Effect of Oxygen on Pulmonary Vascular Resistance in Patients with Pulmonary Hypertension Associated with Atrial Septal Defect

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The present studies are concerned with the effect of high oxygen inhalation on patients with atrial septal defects. The problem of the amount of pulmonary vascular resistance and the relative contribution of irreversible structural changes and vascular tone may be of important prognostic significance in evaluation of such patients for cardiac surgery.

LOWERED concentrations of oxygen in the inspired air have been shown to produce constriction of pulmonary vessels in the cat¹,² and in human subjects.³,⁴ The reaction of canine pulmonary vessels to hypoxia has been studied by many workers, whose consensus appears to favor a constrictor response. However, its variability has caused Lanari-Zubiaur and Hamilton⁵ to question its biologic significance. Conversely, concentrations of oxygen approaching 100 per cent in inspired air have been shown to reduce total pulmonary resistance in normal man⁶ and in patients with ventricular septal defect⁷ and in patients with patent ductus arteriosus⁸.

The present report concerns patients with pulmonary hypertension associated with atrial septal defect, who, in general, fall in an older age group than do patients with ventricular septal defect and who may differ from them in the factors underlying the development of pulmonary hypertension. It will be shown that in these patients with pulmonary hypertension and atrial septal defect, a labile component of the pulmonary vascular resistance can usually be demonstrated whether or not the vascular resistance is increased. Breathing high concentrations of oxygen usually produces a decrease in the calculated pressure-flow ratio (vasomotor tone) even in older patients and in those with severe organic occlusive changes in the pulmonary blood vessels.

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Material and Methods

Forty patients with atrial septal defect in whom the pulmonary-artery systolic pressure exceeded 60 mm. of mercury were studied by cardiac catheterization at the Mayo Clinic between January 1, 1955, and December 31, 1957. In 30 of these, pulmonary blood flows were determined while they were breathing air and also while they were breathing concentrations of oxygen that approached 100 per cent. Seventeen of the 30 patients underwent surgical correction of their defect, at which time the diagnosis was confirmed. An eighteenth patient was studied following an unsuccessful attempt at operative closure elsewhere. Of the other 12, 6 were rejected as candidates for corrective operation on the basis of severe pulmonary hypertension, systemic blood flow significantly exceeding pulmonary blood flow in all 6. A variety of reasons kept the remaining 6 patients from undergoing operation.

The age of 1 patient was less than 20 years; 7, 9, and 10 patients were in the third, fourth, and fifth decades of life, respectively; and 3 patients were more than 50 years of age.

Seventeen of the patients breathed 95 to 100 per cent oxygen via a mouthpiece with wide-bore corrugated rubber tubing from a large-volume (approximately 45 L) spirometer, which incorporated a recirculation pump and carbon dioxide absorber and permitted the measurement of oxygen consumption. Thirty patients breathed oxygen from a molded rubber mask strapped to the face, which incorporated a small balloon and into which oxygen flowed at a rate sufficient to produce a large outboard leak. In this way any tendency for air to be drawn into the face-piece was minimized, and appreciable rebreathing was prevented. This technique, however, did not permit the measurement of oxygen consumption.

Pulmonary blood flow was determined by the Fick principle. Oxygen consumption was determined for all patients while breathing air by measuring the volume of gas expired over a 3-minute interval and determining the oxygen concentration in a sample of this expired gas by the Haldane
method. Midway during the collection of expired air for determinations of oxygen consumption, blood samples were drawn simultaneously from the pulmonary artery and the radial artery. In all cases records of pulmonary artery and systemic artery pressures were obtained by means of strain-gage manometers at this time. The right atrial pressure was measured from a record obtained earlier in the procedure.

The oxygen breathing was started, and after a minimal interval of 5½ minutes (average interval for the group: 7 minutes) additional blood samples were withdrawn from the pulmonary and radial arteries. Oxygen consumption was measured in the 17 patients who breathed oxygen from the spirometer, and was assumed to have remained unchanged during oxygen breathing in the others. Recordings of pressure were obtained during the period of collection of blood samples while the patient was breathing 100 per cent oxygen. The catheter then was withdrawn to the right atrium, where a further pressure record was obtained.

Blood samples were analyzed manometrically for oxygen content by the method of Van Slyke and Neill, and the hemoglobin capacity for oxygen was determined by the method of Sendroy as modified by Roughton and associates. Pulmonary blood flow \( Q_p \) (L/min.) was calculated according to the formula:

\[
Q_p = \frac{O_2}{C_{po} - C_{pa}},
\]

in which \( O_2 \) is the oxygen consumption in milliliters per minute and the \( C \)'s with subscripts indicate the oxygen content of pulmonary vein and pulmonary artery bloods, respectively, in milliliters per liter. In 21 of the 30 cases the arterial oxygen saturation was less than 94 per cent when the patients breathed air. One patient from whom a clear history of postoperative pulmonary embolism was elicited was found to have a pulmonary vein oxygen saturation of 93 per cent; but in 6 other patients, 4 of whom had significant desaturation of systemic artery blood, the saturation of pulmonary vein blood ranged from 97 to 99 per cent. Accordingly, when these values were not measured, the assumption was made that the hemoglobin saturation of pulmonary venous blood was 98 per cent when the patient breathed air and 100 per cent when the patient breathed 99 to 100 per cent oxygen, and that 0.3 and 1.8 volumes of oxygen per 100 ml. of blood were present in dissolved form under the two circumstances. These derived values were used in the determination of \( Q_p \).

The ratios of pressure to flow referred to as total pulmonary and pulmonary vascular resistances \( R_p \) and \( R_{pv} \), in dynes sec. cm. \(^{-2} \), were determined according to the formulae:

\[
R_p = \frac{P_{pa} - P_{la}}{Q_p}
\]

\[
R_{pv} = \frac{P_{pa} - P_{la}}{Q_{pv}},
\]

in which the terms \( P_{pa} \) and \( P_{la} \) represent the mean pulmonary artery and mean left atrial pressures (mm. Hg), the mean left atrial pressure being assumed to equal mean right atrial pressure.

Results

The oxygen consumption measured in all 30 patients while breathing air averaged 145 ml. per min. per M.\(^2\). Among the 17 in whom it was measured while they were breathing 95 to 100 per cent oxygen, it averaged 143 ml. per min. per M.\(^2\) during breathing of air and 148 ml. per min. per M.\(^2\) during breathing of oxygen.

During the period of breathing air and breathing 100 per cent oxygen, respectively, the average pressures in the pulmonary circuits were 90 and 81 mm. Hg systolic, 37 and 34 diastolic, and 55 and 50 mean. The mean pulmonary artery pressure declined in 26 cases, was unchanged in 3, and increased in only 1 (fig. 1). This response apparently was not related to the initial levels of pressure. Pulmonary blood flow averaged 4.5 L. per min. per M.\(^2\) while breathing air and 5.5 L. per min. per M.\(^2\) while breathing oxygen (fig. 1). Generally, larger changes in pressure were associated with larger changes in blood flow (fig. 2). Thus the total pulmonary resistance, which averaged 712 dynes sec. cm. \(^{-5} \) while breathing air, declined to an average of 550 dynes sec. cm. \(^{-5} \) while breathing 99 to 100 per cent oxygen. The average pulmonary vascular resistance declined from 635 to 500 dynes sec. cm. \(^{-5} \) with the change of conditions (fig. 3). This decline was not demonstrably related to the values for either mean pulmonary artery pressure or pulmonary blood flow that were recorded while the patients breathed air (fig. 4). No relation between the ages of the patients and either the absolute levels or the magnitude of the changes of resistance on
breathing oxygen could be demonstrated. The average systemic resistance (mean systemic artery pressure divided by systemic blood flow) increased from 1,460 to 1,650 dynes sec. cm.\(^{-5}\) during the period of oxygen breathing. Random changes of considerable magnitude were seen in right atrial pressures of a few patients.

In 6 cases that included necropsy the status of the pulmonary vessels was graded independently according to the severity of structural changes.\(^\text{12}\) The severity of these organic vascular changes was found to have a positive correlation with the pulmonary-systemic resistance ratio recorded during breathing of air and with that recorded during breathing of oxygen. However, in this small group of patients no definite correlation was found between the grade of vascular disease and either absolute or relative changes in pulmonary vascular resistance on breathing oxygen.

**DISCUSSION**

These data indicate that in patients with pulmonary hypertension and atrial septal defect the change from breathing air to breathing 100 per cent oxygen is nearly always associated with an increase in the flow of blood through the pulmonary circuit and a decline in pressure in the pulmonary artery. Further, since changes in left atrial pressure are minor and random, the increase in blood flow and reduction in pressure indicate that a decline in pulmonary vascular resistance has occurred. Therefore it appears that the pulmonary vascular bed in patients with atrial septal defect responds to this stimulus in a manner similar to that of the pulmonary vasculature in patients with ventricular septal defect or patent ductus arteriosus and in normal subjects. Most likely the fall in resistance is due to dilatation of pulmonary blood vessels already open, or to opening of channels that have been closed.

**Assumptions.** Three assumptions have been made concerning the data. First, for the calculation of pulmonary flow it appears entirely reasonable to assume that among the 13 patients in whom oxygen consumption was not
OXYGEN AND PULMONARY VASCULAR RESISTANCE

69
determined while breathing oxygen it was not less than it had been while they were breathing air. Calculated with these values, the changes in pulmonary flow were of the same order of magnitude as in the group of 17 from whom the data for both circumstances were available. Since a slight increase of oxygen consumption with the change had been demonstrated in that group, the assumption of constancy among the 13 actually tends to minimize the volume of their pulmonary blood flows.

Second, in the presence of atrial septal defect the close similarity of pressures in the 2 atria assumed in this study has been demonstrated by Dexter and by others. In these patients the differences between mean pulmonary artery pressures and left atrial pressures were considerable, and the defects usually were of large size. In only 8 of the 30, however, did the pulmonary flow exceed the upper range of normal—a fact that implies the flow across the defect was not great in the majority of cases under study.

The final assumption concerns the values used for saturation of pulmonary vein blood. Desaturation of pulmonary vein blood is unusual in cases of atrial septal defect. Confirmation that the significant desaturation of systemic artery blood seen in 21 of the 30 patients while they were breathing air was due to right-to-left shunting of venous blood was obtained from indicator dilution curves. Indeed, by this technic all the remaining 9 patients showed evidence of right-to-left shunting, though of magnitudes too small to be associated with desaturation of systemic artery blood, as is common in patients having atrial septal defect without pulmonary hypertension. In only 1 patient did the magnitude of the right-to-left shunt as demonstrated by dilution curves appear insufficient to account for the desaturation of systemic artery blood; and in this case, as mentioned earlier, the saturation of pulmonary vein blood was found to be 93 per cent. With the support of measurements of the saturation of pulmonary vein blood in 6 patients, it was assumed that full

![Figure 2. Relation of change in pulmonary blood flow to change in pulmonary artery mean pressure on breathing 95 to 100 per cent oxygen. Values for pressure and flow during breathing of oxygen are expressed as fractions of values obtained during breathing of air. Dashed lines indicate unchanged pressure (abscissa) or flow (ordinate). A rough correlation between increase in flow and reduction in pressure is present.](http://circ.ahajournals.org/doi/fig/10.1161/01.CIR.38.3.69)

oxygenation of pulmonary vein blood occurred in all other cases; and the values for oxygen saturations of hemoglobin and the average quantities of dissolved oxygen, as found in normal subjects under conditions of breathing air and breathing 100 per cent oxygen, were used in the calculations of pulmonary blood flow. Such an assumption could introduce a systematic underestimation of pulmonary blood flow during breathing of air, and hence might permit the estimation of an increase of pulmonary blood flow in response to oxygen when no such change in fact occurred. As outlined above, the available evidence makes this possibility an unlikely one, however; and independent collaborative data are provided by the consistent fall in pulmo-
nary artery mean pressure associated with the breathing of 100 per cent oxygen (fig. 2).

Response of the Pulmonary Blood Vessels. The data are regarded as demonstrating a decrease in pulmonary vascular resistance associated with the breathing of 95 to 100 per cent oxygen in patients with pulmonary hypertension and atrial septal defect. The change in vascular resistance probably is not confined to those patients with pulmonary hypertension, since a decline in total pulmonary resistance which averaged 13 per cent has been found in 15 patients who had atrial septal defect without pulmonary hypertension. This response is similar to that seen in patients having ventricular septal defect with or without pulmonary hypertension. Further, the change in pulmonary artery pressure usually follows a similar time course, commencing within 15 seconds of the start of oxygen breathing and being virtually completed in 2½ to 3 minutes, which suggests that the underlying mechanism is similar in both conditions.

Vasoconstrictive Element. The significance of the present observations lies in the demonstration of a labile component of the pulmonary vascular resistance in patients with atrial septal defect and pulmonary hypertension, which component is affected by the concentration of oxygen in the inspired air. This apparent ability of the caliber of the pulmonary vessels to change implies the presence of a vasoconstrictive element in the increased vascular resistance seen in such patients. However, since similar changes in pulmonary vascular resistance occur in normal subjects and in patients having ventricular or atrial septal defects without pulmonary hypertension—although these are more difficult to demonstrate because of the lower absolute values for pulmonary artery pressures and pulmonary resistances—it is not possible to say whether the degree of tone of the individual smooth-muscle fibers is normal or abnormal.

Studies of the effect of acetylcholine on the pulmonary circulation provide additional evidence for the contribution of vessel tone to the pulmonary vascular resistance in the presence of pulmonary hypertension in atrial septal defect. Harris investigated 5 cases of atrial septal defect, in 3 of which pulmonary hypertension was severe. Injections of acetylcholine (average dose for a larger group, 2.3 mg.) produced no change in pulmonary artery pressure. However, when Shepherd and co-workers studied the effect of continuous infusion of 2 to 24 mg. per minute of acetylcholine in 6 cases of atrial septal defect with pulmonary hypertension, both a fall in pulmonary artery pressure and an increase in pulmonary flow occurred. The greatest fall in resistance was observed when acetylcholine was infused during breathing of oxygen. Most probably acetylcholine caused dilatation of the pulmonary blood vessels by direct local action. The mechanism whereby inspired oxygen acts is not known.

Development of Pulmonary Hypertension with Atrial Septal Defect. Pulmonary hypertension associated with atrial septal defect differs from the hypertension associated with ventricular septal defect or patent ductus arteriosus in that it appears to be an acquired complication, rather than an immediate hemodynamic consequence of—indeed an integral component of the situation arising from—a communication between the pulmonary artery and aorta or between ventricles...
which is large enough to equalize pressures between the two circuits from birth. In our experience,\textsuperscript{18} as in that of Dexter,\textsuperscript{13} it is uncommon to find pulmonary hypertension of the levels discussed herein associated with atrial septal defect in patients less than 20 years of age. In certain patients, however, for reasons not understood, pulmonary artery pressure increases slowly or rapidly during early adult life, usually with persistence of an increased level of pulmonary blood flow. Development of hypertension in the pulmonary circuit, whether associated with increased pulmonary blood flow or not, is unlike the response of normal pulmonary vessels that dilate, with but a small change in pressure, when the flow through them is increased. This development of pulmonary hypertension in atrial septal defect with a raised pulmonary blood flow is associated with an increase in pulmonary vascular resistance from levels below the range of normal to values that equal or slightly exceed normal, with a considerable increase in pulmonary blood flow. Study of a relatively few patients seen over a period of 6 to 8 years suggests that once the level of pulmonary artery systolic pressure is significantly elevated, it may remain virtually the same while the progression of organic change in the pulmonary vessels is manifested only by a steady decline in pulmonary blood flow. Why pulmonary hypertension develops in certain patients and not in others is uncertain. Histologic studies of the small pulmonary vessels of such patients have shown that once pulmonary hypertension is established a distinct muscular media forms in the arterioles, and the media of the muscular pulmonary arteries hypertrophies. The progression of such changes seems identical to that of the changes in pulmonary hypertension associated with ventricular septal defect or patent ductus arteriosus, and hence the similarity of the responses of these vessels to dilating influences is not surprising.

\textit{Prognosis from the Tests.} The prognostic significance of the change in pulmonary vascular resistance is uncertain, but the follow-
ing data suggest that a fall of considerable magnitude in the pulmonary vascular resistance when the patient breathes oxygen indicates a greater likelihood of immediate survival following surgical correction. While the mortality among patients with uncomplicated atrial septal defect is small—less than 2 per cent—the finding of pulmonary artery systolic pressure in excess of 60 mm. Hg, or of total pulmonary resistance in excess of 50 per cent of systemic resistance while breathing air, is associated with significant increase in the rate of surgical deaths. Seventeen of the patients herein considered underwent operation following cardiac catheterization in this institution. Of the 4 whose ratio of pulmonary resistance to systemic resistance exceeded 0.50, only 1 survived operation; of the 13 with ratios of 0.50 or less, 9 survived. Of 7 patients in whom the pulmonary vascular resistance during breathing of oxygen exceeded 80 per cent of the value obtained while breathing air, only 2 survived; but of the 10 in whom this ratio was less than 80 per cent, 8 survived.

In spite of the absence of a correlation between the histologic picture and the change in resistance on breathing oxygen, those patients in whom the pulmonary vascular bed shows evidence for a greater lability might logically be expected to have a less severe degree of organic pulmonary vascular disease. In such patients a more favorable long-term prognosis with regression of vascular disease might be anticipated. However, the number of follow-up studies is not yet sufficient for solving this aspect of the problem.

**Summary**

Pulmonary blood flows, and the pressure gradient across the pulmonary vascular bed, were measured in 30 cases of atrial septal defect in whom the pulmonary artery systolic pressure exceeded 60 mm. Hg, both while the patients breathed air and while they breathed 95 to 100 per cent oxygen.

The breathing of 95 to 100 per cent oxygen caused an average increase in pulmonary blood flow from 4.5 L. per min. per M.² to 5.5 L. per min. per M.² and an average reduction in pulmonary artery mean pressure from 55 to 50 mm. Hg.

The average calculated ratio of pressure to flow (vascular resistance) across the lung declined from 635 to 300 dynes sec. cm⁻². This was interpreted to indicate dilatation of the pulmonary blood vessels.

The magnitude of the change in vascular resistance on breathing 95 to 100 per cent oxygen was not related to the initial level of pulmonary pressure or of pulmonary blood flow, nor to the resistance values determined when breathing air.

In a small group of patients for whom histologic sections of the lungs became available, the change in resistance on breathing oxygen could not be related to the severity of the vascular disease. Those patients in whom the breathing of oxygen caused the greater decline in resistance had a higher operative survival rate.

**Summario in Interlingua**

Le fluxos de sanguine pulmonar e le differentias de tension trans le vasculatura pulmonear esseva mesurate in 30 patienes con defectos del septo atrial in qui le tension systolic del arterias pulmonar exceedeva 60 mm de Hg tanto quando illes respirava aere como etiam quando illes respirava inter 95 e 100 pro cento de oxygeno.

Le respiracion de inter 95 e 100 pro cento de oxygeno causava un augmento medie del fluxo de sanguine pulmonar de inter 4.5 1/min/m² a 5.5 1/min/m² e un reduction medie del tension pulmo-arterial medie de inter 55 mm de Hg e 50 mm de Hg.

Le calculate proportion medie de tension a fluxo (= resistentia vascular) trans le pulmon descendeva ab 635 a 500 dyna/sec/cm³. Isto esseva interpretate como indicazione de un dilatazion del vasos de sanguine pulmonar.

Le magnitude del alteration in le resistentia vascular, resultante del respiracion de inter 95 e 100 pro cento de oxygeno non esseva relacionate al nivello initial del tension pulmonoar o del fluxo de sanguine pulmonar e non al valores del resistentia determinate quando aere esseva respirate.
OXYGEN AND PULMONARY VASCULAR RESISTANCE

In un micre gruppo de patientes ab qui sectiones histologic del pulmones deveniva disponibile, le alteration del resistentia per le respiration de oxygeo non poteva esser relacione al severitate del morbo vascular. Le patientes in qui le respiration de oxygeo causava le plus grande reduction del resistentia se distingueva per le plus alte procentages de superviventia al intervention chirurgic.

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