>
<th>SaO(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Histamine</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Serotonin</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*+ = increase; — = decrease; ± = variable; CBP = carotid artery blood pressure; Resp. = respiration (spontaneous); ITP = intrathoracic pressure (controlled ventilation); P.A.P. = pulmonary artery blood pressure; Perf. P.A.P. = perfusion blood pressure (blood flow constant); SaO\(_2\) = arterial blood oxygen saturation (including intact dog, controlled ventilation, and constant blood flow). See text for more detailed description of responses.

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significance is in question. Second, all the drugs tested have profound circulatory effects and thus could alter these vascular channels—serotonin apparently closing them, the other drugs opening them. Finally, the arteriovenous anastomoses in the peripheral circulation (rabbit’s ear) have been shown to respond dramatically to drugs.14 Regardless of the mechanism involved, these drugs do produce a moderate amount of local shunting of blood in the lungs (either physiologic or anatomic).

Summary

The effect of Z-epinephrine, acetylcholine, histamine, aminophylline, and serotonin on the pulmonary circulation and ventilation was studied in anesthetized dogs. The following observations were noted: Serotonin produced an increase in arterial oxygen saturation, the other drugs a decrease. Although reduced, the effect was not eliminated by controlling the volume of ventilation or by the inhalation of 25 or 30 per cent oxygen. The administration of 100 per cent oxygen eliminated the response in all dogs studied. The effect was not abolished by controlling blood flow in addition to ventilation. Changes in the overall ventilation/perfusion ratio appeared of major importance. In addition, these drugs apparently produced local changes in ventilation/perfusion ratios (physiologic shunting) and/or in the degree of anatomic intrapulmonary shunting of blood.

The effects of changes in pulmonary blood flow on peripheral arterial oxygen saturation were also investigated. With the volume of ventilation constant, the following was observed: Increasing pulmonary blood flow by whatever means decreased SaO₂; decreasing blood flow resulted in an increase in SaO₂.

Acknowledgment

The authors are grateful to Nadia Farid for her technical assistance in this project.

Serotonina produceva un aumento del saturación oxigeno del sanguine arterial, lo altere drogas un redution. Le effecto esseva reducite sed non eliminata per regular le volume del ventilation o per le inhalation de 25 o 30 pro cento de oxigeno. Le administration de 100 pro cento de oxigeno eliminava le response in omne le canes studiate. Le effecto non esseva abolite per un regulation del fluxo de sanguine si ben como del ventilation. Alterationes in le proportion total de ventilation a perfusion pareva esser de importantia major. In plus, le mentionate drogas pareva produce alterationes local del proportion de ventilation a perfusion (shunting physiologic) e/o del grado de anatomic shunting intrapulmonar de sanguine.

Le effectos exercite per alterationes del fluxo de sanguine pulmonar super le saturation oxigenico del sanguine arterial peripherico esseva examinate. In le presentia de un constante volume de ventilation le sequente observationes esseva facilitate: Augmento del fluxo de sanguine pulmonar non importa quale causas reduciva le saturation oxigenico de sanguine arterial. Isto esseva augmentata per un redution del fluxo.

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