Effect of Breathing Oxygen in Patients with Severe Pulmonary Vascular Obstructive Disease

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SUMMARY
During cardiac catheterization in nine patients with ventricular septal defect and seven patients with truncus arteriosus, all with severe pulmonary vascular obstructive disease, hemodynamics were compared while they were breathing first room air and then 100% oxygen. Patients with higher pulmonary vascular resistance had higher systemic vascular resistances. With 100% oxygen, pulmonary vascular resistance decreased and systemic vascular resistance increased in both groups. The effect of oxygen was found to be more pronounced on the systemic than on the pulmonary vascular bed in the patients studied. Indicator-dilution dye curves changed and exhibited characteristics of left-to-right shunts in patients with severe pulmonary vascular obstructive disease, as a result solely of an increase in systemic resistance; that is, without a decrease in pulmonary resistance. It is suggested that in patients with severe pulmonary vascular obstructive disease maintenance of an increased systemic resistance is essential to well being and is a factor in longevity. It is also suggested that any transient decrease in systemic resistance in these patients might initiate a vicious cycle leading to sudden death.

Additional Indexing Words:
Ventricular septal defect  Truncus arteriosus

An increase in peripheral systemic resistance was noted in normal humans breathing high concentrations of oxygen.1, 2, 3 This effect was found to be proportional to the increase in partial pressure of oxygen to which the subject was exposed.1, 4

The effects of breathing 100% oxygen on the systemic and pulmonary circulations were also studied in patients with various congenital heart diseases.5, 6, 7 These studies were on patients with pulmonary vascular obstructive disease (PVOD) of different degrees of severity. The main effect of breathing oxygen in these patients was considered to be a decrease in pulmonary resistance.

The study reported here was undertaken to determine the hemodynamic effect of breathing 100% oxygen in patients with ventricular septal defect and truncus arteriosus complicated by severe PVOD.

Materials and Methods
Sixteen patients, nine with ventricular septal defect and seven with truncus arteriosus, were studied. All patients had severe PVOD and therefore were not candidates for surgical correction of their lesions. The ages ranged from 6 to 46 years (mean 19 years) in the patients with ventricular septal defect and from 3 to 18 years (mean 7½ years) in the patients with truncus arteriosus.

The diagnosis was established by clinical evaluation and cardiac catheterization according to previously described techniques.6-11 The arterial oxygen saturation was recorded by a cuvette oximeter (Waters, model no. XC5OB) and verified by a reflection oximeter (American Optical, model no. 10800). Mixed venous blood saturation was estimated from samples obtained in the midright atrium or superior vena cava. Systemic saturation was measured in femoral or brachial arterial blood. The same site was used to measure systemic pressure. Pulmonary artery samples and pressures were taken in the pulmonary artery in all patients.

After collection of data while the patients were breathing air, 100% oxygen was supplied at high flow through a rubber molded face mask with a small mechanical dead space attached to an anesthesia machine washed out with 100% oxygen. After at least 10 min of oxygen breathing, blood samples were drawn and pressures were recorded.

The arterial pH, PₐO₂ and PᵥO₂ were measured by an Instrumentation Laboratories analyzer (model 113) in 15 of the 16 patients breathing air and in 11 patients breathing oxygen. There was good agreement between the PᵥO₂ and the oxygen saturation measured by oximetry. Hemoglobin was determined by a hemoglobinometer (Fisher, model 55).

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Received August 3, 1971; revision accepted for publication August 21, 1972.
In nine of the 16 patients, the pulmonary artery, mixed venous, and systemic blood samples were drawn simultaneously by a double-venous catheter technique. In cases in which only one venous catheter was used, the samples were taken in rapid succession from similar locations during both conditions. Indicator-dilution dye curves (indocyanine green) were recorded in all patients while they were breathing room air and in eight while they were breathing 100% oxygen.

The patients were premedicated with various combinations of drugs. The studies reported were made almost an hour after premedication was given.

**Calculations**

Systemic ($Q_s$) and pulmonary ($Q_o$) blood flows were calculated by the Fick principle (the oxygen consumption is divided by the systemic and the pulmonary arteriovenous oxygen content difference, respectively). The assumed oxygen consumption based on age, sex, and heart rate as recommended by LaFarge and Miettinen,12 and the same values were used for calculations on 100% oxygen.6,13 The pulmonary venous saturation was assumed to be 97% on room air and 100% on 100% oxygen.14 The pulmonary venous dissolved oxygen was assumed to be 1.8 vol %14 on 100% oxygen. The dissolved oxygen in the systemic circulation was calculated from the oxygen tension ($P_O2$).

Estimations usually reported as left-to-right and right-to-left shunts were calculated as follows:15

\[
\text{Percentage left-to-right} = \frac{Q_{PA} - Q_{MV}}{Q_{PV} - Q_{MV}} \times 100 \quad (1)
\]

\[
\text{Percentage right-to-left} = \frac{Q_{PV} - Q_s}{Q_{PV} - Q_{MV}} \times 100 \quad (2)
\]

in which $Q_{PV}$ = oxygen content, pulmonary venous blood; $Q_{MV}$ = oxygen content, mixed venous blood; $Q_s$ = oxygen content, systemic arterial blood; and $Q_{PA}$ = oxygen content, pulmonary artery blood.6

The total truncal valve flow ($Q_T$) times the systemic arterial oxygen content is equal to the amount of pulmonary venous return and its oxygen content plus the total systemic return and its oxygen content: $Q_sC_{PV} + Q_oC_{MV} = Q_TC_s$.

\[
Q_sC_{PV} + Q_oC_{MV} = Q_TC_s. \quad (3)
\]

Since $Q_T = Q_s + Q_o$ or $Q_T = Q_s - Q_o$ and $C_s = C_{PA}$ as seen in our patients (table 1), $Q_T - Q_s$ can be substituted for $Q_s$ in equation 3 as follows:

\[
Q_oC_{PV} + Q_TC_{MV} - Q_oC_{MV} = Q_tC_s \quad (4)
\]

\[
\frac{Q_T}{Q_o} \text{ or } \frac{Q_T}{Q_s} \text{, respectively, in patients with VSD. In patients with truncus arteriosus (with a mixing chamber distal to the truncal valve), they signify}
\]

\[
\frac{Q_T}{Q_o} \text{ and } \frac{Q_T}{Q_s}, \text{ respectively.}
\]

\[
\frac{Q_T}{Q_o} + \frac{Q_T}{Q_s}, \text{ respectively.}
\]

\[
\text{or } Q_s (C_{PV} - C_{MV}) = Q_T (C_s - C_{MV}). \quad (5)
\]

This rearranges to:

\[
\frac{Q_T}{Q_s} = \frac{C_s - C_{MV}}{C_{PV} - C_{MV}}. \quad (6)
\]

By substituting $Q_T - Q_o$ for $Q_s$ in equation 3, the equation for the $\frac{Q_s}{Q_T}$ ratio is derived.

The terms "right-to-left shunt" and "left-to-right shunt" are retained below for the sake of brevity in relation to all cases.

Left-to-right shunts and right-to-left shunts were also calculated from dye curves.16,17 Percentage of left-to-right shunts were calculated from double sampling dye curves only.

The total pulmonary and total systemic resistances were calculated by dividing the mean pulmonary artery pressure by the pulmonary flow and the mean systemic pressure by the systemic flow, respectively. The resistance values are expressed as units • m². In the absence of mitral valve disease or obstruction at the pulmonary veins, the high total pulmonary resistance is considered to reflect predominantly the pulmonary arteriolar resistance.

**Illustrative Case**

The hemodynamic data in table 2 are from two successive cardiac catheterizations 7 years apart in a patient with ventricular septal defect and severe PVOD. Calculations on room air at the second cardiac catheterization were made using measured oxygen consumption. The results suggest that the progression and severity of the disease cannot be estimated from the ratio of total pulmonary resistance to total systemic resistance since this ratio remained the same over the years. In addition, a marked increase in calculated systemic resistance is noted at the second cardiac catheterization on air as well as on oxygen. This increase in systemic resistance is advantageous in maintaining some pulmonary flow in the presence of increased pulmonary resistance. However the marked increase in systemic and pulmonary loads is reflected by the marked decrease in pulmonary and systemic flows. This combined load will eventually lead to heart failure. A sudden transient decrease in the systemic resistance might lead to decreased pulmonary flow and thus to hypoxia and further systemic vasodilatation, pulmonary vasoconstriction, and a vicious cycle leading to sudden death.

**Results**

The data acquired from the 16 patients are summarized in table 1. The data were analyzed throughout using Student's t test.

**Hemoglobin Content.** The hemoglobin content ranged from 12.8 to 19.2 g/100 ml (mean ± se, 15.4 ± 0.6 g/100 ml) in the patients with ventricular septal defect and from 12.6 to 17.8 g/100 ml
Table 1
Cumulative Hemodynamic Data in Nine Patients With Ventricular Septal Defect and Seven With Truncus Arteriosus Breathing Room Air and 100% Oxygen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
<th>Mean ± SE</th>
<th>Mean ± SE</th>
<th>Mean diff</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Room air</td>
<td>100% O2</td>
<td>Room air</td>
<td>100% O2</td>
<td></td>
</tr>
<tr>
<td>Systemic saturation (%)</td>
<td>72 - 93</td>
<td>95 - 100</td>
<td>88.3 ± 2.2</td>
<td>97.2 ± 1.3</td>
<td>8.9 ± 1.1</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>saturation (%)</td>
<td>58 - 82</td>
<td>74 - 94</td>
<td>72.6 ± 2.65</td>
<td>85.7 ± 2.2</td>
<td>13.1 ± 1.2</td>
</tr>
<tr>
<td>Pulmonary artery mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pressure (mm Hg)</td>
<td>67 - 89</td>
<td>65 - 97</td>
<td>76.2 ± 2.2</td>
<td>78.3 ± 3.3</td>
<td>2.1 ± 1.4</td>
</tr>
<tr>
<td>Systemic mean pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>69 - 101</td>
<td>75 - 107</td>
<td>83.1 ± 3.1</td>
<td>88.1 ± 3.7</td>
<td>5.0 ± 1.8</td>
</tr>
<tr>
<td>Rq (units · m²)</td>
<td>14.3 - 63.0</td>
<td>14.4 - 27.8</td>
<td>29.8 ± 4.7</td>
<td>26.1 ± 4.6</td>
<td>-3.6 ± 1.3</td>
</tr>
<tr>
<td>Rv (units · m²)</td>
<td>12.3 - 36.2</td>
<td>15.7 - 48.6</td>
<td>25.9 ± 2.7</td>
<td>34.5 ± 3.6</td>
<td>8.6 ± 1.9</td>
</tr>
<tr>
<td>Qp (liters/min/m²)</td>
<td>1.4 - 5.6</td>
<td>1.6 - 5.7</td>
<td>3.0 ± 0.4</td>
<td>3.5 ± 0.4</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>L → R (%)</td>
<td>2.1 - 5.6</td>
<td>1.9 - 4.9</td>
<td>3.5 ± 0.4</td>
<td>2.8 ± 0.3</td>
<td>-0.7 ± 0.15</td>
</tr>
<tr>
<td>L → R (%)</td>
<td>0 - 37</td>
<td>15 - 53</td>
<td>15.3 ± 4.6</td>
<td>31.3 ± 3.8</td>
<td>16.0 ± 4.0</td>
</tr>
<tr>
<td>R → L (%)</td>
<td>13 - 59</td>
<td>8 - 43</td>
<td>29.1 ± 4.6</td>
<td>25.2 ± 3.5</td>
<td>-3.9 ± 3.0</td>
</tr>
</tbody>
</table>

Cardiac output (ml) decreased significantly (P < 0.01) in both groups when shifted to breathing 100% oxygen. The increase in the patients with truncus arteriosus for the systemic vascular resistance was significantly greater than that in the patients with ventricular septal defect. The values were similar in the two groups. The patients with higher pulmonary vascular resistance with room air had higher systemic resistance (P = 0.02). The relationship between pulmonary and systemic vascular resistances is shown in figure 1. After the shift to 100% oxygen, a decrease in cardiac output was shown.

Abnormal values are shown in Table 1.
oxygen, the calculated systemic vascular resistance increased in 15 of the 16 patients, the increase ranging from 3.0 to 18.1 units \cdot m^2 in the patients with ventricular septal defect and from -2.2 to +10.8 units \cdot m^2 in the patients with truncus arteriosus. For both groups, the mean increase in systemic resistance was significantly \((P = 0.02)\) greater than the mean decrease in pulmonary resistance.

### Pulmonary Blood Flow

The pulmonary blood flow increased in eight of the nine patients with ventricular septal defect and no change was noted in one when they were breathing 100% oxygen; it increased in six of the patients with truncus arteriosus and decreased slightly in one.

### Systemic Blood Flow

On institution of oxygen breathing, the systemic blood flow decreased in all
patients with ventricular septal defect, the decrease ranging from 0.1 to 1.4 liters/min/m². It also decreased in six of the patients with truncus arteriosus and increased in one; these changes ranged between -1.5 and +0.8 liters/min/m².

**Effect of 100% Oxygen on Left-to-Right and Right-to-Left Shunts.** An increase in calculated left-to-right shunt was noted in all patients with ventricular septal defect when breathing 100% oxygen. Among the patients with truncus arteriosus, in six there was an increase and in one there was a decrease of 4%. A decrease in right-to-left shunt was noted in both groups. Three of the patients with ventricular septal defect had an increase; in this group the range of changes was from +13 to -16%. Six of the seven patients with truncus arteriosus showed a decrease and one showed no change; the range of changes was from 0 to -22%. Figure 2 demonstrates the decrease in right-to-left shunt and the appearance of left-to-right shunt on institution of breathing 100% oxygen in a patient with ventricular septal defect. In this patient the changes in the shunts are solely due to the marked increase of the systemic resistance.

![Figure 2](image)

*Figure 2*  
**Indicator-dilution curves in patient with ventricular septal defect and severe pulmonary vascular obstructive disease breathing room air and 100% oxygen.** For demonstration of change in right-to-left shunt, injection site on room air is in superior vena cava (S.V.C.) and sampling site is in brachial artery (B.A.). The injection site on 100% oxygen is in mid-right atrium (Mid R.A.) and sampling is from B.A. In absence of atrial communication, this change in position is inconsequential. Similarly, change of catheter positions when demonstrating left-to-right shunt from injection into right pulmonary artery (R.P.A.) and sampling from main pulmonary artery (M.P.A.) on room air to injection into left pulmonary artery and sampling from right pulmonary artery is inconsequential. Note appearance of left-to-right shunt and decrease in right-to-left shunt associated with breathing 100% oxygen. While this patient was breathing 100% oxygen, pulmonary vascular resistance increased 1.4 units × m² while systemic resistance increased 14.9 units × m².

**Discussion**

The patients in the present study were different from any group hitherto reported in that each had pulmonary hypertension and severe PVOD.

The observed high systemic resistance while breathing room air could not be explained by the hemoglobin content. Although there was a correlation between the hemoglobin content and the systemic resistance \( P = 0.025 \), the resistance was far greater than the values predicted from increased viscosity secondary to increases in the hematocrit value alone in our patients. This is demonstrated by the data in table 2: The hemoglobin content was 17.3 g/100 ml and the systemic resistance was 60.6 units-m². The pulmonary resistance at this time was 43.5 units-m².

Sudden death is the most common cause of death among patients with severe PVOD. Young and Mark\(^{14} \) recently reported on the fate of patients with severe PVOD (Eisenmenger's syndrome). Ten of 17 patients died suddenly. Clarkson and associates\(^{19} \) stated that the most common cause of death was "sudden" or "unknown." Nine of the 17 patients reported by them died "suddenly" or from unknown causes; one died during an episode of influenza (high fever?).

Because the pulmonary blood flow in our patients is necessarily a reflection of the \( R_s/R_e \) ratio, an increase in systemic resistance should have a favorable effect. Any decrease in systemic resistance—induced by drugs, anesthesia, exercise, heat, fever, or angiographic contrast media—will decrease pulmonary blood flow unless pulmonary resistance also decreases. Indeed, a decrease in systemic resistance in such patients could lead to episodes similar to the hypoxic spells of patients with tetralogy of Fallot or to a vicious cycle of progressive hypoxia, progressive systemic vasodilatation associated with pulmonary vasoconstriction leading to death.

It might be postulated that PVOD causing an increase in pulmonary resistance leads to an increase in systemic resistance as well. It is interesting to note that the patients with truncus arteriosus, with a mean age of 7½ years, had a mean systemic resistance similar to that reported for adults.\(^{11} \) and significantly higher than the values obtained in the pediatric age group in patients without heart disease in our cardiac catheterization laboratory.\(^{11} \) In the group with ventricular septal defect, the mean systemic resistance, with room air, was similar to that reported in adults; however,
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those patients with higher pulmonary resistance had higher systemic resistance.

The marked increase in systemic resistance observed in patients with severe PVOD tends to cause underestimation of the severity of the disease if the $R_s/R_a$ ratio is used as the only index of severity. Thus, this ratio should always be considered along with the resistance in absolute units.

Despite the similar pulmonary and systemic vascular resistances, the systemic saturations in the two groups differed significantly on room air as well as in response to 100% oxygen. Although influenced by the $R_s/R_a$ ratio, the systemic saturation in patients with truncus arteriosus cannot be as high on room air or oxygen as in those with ventricular septal defect, because of the “common mixing chamber” at the truncal level (see previous footnote). In none of the patients with truncus arteriosus breathing oxygen did the systemic saturation exceed 96% while in five of nine patients with ventricular septal defect the systemic saturation reached 100% with a $Po_2$ greater than 150 mm Hg. The hemodynamic effect of the “common mixing chamber” in the patients with truncus arteriosus is indicated by the essential identity of the mean systemic saturation and the mean pulmonary artery saturation, as seen in our patients, by the similar magnitudes of the calculated left-to-right and right-to-left shunts on room air, and by the similar changes in left-to-right and right-to-left shunts on 100% oxygen. In patients with truncus arteriosus, the systemic artery saturation is directly proportional to the amount of total pulmonary flow, a situation similar to that found by Burchell in total anomalous pulmonary venous drainage.

The decrease in pulmonary vascular resistance while breathing oxygen is compatible with observations made by others. Since only three of 16 patients did not show any decrease in pulmonary vascular resistance, it is apparently uncommon to obtain no response at all even in the presence of severe PVOD.

The single most important hemodynamic change while breathing oxygen was the increase in systemic vascular resistance. A similar change (an increase of 25% in the calculated systemic resistance) was reported by Marshall et al. in patients with ventricular septal defect and mild-to-severe pulmonary vascular obstructive disease. The observation is made by these authors that the increase in systemic resistance was mainly due to an increase in the younger age group. In our study, there was no difference in the response of the systemic vascular bed in patients of different ages.

Methodologic Considerations

The oxygen consumption for the calculations of pulmonary and systemic blood flows was estimated according to the tables of LaFarge and Miettinen and was assumed not to change while the patient was breathing oxygen. The difference between the actual and the estimated $V_o_2$ might cause a change in the calculated pulmonary and systemic flows in either direction. A random change toward one direction—a decrease or increase in the calculated $Q_o$ or $Q_s$—cannot be ruled out. Our assumption of constancy will cause underestimation of pulmonary and systemic flows and overestimation of pulmonary and systemic resistances, if indeed there were an increase in oxygen utilization. However, Barratt-Boyce and Wood found no change in $V_o_2$ in normal humans breathing air and oxygen. Swan and Marshall and their associates found an increase of 3% and 5% in $V_o_2$ in patients with atrial septal defect and ventricular septal defect with varying severity of PVOD.

Such a change, if it occurred, would not significantly affect our results with an increase of 22% and 33% in the systemic resistance and a decrease of 12% and 17% in the pulmonary resistance. Marshall et al. also noted an increase of 25% in systemic resistance. This observation is similar to that found in our patients. Since our observations are similar in direction and magnitude to the previously reported observations, it seems unlikely that a change in oxygen consumption of significant degree had occurred.

Pulmonary venous saturation was assumed to be 97%. Because patients with evidence of lung disease or respiratory depression due to premedication were excluded from this study, it is unlikely that the pulmonary venous saturation deviated significantly from this value. In addition, the total right-to-left shunt (intracardiac and intrapulmonary) while breathing oxygen was estimated in eight patients by calculations based on oxygen content differences and using an assumed pulmonary venous saturation of 100% and a value of 1.8 vol % for dissolved oxygen. These calculations were compared with the intracardiac right-to-left shunt estimated from dye curves in the same eight patients while breathing oxygen. The difference in shunt estimates between the two methods ranged between +13% and −13% with a mean for the group.
of −3%. These data indicate that our assumption of pulmonary venous saturation of 100% and dissolved oxygen of 1.8 vol % in these patients while breathing oxygen is accurate. These data also indicate that, if intrapulmonary shunts do exist in these patients, they are most probably of small magnitude.

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Circulation. 1973;47:94-100
doi: 10.1161/01.CIR.47.1.94

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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