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Research Article

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ABSTRACT We studied the effect of diffuse granulomatous pulmonary disease on the reponse of the pulmonary circulation to hypoxia in two series of experiments in intact dogs. First, in animals with unilateral disease, vasoconstriction in the diseased lung was compared to that in the contralateral control lung. Second, in animals with bilateral disease, the vasoconstriction of pulmonary shunt pathways was compared to that of the rest of the pulmonary vasculature. We assessed vasoconstriction in each study by measuring the distribution of pulmonary blood flow between the test and control set of vessels during 21 and 12% oxygen breathing. In the first set of experiments, we measured apportionment of the blood flow between the two lungs by bronchospirometry and the krypton bolus method. In normal dogs, hypoxia did not shift blood flow systematically from one lung to the other. In 10 dogs with unilateral disease, general hypoxia increased the proportion of blood flow to the diseased lung. The mean percent of blood flow to the left lung in eight dogs with disease in that lung rose from 29% during air breathing to 32% ($P < 0.001$). In the second set of experiments, we measured apportionment of the blood flow between shunt pathways and gas-exchanging pathways by a constant infusion of radioactive krypton and the standard shunt formula. In eight dogs with bilateral disease, hypoxia consistently increased the flow through shunt pathways, from a mean value of 10% of pulmonary blood flow to 14% ($P < 0.005$).

Thus, diffuse granulomatous disease causes a decreased vasoconstrictive response to hypoxia both in diseased, gas-exchanging regions and in shunt pathways. In proliferative interstitial pulmonary disease, generalized hypoxia causes shifts in pulmonary blood flow which do not ameliorate but rather worsen the hypoxemia of systemic arterial blood.

INTRODUCTION

Numerous studies in normal people and in patients with chronic obstructive pulmonary disease have shown that hypoxia produces two related effects on the vessels of the lung. On the one hand, hypoxia causes a predictable rise in pulmonary artery pressure; on the other hand, it can influence the distribution of pulmonary blood flow. For instance, when normal subjects breathe an hypoxic mixture with both lungs, the pulmonary arterial pressures rises in proportion to the degree of arterial unsaturation (1–3); the administration of an hypoxic mixture to one lung causes a shift of blood flow to the other side (4, 5). Similarly, in patients with chronic airways obstruction, the pulmonary arterial pressure can be predicted from the level of arterial saturation if the modifying influence of the hydrogen ion concentration is taken into account (6). Also, as is true for normal subjects, regional hypoxia can cause diversion of pulmonary blood flow away from areas where the alveolar tension is low (7). Such observations have led to the view that hypoxia plays an important role in controlling both the overall and regional pulmonary vascular resistance in normal individuals and in patients with chronic obstructive pulmonary disease.

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Whether the effect of hypoxia is equally important for patients with proliferative interstitial pulmonary disorders is not known. In the data reported on a few patients with silicosis and sarcoidosis, correlations between arterial blood gases and pulmonary arterial pressures have been poor and unpredictable (8, 9). Furthermore, the effect of hypoxia on regional distribution of blood flow has not been examined in these diseases.

Therefore, in order to characterize the effect of proliferative interstitial lung disorders on the response of the pulmonary circulation to hypoxia, we studied a canine model of diffuse granulomatous pulmonary disease that physiologically and pathologically resembles sarcoidosis in man (10–12). To test the effects of disease on hypoxic vasoconstriction, we performed two sets of experiments, using changes in apportionment of blood flow to measure the vasoconstrictive response of diseased regions. In the first set, in which dogs with unilateral granulomatous disease were studied, we examined the effect of hypoxia on the distribution of blood flow between vessels in diseased regions and vessels in normal regions. In the second set of experiments, we examined the effect of hypoxia on the distribution of flow between gas-exchanging vessels and shunt pathways in dogs with bilateral granulomatous disease.

METHODS

Production of granulomatous disease. Granulomatous pulmonary disease was produced in dogs by injecting complete Freund's adjuvant[1] (0.5–0.75 ml/kg) into a peripheral vein. 3–4 wk after injection, the lungs contained many lesions with structures characteristic of granulomas, interspersed with regions of normal lung (10). To produce unilateral disease, we injected complete Freund's adjuvant while blood flow to one lung was obstructed by a balloon tip catheter. Extent and location of disease were verified at autopsy.

Unilateral disease study. Earlier studies have shown that the disease reached its height at about the 4th wk after injection of complete Freund's adjuvant. Hence, during the 4th wk each dog was anesthetized with sodium thiamylal (25 mg/kg), and was then studied while breathing spontaneously in the supine position. A femoral artery cannula and four transvenous catheters were placed, one in the pulmonary artery for blood sampling and pressure measurement, and three in the inferior vena cava with their tips just above the diaphragm, for injection of radioactive krypton, injection of indocyanine green, and infusion of sodium thiamylal to maintain a constant level of anesthesia. A pliable silastic bronchospirometry tube (Dow-Corning Corp., Midland, Mich.) (13) containing catheters for sampling end-tidal gas in both sides was advanced to the carina through a tracheostomy. It was then withdrawn 1.0–1.5 cm to insure that the tube did not block the left upper lobe bronchus. Tracheal division was accomplished by first inflating the left, distal balloon with 1.5–2.0 ml of air, and then inflating the proximal balloon with 10 ml of air. To guard against leaks we performed the following tests before each run: (*a*) after inflation of each lung, we made certain that passive expiration was not prolonged or high pitched; (*b*) we then inflated each lung to 50 mm Hg pressure and listened for a leak; and (*c*) we checked the end-tidal oxygen partial pressure (P_{O_2}) of each lung while administering 50% oxygen to the other lung. Finally, we opened the chest at the end of the study and repeated the first two tests. In the absence of partial obstruction, all lobes on the same side emptied synchronously.

After the bronchospirometry catheter had been positioned, each side was connected to a breathing valve so that the two lungs inspired the same oxygen mixture while the expired gas from each side was collected separately. The animals breathed 21 and 12% oxygen sequentially for 20 min each. The order of these periods was reversed in alternate dogs. During each period the following were measured: mean pulmonary and femoral artery pressure; cardiac output using indocyanine green (14); arterial pH, P_{O_2}, and carbon dioxide partial pressure (P_{CO_2}) with simultaneously sampled end-tidal P_{O_2} and P_{CO_2}; respiratory quotient; and hematocrit.

To measure the distribution of blood flow between the two lungs, we injected into the right atrium a bolus of radioactive krypton dissolved in saline (5 mCi in 5 ml saline). The total radioactivity in the expired gas collected from each lung over a 7-min period was then calculated by multiplying the volume of expired gas by the concentration of krypton in the mixed expired volume as measured with a Geiger-Muller tube. Because the krypton tracer is poorly soluble in blood, it is readily cleared from vessels which participate in gas exchange. Therefore, the proportion of the total exhaled radioactivity collected from each lung measures the proportion of blood flow perfusing the gas-exchanging vessels of that lung (15). Because krypton traversing shunt pathways is not cleared into the gas phase, pulmonary shunt flow is not included in this measurement of pulmonary blood flow to the individual lungs.

After the first two breathing periods, the dogs inspired 100% oxygen for 20 min and shunt flow was calculated by the standard shunt formula.

The 17 animals in this experiment included 7 normal dogs and 10 dogs with unilateral disease, 8 with disease on the left and 2 with disease on the right. All met the criteria for proper bronchospirometry tube placement and had respiratory quotients between 0.66 and 1.02 during each run.

Bilateral disease study. Anesthesia, arterial, and venous catheterizations and cardiac catheterization were performed as in the unilateral disease study. Instead of bolus injections of krypton, a solution of radioactive krypton in saline (100 μCi/min) was infused continuously and instead of the bronchospirometry tube, a single-lumen cuffed endotracheal tube containing a catheter for sampling end-tidal gas was used.

After these initial steps, the animals inspired 12, 21, and 100% oxygen for 20 min each, in random order. As mentioned earlier, the lungs were hyperinflated three times to a pressure of 50 mm Hg before each run. During the run, the same measurements were made as in the unilateral study, plus mixed venous oxygen content and capacity (16), and simultaneously sampled arterial, mixed venous, and end-tidal krypton concentrations. Using these values for krypton and the standard shunt formula, pulmonary shunt flow was calculated (17). During the 100% oxygen period, total shunt flow by the oxygen method was also calculated using arterial, mixed venous, and alveolar oxygen concentrations. During the 12% oxygen period, hyperventilation was minimized by increasing the rate of infusion of anesthetic agent.

[1] Complete Freund's adjuvant (Difco Laboratories, Detroit, Mich.) contains 5 mg of Mycobacterium butyricum, killed and dried in 8.5 ml of paraffin oil and 1.5 ml of emulsifier.

Autopsy confirmation of pulmonary disease. At the conclusion of each study, the dogs were exsanguinated and the lungs inspected and weighed. No areas of pneumonia, infarction, or collapse and no intracardiac shunt pathways were detected. In dogs with disease, granulomas were evident on inspection. In unilateral disease experiments, inspection confirmed the unilateral distribution of granulomas; the weight of the diseased lung was a larger percent of total lung weight than normal ($t = 4.1$, $P < 0.005$) (Fig. 1). In bilateral disease experiments, the diseased lungs were almost twice as heavy as those of control animals ($t = 2.3$, $P < 0.05$) (Fig. 2).

RESULTS

Unilateral disease study, 21% oxygen breathing. Diffuse granulomatous disease reduced both the ventilation and perfusion of the diseased lung. Whereas in the seven normal dogs the left lung received 45% of the total ventilation and perfusion (a mean of 45% of minute ventilation, 43% of alveolar ventilation, and 45% of capillary blood flow), in the eight dogs with disease in the left lung, the left lung received an average of 37% of the minute ventilation, 28% of the alveolar ventilation, and 29% of the capillary blood flow (Fig. 1 and Table I). The difference of each of these values from that of the control group was statistically significant; values of t were 2.5, 3.2, and 3.9, corresponding to P values of <0.05, <0.01, and <0.005, respectively. Because alveolar ventilation and capillary blood flow were reduced proportionately, the $\dot{V}_A/\dot{Q}_c$ ratio was unchanged in diseased dogs. Arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$), pH, pulmonary artery mean pressure, and cardiac output also were similar in diseased and control animals.

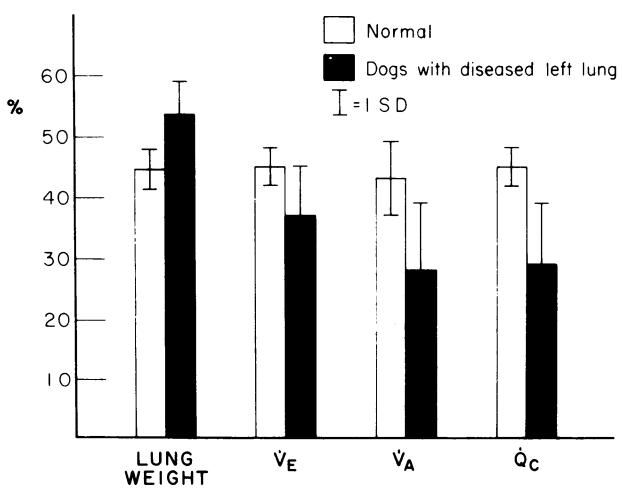

FIGURE 1 Effects of unilateral granulomatous disease on lung weight, minute ventilation ($\dot{V}_E$), alveolar ventilation ($\dot{V}_A$), and capillary blood flow ($\dot{Q}_C$); for each variable, the value for the left lung is expressed as a percentage of the value for both lungs.

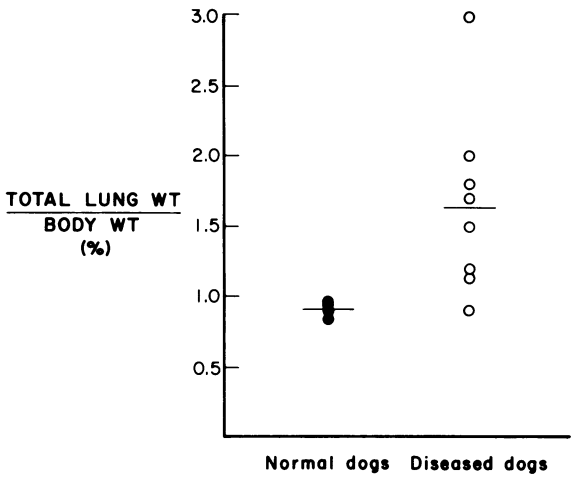

FIGURE 2 Lung weight is expressed as percent of body weight in normal dogs and dogs with bilateral diffuse granulomatous disease. The mean lung weight of dogs with bilateral granulomatous disease is almost twice that of normals.

The two dogs with unilateral disease of the right lung showed the same effects. The affected lungs received less ventilation and perfusion than the right lungs of the normal controls (Table I).

Unilateral disease study, effect of 12% oxygen breathing. The inhalation of 12% oxygen altered the relative resistance to blood flow of the normal and diseased lungs: the proportion of blood flow to the diseased lung increased in 9 of 10 animals and was unchanged in 1 animal. In dogs with left-sided disease, the mean percentage of capillary blood flow going to the diseased lung rose from 29 to 32% (Fig. 3), whereas in the left lung of normal dogs the value was 45% during both the 21 and 12% oxygen period. The increase in the proportion of blood flow to the diseased left lung is statistically significant either when comparing paired values during 12 and 21% breathing (Fig. 3) ($t = 5.7$, $P < 0.001$) or when comparing the change in diseased animals with that in normal dogs ($t = 2.6$, $P < 0.02$). The two dogs with right-sided disease showed similar results: the proportion of blood flow to the diseased lung rose during hypoxia.

Aside from hypoxia, inhalation of 12% oxygen caused little change in other measured variables (Table I). Pulmonary artery pressure was measured in six normal dogs and five with unilateral disease and did not change significantly with 12% oxygen breathing (Table I). There was no significant change in tidal volume, cardiac output, or respiratory quotient in the hypoxia period. A tendency to hyperventilate during hypoxia could be demonstrated only if normal and abnormal dogs were grouped together; the mean decrease in $PaCO_2$ of 4 mm Hg then reached statistical significance ($P < 0.005$).

TABLE I

Effect of Hypoxia on Apportionment of Pulmonary Blood Flow Between Right and Left Lungs and on Related Hemodynamics and Gas-Exchange Measurements in Normal Dogs and in Dogs with Unilateral Diffuse Granulomatous Pulmonary Disease

		Normal dogs Group 1 (n = 7)		Disease in left lung Group 2 (n = 8)		Disease in right lung Group 3 (n = 2)	
		21% O_2	12% O_2	21% O_2	12% O_2	21% O_2	12% O_2
Pulm. cap. blood flow* (*liter/min*)	Total‡	4.0±0.7	4.0±0.7	3.9±0.9	4.1±0.8	3.8	3.6
	R;L	55;45±3	55;45±2	71;29±10	68;32±10	46;54	48;52
PaO_2 (mm Hg)		88±7	47±6	81±6	43±9	80	44
Mean pulmonary artery pressure (mm Hg)		12±3 (n = 6)	10±3	15±1 (n = 4)	20±4	11 (n = 1)	13
Minute ventilation (*liter/min*, BTPS)§	Total	8.3±2.1	10.3±2.8	7.8±2.7	11.5±3.9	11.6	13.8
	R;L	55;45±3	54;46±2	63;37±8	59;41±5	52;48	50;50
Alveolar ventilation (*liter/min*, BTPS)§	Total	4.3±1.5	5.5±2.1	4.2±0.9	5.3±1.3	4.5	5.0
	R;L	57;43±6	56;44±5	72;28±11	69;31±12	46;54	48;52
Oxygen uptake (*ml/min*, STPD)§	Total	168±33	178±28	167±24	175±27	154	150
	R;L	56;44±3	55;45±4	70;30±11	69;31±11	45;55	48;52
Ventilation-perfusion ratio	Total	1.08±0.40	1.36±0.43	1.10±0.28	1.37±0.47	1.18	1.37
	R lung	1.13±0.39	1.42±0.40	1.15±0.33	1.40±0.50	1.18	1.38
	L lung	1.10±0.50	1.40±0.53	0.97±0.22	1.30±0.50	1.16	1.36
$PaCO_2$ (mm Hg)		31±6	28±4	38±4	32±7	34	29
pHa		7.40±0.04	7.46±0.04	7.39±0.05	7.43±0.08	7.38	7.42
% Shunt‖		3.3±1.8		7.6±3.0		4.5	

Data is given as mean±SD.

* Pulmonary capillary blood flow = cardiac output × (100 − % shunt)/100.

‡ Apportionment of each variable to the right (R) and left (L) lungs is given as percent to the right lung; percent to the left lung±SD (which applies to both R% and L%.

§ BTPS, body temperature, pressure, saturated with water; STPD, standard temperature pressure, dry (0°C, 760 mm Hg).

‖ % Shunt was measured during 100% O_2 inhalation.

Bilateral disease study, effect of 12% oxygen breathing. In all eight dogs with bilateral disease, the inhalation of 12% oxygen was associated with an increase in the percent of cardiac output perfusing shunt pathways (Table II; Fig. 4). The mean shunt measured by the radioactive krypton infusion method was 10.2 ±6.0% SD during the 21% oxygen period and 14.2 ±5.9% SD during the 12% oxygen period. The difference in shunt flow was statistically significant by paired t test (t = 4.4, $P < 0.005$). In contrast, in four normal dogs, shunt increased in two and decreased in

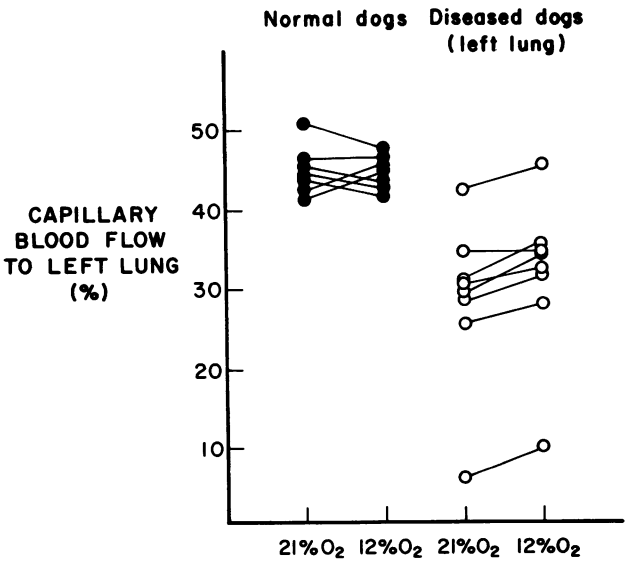

FIGURE 3 The percent of capillary blood flow going to the left lung in normal dogs and cats with unilateral disease is plotted during 21 and 12% oxygen breathing periods. With hypoxia, flow was increased in the diseased lung of seven of eight dogs. In seven normal dogs, hypoxia did not systematically shift blood flow.

TABLE II

Effect of Hypoxia on Perfusion of Pulmonary Shunt Pathways and on Related Gas-Exchange Measurements in Normal Dogs and in Dogs with Bilateral Diffuse Granulomatous Pulmonary Disease

	Normal dogs Group 4 (n = 7)		Bilateral disease Group 5 (n = 8)	
	21% O_2	12% O_2	21% O_2	12% O_2
% Shunt by krypton infusion	7.5±4.4	8.6±5.9	10.2±6.0	14.2±5.9
PaO_2, mm Hg	74±16	40±4	69±5	36±4
Mean pulmonary artery pressure, mm Hg	11±4	16±2	12±2	14±3
Minute ventilation (*liter/min*, BTPS)*	7.8±1.6	10.0±2.3	6.4±1.3	7.6±1.4
Alveolar ventilation (*liter/min*, STPD)	4.8±0.7	5.9±0.9	3.8±0.8	4.0±1.3
Oxygen uptake (*ml/min*, STPD)	166±24	156±15	134±26	124±34
$PaCO_2$ (mm Hg)	32±4	26±1	34±3	30±2
pHa	7.39±0.07	7.44±0.08	7.36±0.06	7.40±0.04
Lung weight/body weight	0.91±0.04%		1.65±0.64%	

Data is given as mean±SD.

* Abbreviations as in Table I.

two during the 12% oxygen period; the mean change was not statistically significant.

Mean pulmonary artery pressure was 12±2 SD mm Hg during the 21% oxygen period and rose to 14±3 SD mm Hg during the inspiration of 12% oxygen (t = 4.2, $P < 0.005$). Mean pulmonary artery pressure did not change significantly in the four normal dogs.

Other than a decrease in alveolar and arterial P_{O_2}, inhalation of 12% oxygen produced little change in oxygen uptake, alveolar ventilation, cardiac output, respiratory rate, tidal volume, CO_2 production (Table II), or in respiratory quotient. A tendency to hyperventilate during hypoxia, demonstrated by a fall in $PaCO_2$, reached statistical significance only if normal and abnormal dogs were grouped together. (The mean decrease in $PaCO_2$ was 4 mm Hg, $P < 0.005$.)

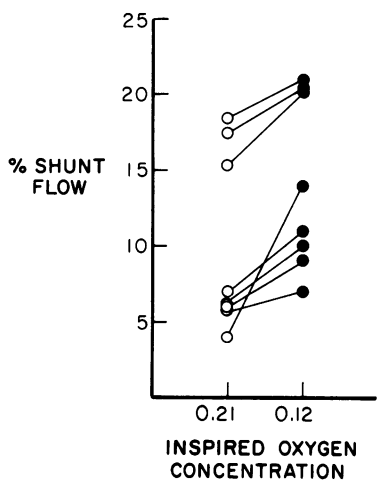

FIGURE 4 The percent of shunt flow in bilateral disease animals is plotted during 21 and 12% oxygen breathing periods. In these eight dogs, the inhalation of 12% oxygen consistently increased the fraction of pulmonary blood flow perfusing shunt pathways.

DISCUSSION

The results of this investigation indicate two findings. First, diffuse granulomatous pulmonary disease has a detectable influence on the pulmonary circulation and second, the presence of this disease alters hypoxic vasoconstriction.

Effects of diffuse granulomatous pulmonary disease on the pulmonary circulation during air breathing

Alteration of resistance to blood flow was demonstrated in animals with unilateral disease but was not found in those with bilateral disease. The pulmonary circulation in the latter animals appears to be comparable to that of patients with proliferative interstitial disease of mild to moderate severity (as assessed by a vital capacity greater than 55% of predicted). In such patients, as in the dogs, pulmonary artery pressure is normal (18). It appears that because of the reserve capacity of the pulmonary circulation, disease of this severity causes impingement on the pulmonary vasculature in involved regions resulting in locally increased resistance to blood flow and redistribution to relatively underperfused vessels in normal regions but does not produce an elevation in pulmonary artery pressure. Indeed, such a redistribution of blood flow away from diseased lung, indicating a regional increase in resistance to blood flow, was demonstrated in the unilateral experiments: the pro-

portion of the pulmonary blood flow perfusing the diseased lung was decreased by one-third.

Diffuse granulomatous pulmonary disease also increased shunt flow above control values, but the size of the shunts was relatively small, again comparable to human interstitial disease of mild to moderate severity. We assessed the pathway of perfusion of these shunts by obtaining simultaneous measurements of intrapulmonary right to left shunt by using the krypton infusion method and total right to left shunt by using the oxygen method. Inasmuch as the krypton method does not include bronchial vessel perfusion, the observation that the two measurements of shunt flow did not differ (Fig. 5) indicates that bronchial artery blood does not contribute substantially to pulmonary shunt flow in this disease.

Effect of granulomatous disease on hypoxic vasoconstriction

Hypoxia produced a redistribution of pulmonary blood flow in dogs with diffuse granulomatous pulmonary disease, increasing the proportion of blood flow to diseased regions and shunt pathways and decreasing the proportion to normal lung. Before we discuss the significance of these findings in terms of alterations of hypoxic vasoconstriction, we shall consider alternative explanations for the experimental results.

Methodological considerations. In dogs with unilateral disease, the relative amount of Krypton-85 expired from each of the two lungs was used as a measure of the distribution of pulmonary blood flow to gas-exchanging regions of the two lungs (19). The observed increase in the proportion of krypton excreted from the diseased lung during hypoxia could have occurred for two reasons related to technique of measurement rather than to a shift in blood flow. The first reason could be incorrect placement of the bronchospirometry catheter resulting in partial or complete obstruction of upper lobe bronchi (20). We believe that the surveillance of catheter position during the study and the confirmation of bronchial patency at autopsy eliminated this problem. Moreover, the small standard deviations (3% during the 21% oxygen period and 2% during the 12% oxygen period) in the proportion of minute ventilation going to each lung in our normal dogs supported the reliability of our technique. In addition, because krypton excretion consistently increased on the diseased side during hypoxia, no matter which side the disease was on, we think it unlikely that the shift in elimination of krypton was caused by bronchospirometry tube artifact.

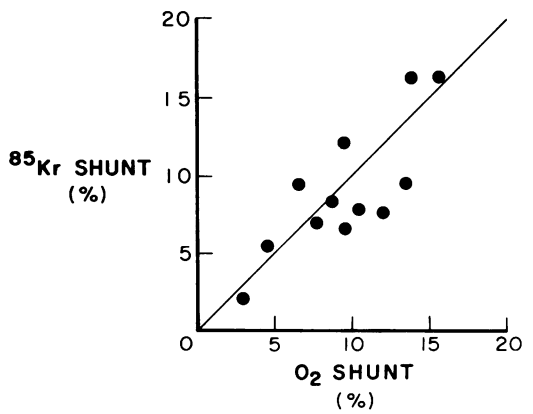

FIGURE 5 Correlation of percent shunt by the oxygen and krypton methods. The correlation coefficient is 0.79 ($P < 0.01$). The line shown is the line of identity.

Another possible explanation for the increased krypton elimination from the diseased lung during hypoxia is that there was substantial redistribution of the ventilation in the diseased lung, with conversion of shunt pathways to ventilated regions. However, in our study of shunt flow in dogs with bilateral granulomatous disease, hypoxia did not decrease shunt flow, as might have occurred with increased ventilation near shunt pathways; we therefore think that such a possibility is unlikely.

Interpretation of the rise in shunt flow during hypoxia in dogs with bilateral disease requires a comment on the krypton infusion technique for measuring shunt flow (17) and consideration that the increase in shunt flow was unrelated to the hypoxic stimulus. First, inasmuch as krypton has a low but not negligible solubility ($\lambda = 0.06$), shunt flow as measured by the constant infusion technique may include some blood perfusing regions with extremely low $\dot{V}_A/\dot{Q}_c$ ratios (17). In the present paper, the term "shunt flow" includes both absolute shunt and extremely low $\dot{V}_A/\dot{Q}_c$ regions. Second, it is conceivable that the increased shunt flow was due to atelectasis in a deteriorating preparation rather than to hypoxia. We do not believe that this was likely because we hyperinflated the lungs of each animal before each breathing period and because shunt flow was consistently higher during the hypoxic period, whether it came before or after normoxic breathing.

From these considerations we conclude that the changes in proportionate krypton excretion and in pulmonary shunt flow were due to actual changes in regional resistance to blood flow with resultant redistribution of perfusion rather than to unrelated factors. In addition, our data demonstrate the usefulness of the krypton tracer methods for assessing relative resistances of different vascular pathways. Whereas the increase in pulmonary artery pressure produced by breathing 12% oxygen was small and variable, the changes in patterns of perfusion were clearly demonstrated.

Alternative physiologic considerations. Hypoxia produced nonuniform alterations in pulmonary vascular resistance, with the increase in normal regions of the lung being relatively larger than that in diseased regions. Both gas-exchanging regions and regions in which there was no gas exchange (shunts) demonstrated this impairment. Two possible mechanisms of altered resistance unrelated to vasomotion should be considered. One is that hypoxia altered lung mechanics in a manner that influenced regional pulmonary vascular resistance. Inasmuch as the breathing pattern of the animals changed minimally with hypoxia, dynamic regional changes in mechanical properties do not seem a likely basis for the changes in vascular resistance. The second possibility is that the rise in pulmonary artery pressure that occurs with hypoxia recruited previously unperfused vessels in diseased regions of the lung. We think this is unlikely because the shifts in perfusion occurred with small and variable increases in pulmonary artery pressure. There was no correlation between the change in pulmonary artery pressure and the change in percent shunt (Fig. 6).

The role of altered hypoxic vasoconstriction. For the above reasons we conclude that vascular resistance increased relatively less in diseased than in normal lung regions because vessels in diseased regions responded subnormally to the hypoxic vasoconstrictive stimulus. At present we are unable to distinguish between two possible mechanisms of decreased vasoconstriction. On the one hand, the disease process may have directly decreased the magnitude of hypoxic vasoconstriction. Either involvement of the vessels by granuloma formation or disruption of mast cell function in the immediate perivascular tissue (21) may have decreased the capacity of the vessels to constrict. On the other hand, vessels capable of constricting normally may not have done so, either because they were already partially or fully constricted during room air breathing or because generalized hypoxia did not substantially alter P_{O_2} at the site of hypoxic vasoconstriction in diseased regions of the lung.

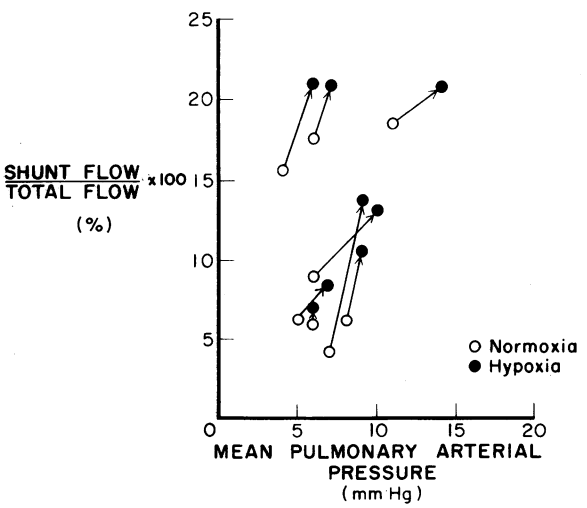

FIGURE 6 Relation of percent shunt flow to mean pulmonary artery pressure, during normoxic and hypoxic periods, in dogs with bilateral diffuse granulomatous pulmonary disease.

Although the shifts of blood flow produced by hypoxia were small relative to total pulmonary flow, hypoxic vasoconstriction must have been substantially impaired in parts of the diseased lungs. In the unilateral disease experiments, it seems likely that the impairment in vasoconstriction occurred predominantly in regions of granulomatous disease. Such regions were heterogeneously distributed throughout the lung. Thus, measurements of the entire lung may have underestimated the degree of impairment in granulomatous regions. Further, in the bilateral disease experiments, the 40% increase in perfusion of shunt pathways with hypoxia (from 10 to 14% of the pulmonary blood flow) indicates that vasoconstriction of shung pathways was substantially less than vasoconstriction of the rest of the pulmonary vessels.

Our results demonstrate that the assumption made in many traditional analyses of pulmonary gas exchange that hypoxia does not alter the distribution of blood flow in the presence of pulmonary disease is not valid. As a particular example, estimates of shunt flow derived from measurements of oxygen concentration during oxygen breathing may be inaccurate under conditions of alveolar hypoxia.

This shift of blood flow toward diseased regions of the lung occurred with hypoxia of all lung regions and does not contradict the established concept that regional alveolar hypoxia causes regional pulmonary artery vasoconstriction and a shift of blood flow away from the hypoxic region with consequent amelioration of hypoxemia. Rather, the present findings indicate that in the presence of proliferative interstitial disease, the capability of the pulmonary vasculature to respond to alveolar hypoxia is not normal in diseased regions, so that general alveolar hypoxia causes shifts of blood toward such regions.

Finally, these studies suggest that in humans with a proliferative interstitial lung disease such as sarcoidosis, hypoxia may represent a double liability. Alveolar hypoxia occurring in such situations as residence at high altitude or hypoventilation due to sedatives may lower arterial oxygen tension not only by the primary effect of lowering alveolar P_{O_2} but also by increasing the relative perfusion of diseased regions of the lung in which gas exchange is impaired or absent.

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