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 K. 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. Schiffin, of Hoffmann-LaRoche, Inc.
†Generously supplied by Dr. James Dugger, Upjohn Company.
Perfusion Methods: A. Innervated lung perfusion. $R =$ blood reservoir; $P =$ pump. Oximeter is placed between femoral artery and vein. B. Isolated lung perfusion. $R =$ blood reservoir; $P_1$ and $P_2 =$ pumps.

Results

Intact Dog

In the intact animal, L-epinephrine (5 $\mu$g./Kg.), acetylcholine (5 $\mu$g./Kg.), histamine (5 $\mu$g./Kg.), aminophylline (5mg./Kg.), and serotonin (5 $\mu$g./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 $S_aO_2$ 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 $S_aO_2$ 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 $S_aO_2$ (fig. 2A). Epinephrine also produced an increase in both the carotid artery and pulmonary artery blood pressures.

Histamine caused a decrease in $S_aO_2$ 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-
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 overall 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.

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Drugs on Pulmonary Circulation

A. B. C. SYS. P.

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 overall 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.

Acetylcholine injections resulted in an average fall in O₂% Sat of 1.3 per cent (table 1, fig. 5A). 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 O₂% Sat 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 O₂% Sat of the intact animal (table 1, fig. 4B). The number of experiments (6) was admittedly small, with an average decrease in O₂% Sat 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 diphasic respiratory response (depression followed by stimulation) was associated with a diphasic O₂% Sat response paralleling the respiration.

Serotonin, in contrast to the above drugs, produced an average increase in O₂% Sat 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.
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 SaO₂ 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 SaO₂ 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 SaO₂ 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 SaO₂ 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</th>
<th>Perfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>±</td>
<td>intact and open chest*</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>-5% ± 3.7%</td>
<td>-3.7% ± 2.8%</td>
<td>-1.5% ± 1.5%</td>
</tr>
<tr>
<td>6 dogs</td>
<td>n=16</td>
<td>14 dogs n=66</td>
<td>8 dogs n=20</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 n=16</td>
<td>7 dogs n=11</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>-1.3% ± 1.7%</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 n=10</td>
<td>7 dogs n=11</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 n=14</td>
<td>8 dogs n=16</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 n=19</td>
<td>5 dogs n=13</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 over-all ventilation and over-all 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 SaO₂ 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 SaO₂ of 1.0 per cent (table 1).

With over-all pulmonary blood flow main-
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 over-all 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 SaO₂ into a steeper portion of the oxygen dissociation curve, these maneuvers would increase the sensitivity of SaO₂ measurements to alterations in ventilation/perfusion ratios from whatever mechanism. This would also explain the findings of Fritts et al., who noted a fall in SaO₂ following the intravenous injection of acetylcholine in normal patients breathing 12 per cent oxygen. No change in SaO₂ occurred with acetylcholine in the same individuals breathing room air.

All the drugs tested produce significant bronchomotor as well as vasomotor 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 can not 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 technics 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
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 arterio-
venous anastomoses in the peripheral circula-
tion (rabbit’s ear) have been shown to re-
respond dramatically to drugs.14 Regardless
of the mechanism involved, these drugs do pro-
duce a moderate amount of local shunting of
blood in the lungs (either physiologic or
anatomic).

Summary

The effect of Z-epinephrine, aceetylcholine,
histamine, aminophylline, and serotonin on
the pulmonary circulation and ventilation was
studied in anesthetized dogs. The follow-
ing 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 administra-
tion of 100 per cent oxygen eliminated the response in
some of the cases studied. Le effecto non essere abolite
per un regulation del fluxo de sanguine si ben como
del ventilation. Alterations in the proportion total de
ventilation a perfusion poreva esser de importancia
major. In plus, le mentionate drogas pareva produce
alterationes local del proportion de ventilation a per-
fusion (shunting physiologic) e/o del grado de an-
tomic shunting intrapulmonar de sanguine.

Le effects exercite per alterationes del fluxo de
sanguine pulmonar super le saturation oxygenic del
sanguine arterial peripherie esseva examinate.

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Summario in Interlingua

Essa studiate le effectos producite in le circula-
tion e ventilation pulmonar de anesthetizate cases per
Z-epinephrina, aceetylcholina, histamina, aminophyllina,
e serotonin. Essa facite le sequente observationes:

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