Effect of Regional Hypoxia on the Distribution of Pulmonary Blood Flow in Man

By Vincent Lopez-Majano, M.D., Ph.D., Henry N. Wagner, Jr., A.B., M.D., Ralph H. Twining, A.B., M.D., Donald E. Tow, M.D. and Victor Chernick, M.D.

The observation that hypoxia causes an elevation of pulmonary arterial pressure probably secondary to pulmonary vasoconstriction led von Euler and Liljestrand¹ to suggest that local pulmonary hypoxia might play a role in controlling the distribution of pulmonary blood flow. One method of studying this proposed mechanism in man has been to induce unilateral hypoxia by means of a bronchospirometry catheter. Fishman et al.² gave 10% oxygen in nitrogen to one lung and failed to find a response. However, Himmelstein et al.³ found approximately a 40% decrease in pulmonary blood flow to the hypoxic lung in three out of five subjects when 5% oxygen was administered. A fourth subject had an increased pulmonary artery pressure but no change in the partition of the pulmonary blood flow. The results on the fifth subject were inconclusive. In contrast, Defares et al.⁴ found approximately a 44% decrease in blood flow to the lung breathing 10% oxygen in 10 normal subjects. Fishman⁵ has reviewed the studies of unilateral hypoxia in man and concludes that the bulk of evidence suggests an increased resistance to perfusion on the hypoxic side probably secondary to ipsilateral vasoconstriction.

Cautious interpretation of the experimental findings has been necessary since conclusions regarding pulmonary vasoconstriction have been based on the finding of an increase in pulmonary vascular resistance or a greater increase in pulmonary artery pressure than can be accounted for by increases in cardiac output.⁶ These studies have required cardiac catheterization and arterial cannulation with measurements of cardiac output by the Fick principle. Defares⁴ has analyzed the sources of error in measurements of cardiac output by the Fick method and feels that some of the contradictory results of acute hypoxia in man may be explained on this basis.

The introduction of radioisotope scanning of the lungs has provided a reliable, safe, simple method of determining the distribution of regional pulmonary arterial blood flow in man.⁷ Estimation from the scan of the partition of pulmonary blood flow to each lung correlates closely with oxygen uptake to each lung as determined by bronchospirometry.⁸ An additional advantage is that conclusions regarding pulmonary vasoconstriction are based on the partition of pulmonary blood flow and not on the complicated relationship between pulmonary artery pressure, pulmonary vascular resistance, and cardiac output. Therefore, we have used the lung scan method to study in man the effect of unilateral nitrogen breathing on the partition of pulmonary blood flow.

Methods

Ten patients with various pulmonary diseases were studied (table 1). One hour after premedication with 10 mg morphine, 0.4 mg atropine and 100 mg of pentobarbital given intramuscularly, the oropharynx, trachea and bronchi were anesthetized with topical cocaine. A Carlens catheter was then inserted to permit separation of the ventilation of each lung, and connected to a modified Gaensler-Collins bronchospirometer containing soda lime carbon dioxide absorption cannisters. All studies were done with the pa-
REGIONAL HYPOXIA AND PULMONARY BLOOD FLOW

TABLE 1

Results of Differential Spirometry with Each Lung Breathing 100% Oxygen

<table>
<thead>
<tr>
<th>Diagnosis and lung with major clinical involvement</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Obstructive emphysema and bullous emphysema, right</td>
<td>34 66</td>
<td></td>
</tr>
<tr>
<td>2 Bullous emphysema, left</td>
<td>53 47</td>
<td></td>
</tr>
<tr>
<td>3 Left tuberculous pleural effusion, far advanced tuberculosis, left</td>
<td>69 31</td>
<td></td>
</tr>
<tr>
<td>4 Bullous emphysema, right</td>
<td>30 70</td>
<td></td>
</tr>
<tr>
<td>5 Far advanced pulmonary tuberculosis, bilateral, right</td>
<td>50 50</td>
<td></td>
</tr>
<tr>
<td>6 Far advanced pulmonary tuberculosis, left, welder’s lung</td>
<td>62 38</td>
<td></td>
</tr>
<tr>
<td>7 Lung abscess, left</td>
<td>55 45</td>
<td></td>
</tr>
<tr>
<td>8 Far advanced pulmonary tuberculosis, resection of left upper lobe</td>
<td>75 25</td>
<td></td>
</tr>
<tr>
<td>9 Right tuberc. pleural effusion (r. decortication, 1959), paralysis right diaphragm</td>
<td>49 51</td>
<td></td>
</tr>
<tr>
<td>10 Moderately advanced pulmonary tuberculosis, left</td>
<td>65 35</td>
<td></td>
</tr>
</tbody>
</table>

Patient in the supine position. Initially, both bronchospirometer bells were filled with 100% oxygen. Following initial differential spirometry, one of the lungs was ventilated for seven minutes with 100% nitrogen, while the other continued to be ventilated with 100% oxygen. The adequacy of the airway partition was indicated by the observation that the oxygen uptake/minute remained constant on each side when the bronchospirometer bells were weighted alternately for a short period of time. This was demonstrated both during the control study and during unilateral N₂ breathing. Seven minutes after the onset of unilateral hypoxia approximately 0.5 cc of 1% macroaggregated serum albumen (MAA) labeled with 300 microcuries of I¹³¹ was injected intravenously. The patient was then disconnected from the bronchospirometer and the Carlens catheter removed. A lung scan was performed within the ensuing 1 to 1.5 hours since the distribution of the radioactivity does not change with this short lapse of time. Control lung scans were performed following MAA injection with the patient in the supine position while breathing room air either 24 to 48 hours before or after the unilateral nitrogen study. The control scans were performed without bronchospirometry. Since changes in cardiac output and ventilation have no effect on the distribution of blood flow to each lung, the effect of the Carlens catheter was considered to be negligible. On six occasions additional scans were performed following injection of I¹³¹ MAA at the end of seven minutes 100% oxygen breathing by face mask. In four patients (no. 1, 4, 5, 6) arterial blood was withdrawn during the seventh minute of unilateral N₂ breathing for PaO₂, PaCO₂ and pH determinations.

It was possible that a decrease in the partition of pulmonary blood flow to the lung receiving 100% nitrogen was secondary to an increase on the contralateral side due to 100% oxygen breathing. Therefore, in an additional four subjects the same experimental procedure was followed except that one lung received room air while the more severely diseased lung breathed 100% oxygen. The partition of pulmonary blood flow between the right and left lungs was determined from the scans using the method described by Chernick et al. (fig. 1). The optical density of the radioscan is a nearly linear function of the amount of radioactivity at that locus. Therefore, the optical density of each lung field on the scan is proportional to the distribution of MAA between the two lungs. The average density of each lung field was measured using a photometer with a one-inch porthole in the following manner. The amount of light transmitted (foot-
candles) through nine 1-inch areas of each lung
(I') was compared with a clear area of the
film (I), since:

Transmission (T) = \frac{\text{actual reading}}{\text{control reading}} = \frac{I'}{I}

and density = \log_{10} \frac{1}{T}

The sum of eighteen individual densities was
considered the total density for that lung scan.
The percentage of the total density for each
lung was calculated by comparing the total densi-
ity for each lung to the total density for both
lungs and taken as an index of the percentage
of pulmonary blood flow to each side. Within the
limits of the radioactive count rates obtained
during lung scanning, the relationship between
count rate and film density was nearly linear.
At the time of the readings the observer had no
knowledge of the composition of inspired gas
associated with a particular scan or the results
of bronchospirometry.

Results

Although pulmonary disease was present
in all patients studied, the partition of
oxygen uptake (\%\textsuperscript{O}_{2}) between the right and
left lung was normal in four cases (no. 2, 5,
7, 9, table 1, fig. 2). However, distribution of
pulmonary arterial blood flow between each
lung estimated from the lung scan was normal
in only two cases (no. 5 and 6, table 2, fig. 2).
Nevertheless, in general, good correlation was
found between \%\textsuperscript{O}_{2} obtained by bronchospio-
metry and the scan measurement for each side,
obtained from the control study while breathing air \((r = 0.86; P < 0.01)\). A wide
range of control values for blood flow to each lung was present with either method. Control
scans taken during air and 100% oxygen
breathing showed no significant difference in
the partition of blood flow between the two
lungs (table 2).

The scans done on the four additional pa-
tients during bronchospirometry with one
lung receiving 100% oxygen and the other
lung breathing air showed no consistent effect
on the partition of blood flow. The changes
in per cent flow to the lung receiving oxygen
ranged from +4 to −3% and on the average
there was no significant change from the
control scan.

Unilateral nitrogen breathing was well tol-
erated in all patients with no clinical evidence
of distress or cyanosis. Arterial oxygen ten-
sions during the nitrogen study were 220,
171, 198 and 122 mm Hg for patients 1, 4,
5, and 6 respectively (table 2).

All lungs that were ventilated unilaterally
by nitrogen responded with a decrease in
per cent flow to the ipsilateral side, with an
average decrease of 42% (range 15 to 100%;
table 2, figs. 3, 4). Reduction in per cent flow
occurred regardless of whether 100% N\textsubscript{2} was
given to the more diseased or less diseased
lung. There was no correlation between the
percentage decrease in flow to the N\textsubscript{2} side
and the per cent decrease from the predicted
value found on the control scan for the most
severely involved side, suggesting that the
variability in response to N\textsubscript{2} was not related
to the initial change in per cent flow caused
by lung disease. Five out of six lungs with
an increased control blood flow had less than
a 30% decrease in flow when exposed to 100%
nitrogen. All four lungs which had a decreased
control blood flow responded with more than
a 30% decrease in blood flow upon nitrogen
exposure. This difference was statistically
significant \((P = 0.046)\).

Correlation between per cent oxygen uptake of the
right lung and the per cent pulmonary blood flow
to the right lung measured from the lung scan
\((r = 0.86, P < 0.01)\).
TABLE 2
Per Cent Blood Flow to Each Lung by the Scan Method During Control and Nitrogen Studies

\[
\begin{array}{ccccccccccc}
\text{Exp. no.} & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\
\hline
\text{100\% O}_2 \text{ to both lungs} & 22 & 59 & 66 & 49 & 78 & 61 & 100\% & 73 & 27 & 34 \\
\text{Per cent deviation from predicted flow breathing room air} & R & L & R & L & R & L & R & L & R & L \\
\text{100\% N}_2 \text{ to lung} & 27 & 61 & 66 & 32 & 48 & 56 & 72 & 73 & 34 & 64 \\
\text{Per cent decrease flow in N}_2 \text{ lung} & R & L & R & L & R & L & R & L & R & L \\
\end{array}
\]

\[
\begin{array}{ccccccccccc}
\text{PaO}_2 \text{ (mm Hg)} & 100 & 48 & 34 & 78 & 73 & 54 & 43 & 38 & 28 & 52 \\
\text{PaCO}_2 \text{ (mm Hg)} & 77 & 140 & 168 & 145 & 233 & 148 & 179 & 284 & 238 & 284 \\
\text{pH} & 220 & 171 & 198 & 122 & 220 & 171 & 198 & 198 & 198 & 198 \\
\text{Mean} & 422 & 422 & 422 & 422 & 422 & 422 & 422 & 422 & 422 & 422 \\
\text{±} & 9.9 & 9.9 & 9.9 & 9.9 & 9.9 & 9.9 & 9.9 & 9.9 & 9.9 & 9.9 \\
\end{array}
\]

\[
\begin{array}{ccccccccccc}
\text{Per cent decrease flow in N}_2 \text{ lung} & R & L & R & L & R & L & R & L & R & L \\
\end{array}
\]

*Lung in communication with 100\% \text{N}_2.
†Decrease in flow on the nitrogen side was calculated using the following formula:

\[
Q\% = \frac{Q_1(\%) - Q_2(\%)}{Q_1(\%)} \times 100
\]

\[
Q_1(\%) = \text{percentage of flow from the scan when the lung was breathing room air.}
\]

\[
Q_2(\%) = \text{percentage of flow from the scan when the lung was in communication with 100\% nitrogen.}
\]

For calculating the per cent deviation from predicted breathing air:

\[
Q_1 = \text{per cent blood flow on the control scan while breathing room air.}
\]

\[
Q_2 = 55\% \text{ for the right lung, 45\% for the left lung.}
\]

Discussion

After intravenous injection, macroaggregated albumin particles (MAA) are distributed within the pulmonary arterial circulation in proportion to the blood flow to a particular region. Since these large particles are de-

TABLE 3
Oxygen Uptake (cc/min) During Control and Nitrogen Study

\[
\begin{array}{ccccccccccc}
\text{Exp. no.} & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\
\hline
\text{Oxygen uptake (cc/min)} & R & L & R & L & R & L & R & L & R & L \\
\text{Control*} & 71 & 157 & 84 & 276 & 107 & 251 & 145 & 225 & 179 & 275 \\
\text{N}_2 \text{ study} & 139 & 369 & 276 & 324 & 305 & 275 & 233 & 284 & 196 & 233 \\
\text{Total} & 210 & 546 & 366 & 600 & 521 & 526 & 428 & 568 & 438 & 513 \\
\text{± se} & 257 & 257 & 257 & 257 & 257 & 257 & 257 & 257 & 257 & 257 \\
\end{array}
\]

* Determined during differential spirometry with 100\% oxygen.
†Lung in communication with 100\% nitrogen.
A. Chest radiograph of patient no. 3. B. Control lung scan which indicated 60% flow to the right lung and 34% flow to the left lung. C. Lung scan of same patient receiving 100% N₂ to the left lung. Flow to the left lung measured 3%, a 91% decrease from control.

Deposited within pulmonary blood vessels on their first passage through the lung, their deposition occurs while the pulmonary blood flow is distributed in a particular manner at the time of injection. In this study the effect of gravity was reduced to a minimum by placing the patient in the supine position while the effect of anoxia on the distribution of lung circulation was studied. A scan of the distribution of radio-activity can be done up to several hours later before the particles are broken down and excreted in the urine. Thus, the lung scan yields a picture of the distribution of blood flow at the moment of injection. Since the radioactive particles are distributed in proportion to blood flow, any change in their distribution reflects a change in the regional flow. In four patients we have shown that 100% oxygen administered to the more diseased lung had no significant effect on the distribution of the pulmonary blood flow. There is no conclusive proof for a vasodilating effect of 100% oxygen in patients who do not have hypoxemia and pulmonary hypertension. Since the majority of our subjects had pulmonary tuberculosis, causing local areas of obliterator endarteritis and vascular destruction, one would not expect the uninvolved areas to respond to the high inspired oxygen mixture. Therefore, the de-
A. Chest radiograph of patient no. 5. B. Control lung scan. Flow to the right lung was 48%. C. Lung scan of the same patient receiving 100% N₂ to the right lung. Flow to the lung measured 27%, a 44% decrease from control.

Increased density of the scan on the side that received nitrogen can be explained only by ipsilateral vasoconstriction with a concomitant decrease in per cent flow.

Bronchospirometer tracings from the nitrogen breathing side in our study had a slightly negative slope, even though excreted CO₂ was absorbed, since oxygen was also excreted by that side. Thus, alveolar gas must have been in near equilibrium with mixed venous Po₂ by the end of the seven-minute period of nitrogen breathing. Since arterial Po₂ measurements during unilateral N₂ breathing did not reveal hypoxemia, it is probable that all patients had normal mixed venous Po₂ values around 40 mm Hg. Thus, pulmonary vasoconstriction occurred in the N₂ lung when the pulmonary vascular bed was exposed to an oxygen tension of about 40 mm Hg. This is the usual Po₂ for precapillary vessels but is significantly lower for capillary and postcapillary vessels. Blakemore et al. studied four subjects during unilateral rebreathing of a mixture containing 4.8% CO₂ and 6.7% O₂ in nitrogen and found on the average a 40% decrease in flow to the hypoxic lung. The decrease in flow of 42% in the present study also agrees with the results of Himmelstein et al. using 5% oxygen in nitrogen. It is interesting that a greater response to N₂
TABLE 4
Ventilation (liters/min) During Control Period and During Nitrogen Breathing

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Control* R liters/min</th>
<th>Control* L liters/min</th>
<th>N2 breathing R liters/min</th>
<th>N2 breathing L liters/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.9</td>
<td>7.2</td>
<td>10.1</td>
<td>12.9</td>
</tr>
<tr>
<td>2</td>
<td>6.7</td>
<td>7.6</td>
<td>14.3</td>
<td>14.3</td>
</tr>
<tr>
<td>3</td>
<td>3.3</td>
<td>1.0</td>
<td>4.3</td>
<td>6.6</td>
</tr>
<tr>
<td>4</td>
<td>2.4</td>
<td>5.7</td>
<td>8.1</td>
<td>7.6</td>
</tr>
<tr>
<td>5</td>
<td>5.9</td>
<td>5.1</td>
<td>11.6</td>
<td>5.6</td>
</tr>
<tr>
<td>6</td>
<td>8.0</td>
<td>5.3</td>
<td>13.3</td>
<td>13.6</td>
</tr>
<tr>
<td>7</td>
<td>4.7</td>
<td>3.1</td>
<td>7.8</td>
<td>12.6</td>
</tr>
<tr>
<td>8</td>
<td>4.7</td>
<td>2.5</td>
<td>7.2</td>
<td>9.3</td>
</tr>
<tr>
<td>9</td>
<td>5.3</td>
<td>6.6</td>
<td>11.9</td>
<td>19.1</td>
</tr>
<tr>
<td>10</td>
<td>7.8</td>
<td>5.0</td>
<td>12.8</td>
<td>16.2</td>
</tr>
</tbody>
</table>

Mean ± SE

<table>
<thead>
<tr>
<th></th>
<th>Control*</th>
<th>N2 breathing</th>
</tr>
</thead>
<tbody>
<tr>
<td>R liters/min</td>
<td>10.1</td>
<td>12.3</td>
</tr>
<tr>
<td>L liters/min</td>
<td>±.98</td>
<td>±1.2</td>
</tr>
</tbody>
</table>

*Determined by differential spirometry while breathing 100% O2.
†Lung in communication with 100% nitrogen.

During unilateral hypoxia in the present study the average VO2 remained unchanged. However, a curious change in ventilation was found. The average increase in total VE of 2.3 liters/min occurred during unilateral N2 breathing despite avoidance of arterial hypoxemia by using 100% O2 for the remaining lung. The increase averaged 1.4 liters/min for the hypoxic lung (P<0.05) but on the oxygen side a nonsignificant increase of 0.9 liter/min was found. This could occur only if compliance increased or airway resistance decreased on the N2 side. It has been shown in the dog that arterial hypoxemia will constrict airways by a reflex mechanism. However, Nisell has demonstrated bronchodilation in the excised cat lung ventilated with 100% N2. Our study suggests that in man, when arterial hypoxemia is avoided, airway hypoxia does lead to bronchodilation with a decrease in airway resistance. Thus, our study has demonstrated that the hypoxic lung has both decreased blood flow and an increased ventilation, a response to hypoxia which is ideally suited to minimize the change in alveolar and pulmonary capillary oxygen tension.

Summary

In ten patients with chronic lung disease unilateral airway hypoxia was produced by having them breathe 100% nitrogen administered for seven minutes via a Carlen catheter while the other lung received 100% oxygen. The partition of pulmonary arterial blood flow between the two lungs was determined by radioisotope scanning following intravenous injection of 131I macroaggregated human vessels, postcapillary vessels, and a combination of both. The experiments of Duke suggest that both precapillary and postcapillary vessels constrict when exposed to low oxygen tensions. In the present study it is probable that only the P02 of blood in postcapillary vessels was significantly altered and constriction of these vessels would seem to account for the decrease in flow. However, the possibility of postcapillary constriction of precapillary vessels has not been ruled out in man.

The exact mechanism of pulmonary vasoconstriction during hypoxia is a subject of considerable debate. Fishman has reviewed the many factors which might influence pulmonary vascular resistance and concludes that pulmonary vasoconstriction probably does occur in response to airway hypoxia. The pulmonary vessels are capable of constricting in the presence of low oxygen but whether this effect is produced by direct action on the vessel, by a reflex, or by a humoral mechanism is unknown. Evidence concerning the exact site of the vasoconstriction is contradictory. Various authors have concluded that it affects the precapillary vessels, postcapillary vessels, and a combination of both. The experiments of Duke suggest that both precapillary and postcapillary vessels constrict when exposed to low oxygen tensions. In the present study it is probable that only the P02 of blood in postcapillary vessels was significantly altered and constriction of these vessels would seem to account for the decrease in flow. However, the possibility of postcapillary constriction of precapillary vessels has not been ruled out in man.
serum albumin (MAA) both during bilateral air breathing and unilateral hypoxia.

Unilateral hypoxia produced a 42% decrease in pulmonary blood flow to the hypoxic lung due to ipsilateral vasoconstriction. The response to N₂ was greater when given to the diseased lung, suggesting that the pulmonary vascular bed of the involved lung was incapable of accepting a large increase in the proportion of the cardiac output because the vascular bed was already compromised by disease.

Ventilation on the hypoxic side increased by 1.4 liters/min while there was no change on the side receiving 100% oxygen. Since unilateral hypoxia produced both a decreased blood flow and an increased ventilation, it is suggested that the lung is capable of altering regional perfusion and ventilation in a manner ideally suited to minimize the change in alveolar and pulmonary capillary oxygen tension.

References
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