The Effects of Progressive General Anoxia on the Pulmonary Circulation

By Albert Hürlimann, M.D., and Carl J. Wiggers, M.D., Sc.D.

The effects of progressive anoxia on the hemodynamic changes in the pulmonary circuit were reinvestigated in anesthetized dogs. Evidence is presented that some increase in pulmonary arterial resistance takes place, but that the augmented output of the right ventricle is dominantly responsible for elevation of the pulmonary arterial pressure when anoxia affects the body as a whole.

In recent years several papers have been published concerning the reaction of the pulmonary circulation to anoxia; von Euler and Liljestrand and later Logaras studied the effects of anoxia on pulmonary arterial blood pressure in cats. From an acute and consistent rise in pulmonary arterial pressure and no change in left atrial pressure they drew the conclusion that this pressure rise was due to an increase in pulmonary vascular resistance. However, since changes in resistance cannot be inferred from pressure gradients alone, the conclusion lacked adequate experimental evidence. Later Nisell and Duke, using isolated perfused lungs of cats in different types of experiments were able to substantiate such a presumptive increase in pulmonary vascular resistance during abrupt change to breathing of low oxygen-nitrogen mixtures.

In 1948, Dirken and Heemstra studied the effects of unilateral nitrogen-breathing on pulmonary blood flow in rabbits. Using a modified Fick principle they found within the course of hours a slowly progressing decrease in blood flow through the lung ventilated with nitrogen, indicating an increase in resistance to blood flow in the lungs. However, Atwell and his associates using a rebreathing method found such a shift in blood flow in only half of the animals.

In unanesthetized man, Cournand reported a rise in pulmonary arterial pressure and an increase in cardiac output as a result of acute as well as chronic anoxia whenever arterial oxygen saturation fell below 79 per cent. It was concluded, however, that this did not entirely explain the elevation of pulmonary arterial pressure; therefore an additional increase in pulmonary resistance was postulated. Similar augmentation of cardiac output, which might account for elevation of pulmonary arterial pressure, had previously been reported by Sands and DeGraff, by Harrison and Blalock, by use of different procedures. Stroud and Rahn, in a preliminary report on anesthetized dogs, concluded that the calculated pulmonary vascular resistance generally increases from 25 to 48 per cent when dogs are exposed to 8 and 15 per cent oxygen, and decreases 11 per cent with administration of 30 per cent oxygen.

After completion of our studies a number of additional reports appeared. Aviado and his associates, working with anesthetized dogs, corroborated previous findings that pulmonary arterial pressure rises both in animals breathing naturally and under artificial respiration. However, through supplementary experiments involving (a) responses following denervation of the carotid sinus and aorta, and (b) controlled perfusion of one of the lungs, they consistently found that anoxemia, per se, reduces pulmonary arterial resistance, and that the rise of pulmonary arterial pressure must be assigned to increased pulmonary blood flow, that is, increased right ventricular output.

Lewis and Gorlin, also using anesthetized dogs, determined changes in cardiac output, pulmonary arterial, and left atrial pressure during breathing of 2.5 to 10 per cent oxygen—
nitrogen mixtures. They found that the effects depended on the level of desaturation reached in arterial blood. When arterial oxygen saturation was above 55 per cent, cardiac output usually remained unchanged and the rise of pulmonary arterial pressure was accompanied by a statistically significant rise of pulmonary vascular resistance. However, when arterial oxygen saturation fell below this level, pulmonary resistance fell, and the rise was due to increase in right ventricular output. Peters and Roos calculated changes in pulmonary resistance from pressure-flow relations on perfused lungs in anesthetized dogs whose oxygen saturation of arterial blood ranged from 10 to 50 per cent. They found pulmonary arterial resistance to be increased. In view of the discordant reports regarding the reaction of the pulmonary circulation further studies appear warranted.

**GENERAL METHODS**

While all previous investigators have studied effects of abrupt changes in the gas mixtures breathed, our experiments were designed to study the effects of progressively diminishing oxygen in the respired air. This was accomplished by use of a positive-pressure rebreathing spirometer designed by Harris. Since the rate and volume of ventilation of the animal remained constant throughout each experiment, the effects of changing alveolar carbon dioxide tensions were minimized.

A tracheal cannula was connected by short-length tubing to the spirometer containing approximately 25 per cent oxygen and 75 per cent nitrogen, soda lime absorbing the carbon dioxide. An internal ventilator circulated the gas mixture. The spirometer was calibrated so that the percentage of oxygen breathed could be read directly. Several control checks were made, however, in each experiment by analyzing samples of the gases with a Henderson-Orsat analyzer.

Several minutes after connecting the animal to the spirometer the oxygen concentration therein dropped to 21 per cent. Thereafter, optical recordings of all three pressures were taken every minute at the end of an expiration, usually for 15 to 20 minutes, at which time a circulatory crisis began to develop. At that point the spirometer was rapidly filled with oxygen to a concentration of 20 to 25 per cent and, as a rule, recordings of the recovery phase were taken.

In the first set of experiments the effects of progressive anoxia were deduced from changes in pressure pulses recorded simultaneously from the aorta, pulmonary artery, and left atrium.

![Fig. 1. Original pulse contours of the aorta, pulmonary artery and left atrium at various stages of progressive anoxia and during recovery.](http://circres.ahajournals.org/)

This method of study has apparently not been used heretofore.

**Method.** Seven dogs were anesthetized with sodium pentobarbital (30 mg. per kilogram intravenously) and two dogs with chloralose (100 mg. per kilogram intravenously); additional small amounts of anesthetics were given during the course of the experiment when necessary. Pressure pulses from the aorta, pulmonary artery, and left atrium were recorded by calibrated Gregg manometers of adequate frequency and sensitivity. In order to diminish possible secondary circulatory and respiratory changes due to anoxia, the chest was opened, both phrenic nerves were cut, and the animal was subjected to mechanically controlled intermittent positive pressure ventilation throughout the experiment. The rate and volume of artificial respiration were adjusted so that spontaneous respiratory movements just failed to occur during the control state.

**Results.** The typical records of pressure pulses in figure 1 illustrate effects of progres-
sive anoxia. The heart rate increased. During the early stages of recovery from severe anoxia, this increase in rate was still present and sometimes even more pronounced. The contours of the aortic pulse changed considerably. Below an oxygen concentration of 12 per cent, systolic pressure, and to a lesser extent diastolic pressure, rose continuously. Despite the increase in heart rate, pulse pressure increased from 58 to 134 mm Hg. The area $X_2$ is obviously much larger than $X_1$. Thus, while the pressure pulse analysis of Hamilton and Remington has not been made, all the changes in ventricle and, together with the cardiac acceleration, represents an increase in the minute volume of the right ventricle.

The left atrial pressure, measured at the end of ventricular systole, remained constant until severe anoxia supervened, then it began to rise. The rise was not directly dependent on changes in aortic and pulmonary arterial pressures. With progressive anoxia left atrial systole rose.

The more brusque ascent of the aortic and pulmonary pressure pulses indicates that the expulsion of blood into the aorta and pulmo-

![Graph showing typical reactions to repeated exposures to progressive anoxia.](http://circres.ahajournals.org/)

Aortic pressure pulses point toward an increase in the systolic discharge of the left ventricle, when the oxygen of inspired air fell below 12 or 10 per cent.

Similar changes were observed in pressure pulses from the pulmonary artery. Beginning at an oxygen concentration of 12 per cent, both systolic and diastolic pressures increased. Since the systolic pressure rose much more than diastolic pressure, pulse pressure became considerably greater during progressive anoxia, despite an increase in heart rate. The area $Y_2$ is very much larger than $Y_1$. This indicates an increase in systolic discharge of the right pulmonary artery during the early phase of ejection was more vigorous as anoxia progressed. The constancy of left atrial pressure until very low oxygen concentrations supervened, while cardiac output increased, demonstrates the ability of the left ventricle to master efficiently the increased minute volume derived from the right heart despite the anoxia. From these facts the conclusion was drawn that the condition of the heart improved during anoxia; it ejected a larger amount of blood at a higher pressure more vigorously.

Figure 2 shows a graph of the changes from another typical experiment. In three successive
tests, separated by a 30-minute breathing of
room air, essentially the same reactions took
place as described before. It should be noted
that elevations of aortic and pulmonary pres-
sures with increase in pulse pressure started
simultaneously when the oxygen breathed was
reduced to 12 per cent. Nor were there other
significant changes up to this time. At low
oxygen concentrations a slowing of the heart
supervened which resulted in a still greater
sure, indicating that failure of the left ventricle
preceded that of the right.

II

While augmented right ventricular output
could be logically inferred from changes in
pulmonary pressure pulses, they did not permit
inferences regarding the magnitude of the
change. Therefore, in a second series of ex-
periments the changes of pulmonary blood flow

table 1.*—Changes in Pulmonary Arterial Flow and Resistance during Progressive Anoxia

<table>
<thead>
<tr>
<th>No.</th>
<th>20-22% Oxygen</th>
<th>9-11% Oxygen</th>
<th>5-8% Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Pulm. Art. Press., in cm. H2O</td>
<td>Flow ml/min.</td>
<td>Resistance increase in % when perfusion pressure kept constant</td>
</tr>
</tbody>
</table>

| 11 |
| 12 |
| 13 |
| 14 |
| 15 |
| 16 |
| 17 |
| 18 |
| 19 |
| 20 |

* Experiments 11 through 14, whole left lung perfused; experiments 15 through 20, perfusion of only one or two
lobes.

increase in aortic and pulmonary pulse pres-
sures. At very low oxygen concentrations, left
atrial pressure rose suddenly, but immediately
after the animal was offered room air the
hemodynamic changes began to return to the
previous control state. Previous to the third
test both vagus nerves were severed. This had
no effect on the coincident elevation of pulmo-
nary and aortic pressures. The final cardiac
slowing, however, was delayed and aortic pres-
sure fell despite an increase in pulmonary pres-
during anoxia were measured directly. For
technical reasons the flow measurements were
limited to the left lung. The recording of flow
through one side of the lung gave only an ap-
proximation of the real changes due to anoxia,
for the introduction of the rotameter into the
pulmonary flow circuit apparently shunted
considerable amounts of flow through the other
lung. This is apparent from the relatively low
rates of flow shown in table 1. Therefore while
one cannot gage quantitative changes in flow,
PROGRESSIVE GENERAL ANOXIA ON PULMONARY CIRCULATION

FIG. 3. Schematic graph showing apparatus and connections used to record blood flow through the perfused lung. In the second series of experiments blood flows from the left pulmonary artery through cannula C1 to rotameter R and via cannula C2 to the left lung. The inner diameter of the cannulas and the plastic tubing was nowhere less than 6 mm. A shunt between C1 and C2, open between anoxia exposures, has been omitted in the graph. The air chamber A served to damp the pulmonary artery pulse and phasic flow changes during the cardiac cycle. M1 leads to a Gregg manometer recording pulmonary artery mean pressure. Clamp C1 and manometer M2 were used to adjust perfusion pressure.

The flow changes recorded are probably smaller than in reality.

Method. Figure 3 shows a scheme of the apparatus and connections used to record flow of blood through an electromagnetic rotameter. Unfortunately, flow to the left lung had to be interrupted for a period varying from 15 to 25 minutes while cannulating. Since the bronchial arterial supply was left intact and since the same changes in pulmonary pressure occurred in the cannulated lobes during anoxia, the lung was not considered damaged. As an anticoagulant, 200 I.U. per kilogram of heparin* was added every 30 minutes.

Four dogs under sodium pentobarbital anesthesia were studied in this manner. They were exposed to the same anoxia procedure as in the previous series. Recordings of aortic pressure pulses, mean pulmonary artery pressure, pressure contours in the left atrium, and flow through the left lung, as well as oxygen concentration readings from the calibrated spirometer were made every minute at the end of an expiration. The rate of flow measured at the end of expiration was taken arbitrarily as mean flow, for the relation of flows during the respiratory cycle did not change noticeably during the different stages of anoxia. Immediately before and after an anoxia period several spot calibrations of the rotameter were made and at the end of an experiment a complete calibration over the whole range of flow was made, using the animal's own blood.

Results. The changes of the several phenomena recorded in a typical experiment are shown graphically in figure 4. Additional data from this and the third series of experiments are combined in table 1.

![Graph showing pressure changes of the aorta, pulmonary artery, left atrium, and changes in the blood flow through the left lung in a typical experiment during progressive anoxia.](image)

* The heparin used in these experiments was supplied in part through courtesy of the Upjohn Co., Kalamazoo, Mich.
With progressing anoxia, aortic systolic and diastolic pressures rose after oxygen in the spirometer reached 15 per cent, that is, a little earlier than in experiments in which less instrumentation was involved. Pulse pressure increased. The heart rate did not change markedly. As in the first series of experiments, mean pressure also began to rise simultaneously with the elevation of aortic pressure, in every experiment reaching values 2 to 15 cm. saline higher than control readings when oxygen concentration reached 10 per cent. Left atrial pressure remained constant or increased to an only moderate degree until very severe anoxia supervened. Furthermore, the augmentation of pulmonary blood flow through the left lung also started simultaneously with the increase in pulmonary arterial pressure or, in some cases, even slightly preceded the rise. This strongly indicated that no pulmonary vascular change preceded the increased blood flow or rise of pulmonary pressure. In the 10 anoxia exposures studied, flow increased 3 to 60 per cent at 10 per cent oxygen, the average being 26 per cent. This substantial increase in pulmonary blood flow was doubtless present in the right lung as well as in the experimental left lung, probably to an even greater degree. The changes noted completely confirm the findings of the first series, namely, that the rise in cardiac output resulted in greater pulmonary blood flow, which is certainly responsible in part for the rising pulmonary artery pressures during progressive anoxia.

Calculations of changes in pulmonary arterial resistance as pressure/flow units were made in the foregoing experiments. As shown by data in experiments 11 to 14 of table 1, a noteworthy increase in calculated resistance supervened in only two out of seven tests; in one it even decreased. However, it is realized on the basis of studies by Green and colleagues\textsuperscript{17} and Edwards\textsuperscript{18} that active vasoconstriction cannot be determined in such a simple way, particularly in the low resistance pulmonary circuit.

![Diagram](http://example.com/diagram.png)

**Fig. 5.** Plot showing augmentation of pulmonary flow as pulmonary arterial pressure rises during progressive anoxia, and the decrease in flow with increase in resistance when pulmonary pressure was maintained at 15 cm. H$_2$O. Left, vagi intact; right, vagi cut.

A third series of experiments was therefore projected in which measurement of pulmonary blood flow during anoxia could be made alternately during induced anoxic pulmonary hypertension and under constant controlled pressure.

**Method.** In six dogs the flowmeter measured flow through only one or two lobes of the left lung. During the anoxia exposure recordings of aortic pulse pressures, pulmonary arterial mean pressure, left atrial pressure and blood flow, as well as oxygen concentration readings were made every other minute, and the data at the end of an expiration were plotted. A clamp distal to the rotameter (indicated in fig. 3) was quickly adjusted so as to lower perfusion pressure during anoxic hypertension to the level of pulmonary arterial pressure present at the beginning of the experiment. The pressure was held at that level for at least 20 seconds and then a record was taken. Following this the clamp was re-
leased. This procedure was repeated throughout the experiment.

**Results.** Figure 5 shows a plot of data from a typical experiment which illustrates the changes in pulmonary blood flow when pulmonary pressure is allowed to rise naturally during progressive anoxia and when it is maintained at a constant level. Blood flow (labeled natural blood flow) increased under the former and decreased under the latter conditions (labeled flow at 15 cm. H2O pressure). Such a decrease in flow under constant pulmonary arterial and left atrial pressures definitely indicated an increase in pulmonary vascular resistance, also plotted in figure 5.

After the first test in this experiment the vagus nerves were severed in the neck region. Aside from the facts that the development of equivalent degrees of anoxia was somewhat prolonged and the changes in flow and resistance were correspondingly delayed, the effects on pulmonary flow and resistance were very similar.

Calculations of changes in resistance in five experiments are incorporated in table 1 (experiments 15, 16, 17, 19, 20). The data reveal that, at ranges of 9 to 11 per cent oxygen in inspired air, pulmonary resistance decreased slightly in two instances and increased to variable extent in 14 tests. Of the latter, resistance calculated by using equivalent pulmonary artery pressures was greater in 10 cases, but less in four cases than resistances calculated on the basis of elevated pulmonary pressures. In summary, the variation in resistance ranged from −29 to +105 per cent.

**Discussion**

The experiments presented indicate that while some variations exist even in consecutive tests on the same animal, the common response to anoxia in the range of 9 to 11 per cent oxygen in inspired air, pulmonary resistance decreased slightly in two instances and increased to variable extent in 14 tests. Of the latter, resistance calculated by using equivalent pulmonary artery pressures was greater in 10 cases, but less in four cases than resistances calculated on the basis of elevated pulmonary pressures. In summary, the variation in resistance ranged from −29 to +105 per cent.

The results indicate clearly that changes in resistance in the pulmonary circuit did not precede the development of increased right ventricular output and that they were not sufficient to prevent the increase in pulmonary flow necessary to cause a simultaneous augmentation in left ventricular output. Since the effects on ventricular output—but not on heart rate—resemble those produced by small doses of epinephrine, the possibility that the ventricular stimulation may not be a direct effect of anoxia must be kept in mind. Such an interpretation would explain observations on heart-lung preparations, in which the adrenals are excluded, that anoxia causes only ventricular depression.19

Hence the conclusions are reached that, while an increase in pulmonary vascular resistance may contribute to the rise in pulmonary artery pressure during anoxia, it is not the major cause. Both the right and left ventricular minute volumes increase concurrently during anoxia. The increase in right ventricular output leads to a rise in pulmonary pressure which ensures the greater flow through the pulmonary vessels to the left atrium. The greater return of blood to the left atrium is pumped out by increase in output of the left ventricle which is so finely balanced that left atrial pressure scarcely changes.

**Summary**

The effects of progressive anoxia on hemodynamic changes in the pulmonary circuit were reinvestigated by a rhythmic, positive pressure rebreather method on barbitalized dogs with open thoraxes. Calibrated optical manometers of adequate sensitivity and frequency were used for simultaneous recordings of pressures from the aorta, pulmonary artery and left atrium.

When air in a spirometer is reduced to the range of 10 or 12 per cent oxygen, the following changes occur simultaneously: aortic and pulmonary pressures and pulse pressures increase, the configuration of the pressure pulses indicates augmented stroke volumes of both ventricles,
and left atrial pressure is relatively unaffected. 

Two groups of supplementary experiments in which blood flow through one entire lung or several lobes was recorded by an electromagnetic flowmeter revealed that pulmonary blood flow increased concurrently with—not previous to—the elevation of pulmonary and arterial pressures when air mixtures had been reduced to 10 or 12 per cent oxygen. Changes in pulmonary arterial resistance, calculated both by using the elevated pulmonary pressure and a pressure equivalent to the control preceding anoxia, indicated that, while some variation occurs even in the same experiment, resistance is usually increased. The nature and locus of resistance and the direct or indirect agents operative were not disclosed in this study.

A consideration of all data indicates that while increase in peripheral pulmonary arterial resistance may contribute to rise of pulmonary arterial pressure, the increased output of the right ventricle is the major cause.

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