Reversible Decrease of Oxygen Consumption by Hyperoxia*

Konrad Reinhart, M.D.; Frank Bloos, M.D.; Frank König; Donald Bredle, Ph.D.; and Lutz Hannemann, M.D.

The hemodynamic and metabolic effects of 90 minutes normobaric hyperoxia were studied in 20 critically ill patients (11 septic, 9 nonseptic) requiring mechanical ventilation with inspired \( O_2 \) fraction (\( F_{\text{I}O_2} \)) \(<0.40\). Thirty minutes after increasing the \( F_{\text{I}O_2} \) to 1.0, arterial \( \text{PO}_2 \) had increased from about 100 to about 400 mm Hg, and whole body oxygen uptake (\( \text{VO}_2 \)) was decreased 10 percent (p\(<0.05\)) due to an 18 percent decrease in \( O_2 \) extraction ratio. During the subsequent 60 minutes of hyperoxia, there was no further significant change in \( \text{VO}_2 \). Cardiac index did not change in hyperoxia, but it increased 10 percent (p\(<0.05\)) in recovery as systemic vascular resistance decreased. \( \text{VO}_2 \) returned to baseline after 30 minutes recovery at original \( F_{\text{I}O_2} \) due to increased \( O_2 \) extraction as well as the increased cardiac output. The decrease in \( \text{VO}_2 \) without a decrease in \( O_2 \) delivery may reflect maldistribution of blood flow and functional \( O_2 \) shunting to protect tissue from unphysiologically high \( \text{PO}_2 \). While brief oxygenation is advisable before periods of hypoventilation, the present data suggest that hyperoxic ventilation in these patients with already adequate \( O_2 \) delivery was counterproductive.

\( \text{CaO}_2 \) = arterial oxygen content; \( \text{CaO}_2 - \text{CvO}_2 \) = arteriovenous \( O_2 \) content difference; \( \text{CvO}_2 \) = mixed venous oxygen content

In contrast, in 35 patients prior to anesthesia, we found a significant decrease of 15 percent in \( \text{VO}_2 \) with \( O_2 \) breathing for 10 minutes. This resulted from decreases of 5 percent in cardiac output and 12 percent in arteriovenous \( O_2 \) content difference. A recent brief report has corroborated this finding. These observations, however, were somewhat limited by the short time of hyperoxic ventilation and the failure to test for reversibility. The present study further explores this \( O_2 \) supply/demand paradox, in particular the time course and reversibility of 100 percent \( O_2 \) breathing for 90 minutes on \( O_2 \) delivery and uptake in critically ill patients.

**METHODS**

Twenty postoperative, critically ill patients with sepsis (n = 9, 5 with peritonitis and 4 with pneumonia) or other cardiorespiratory insufficiencies (n = 11, 8 with pneumonia or tracheobronchitis) were studied after informed consent and approval by the institutional research committee. All patients required mechanical ventilation, with inspired oxygen fraction (\( F_{\text{I}O_2} \)) less than 0.40, and invasive cardiovascular monitoring with pulmonary and radial artery catheters. A Swan-Ganz catheter was percutaneously placed into an internal jugular vein using standard aseptic technique and local infiltration with 1 percent lidocaine. The balloon of the catheter was inflated with 1.5 ml of air and advanced until a typical wedge pressure waveform appeared. Proper location of the catheter tip was verified before each sampling period by observing the wedge pressure tracing. Patients were sedated with continuous infusion of flunitrazepam and Fentanyl as needed to tolerate an endotracheal tube and controlled ventilation. Total parenteral nutrition was continuously provided in all cases. Of the nine patients with sepsis, eight had isotropic support via continuous intravenous (IV) infusion of dobutamine, alone (n = four) or in combination with norepinephrine (n = four). Six of the 11 patients without sepsis received continuous dobutamine infusion. Patients were studied only during hemodyonamically stable periods in which no volume replacement, medication, or change in isotropic support or body temperature was occurring.

*From the Department of Anesthesiology and Intensive Care Medicine, Klinikum Steglitz, Free University of Berlin, Germany (Drs. Reinhart, Hannemann and Bloos and Mr. König), and the Applied Physiology Research Laboratory, Kent State University, Kent, Ohio (Dr. Bredle).

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Reprint requests: Dr. Reinhart, Klinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany

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Table 1—Oxygen Transport Related Variables*

<table>
<thead>
<tr>
<th></th>
<th>Baseline FIO2 &lt; 0.4, 0 min</th>
<th>Hyperoxia FIO2 = 1.0</th>
<th>Recovery FIO2 &lt; 0.4, 120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 min</td>
<td>60 min</td>
<td>90 min</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>113 ± 3†</td>
<td>402 ± 106</td>
<td>407 ± 100</td>
</tr>
<tr>
<td>PCO2, mm Hg</td>
<td>40 ± 4†</td>
<td>52 ± 7</td>
<td>51 ± 7</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>97 ± 2†</td>
<td>99 ± 1</td>
<td>99 ± 1</td>
</tr>
<tr>
<td>SVo2, %</td>
<td>72 ± 9†</td>
<td>83 ± 8§</td>
<td>80 ± 9</td>
</tr>
<tr>
<td>CaO2, ml/dl</td>
<td>14.5 ± 1.8†</td>
<td>15.7 ± 2.0</td>
<td>15.8 ± 2.0</td>
</tr>
<tr>
<td>CVo2, ml/dl</td>
<td>10.4 ± 1.8†</td>
<td>12.1 ± 1.9</td>
<td>11.8 ± 2.0</td>
</tr>
<tr>
<td>PaO2-CvO2, %</td>
<td>4.0 ± 1.4†</td>
<td>3.5 ± 1.1f</td>
<td>3.9 ± 1.2</td>
</tr>
<tr>
<td>O2 er, %</td>
<td>27.4 ± 9.0†</td>
<td>22.5 ± 6.6‡</td>
<td>25.1 ± 7.5</td>
</tr>
<tr>
<td>O2 extraction, ml/min/m-2</td>
<td>581 ± 175</td>
<td>619 ± 166</td>
<td>606 ± 192</td>
</tr>
<tr>
<td>VO2, ml/min/m-2</td>
<td>149 ± 34†</td>
<td>134 ± 33</td>
<td>141 ± 31</td>
</tr>
<tr>
<td>pH, arterial</td>
<td>7.41 ± 0.05†</td>
<td>7.39 ± 0.05</td>
<td>7.38 ± 0.05</td>
</tr>
<tr>
<td>pH, venous</td>
<td>7.40 ± 0.05</td>
<td>7.39 ± 0.05</td>
<td>7.39 ± 0.06</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>35 ± 6</td>
<td>35 ± 5</td>
<td>35 ± 6</td>
</tr>
<tr>
<td>PvCO2, mm Hg</td>
<td>37 ± 6</td>
<td>40 ± 7</td>
<td>39 ± 7</td>
</tr>
</tbody>
</table>

*All values are mean ± SD. PaO2—arterial O2 tension; PV02—mixed venous O2 tension; SaO2—arterial O2 saturation; SvO2—mixed venous O2 saturation; CaO2—arterial O2 content; CvO2—mixed venous O2 content; CaO2-CvO2—arterio-mixed venous O2 content difference; O2 er—O2 extraction ratio; VO2—O2 consumption; PaCO2—arterial carbon dioxide tension; PvCO2—mixed venous carbon dioxide tension.

†p<0.001 between adjacent values.
‡p<0.05.
§p<0.01.

The paired arterial and mixed venous blood samples were drawn simultaneously and slowly from the radial and pulmonary artery, respectively. The blood gas samples were collected as 1.5 ml in 3-mi polystyrene, plastic syringes whose dead space (0.05 ± 0.015 ml) was prefilled with heparin sodium 1,000 UPS units/ml. The samples were icwed and analyzed within 5 to 10 minutes. Oxygen content for arterial (CaO2) and mixed venous (CvO2) blood was derived from measurements of hemoglobin concentration and O2 saturation (IL-282 CO-oximeter) and PO2 (Radiometer ABL-2, Copenhagen). Cardiac output was measured in triplicate by thermodilution. O2 delivery was calculated as the product of cardiac index and CaO2. VO2 was determined via the Fick principle as the product of cardiac index and arteriovenous O2 content difference. O2 extraction ratio was calculated as (CaO2-CvO2)/CaO2. Systemic vascular resistance was determined as follows: (mean arterial pressure—central venous pressure)/cardiac output. Pulmonary vascular resistance was similarly calculated with wedge pressure and cardiac output. Left ventricular stroke work index was calculated as follows: stroke index × (mean arterial pressure− pulmonary capillary wedge pressure) × 0.0136.

Data were analyzed using the Friedman statistic for multiple treatments of the same subjects by a post hoc Wilcoxon signed-rank test.

RESULTS

With 100 percent O2 ventilation, PaO2 increased from about 100 to about 400 mm Hg resulting in an 8 percent increase in CaO2 (Table 1). Cardiac index and O2 delivery remained unchanged throughout hyperoxia (Tables 1 and 2). An 18 percent decrease in O2 extraction ratio at 30 minutes of hyperoxia resulted in a 10 percent decrease in VO2 (Table 1). Throughout the remaining 60 minutes of hyperoxia, VO2 showed no further significant change. Other hemodynamic variables such as heart rate, mean arterial pressure, pulmonary capillary wedge pressure, systemic and pulmonary vascular resistances, and left ventricular stroke work index were not significantly altered by hyperoxia (Table 2).

After 30 minutes' recovery at baseline FIO2, cardiac index increased 10 percent while peripheral vascular resistance decreased. Since CaO2 was significantly reduced, O2 delivery was not significantly increased. The O2 extraction increased slightly, and VO2 returned to the prehyperoxic level.

DISCUSSION

The apparently paradoxical decrease in whole body VO2 during 90 minutes hyperoxic ventilation in critically ill patients extends earlier observations of a similar effect with only 10 minutes O2 breathing. Before animal experiments have yielded similar results. Hyperoxic ventilation depressed in a reversible manner whole body VO2 as well as isolated hind limb VO2 in anesthetized dogs that were anemic, β-blocked, or vagotomized, but not in intact, normocytic animals. In a recent study, 20 minutes hyperoxic ventilation reduced whole body VO2 in chronically instrumented conscious dogs. The present findings are also consistent with reports of decreased regional VO2 and impaired organ function during O2 breathing. For example, short-term hyperoxia was shown to do the following: (1) increase myocardial ischemia in patients with coronary artery disease; (2) to reduce cardiac output; myocardial contractility, and...
Table 2—Hemodynamic Variables*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline FIO₂ &lt; 0.4</th>
<th>Hyperoxia FIO₂ = 1.0</th>
<th>Recovery FIO₂ &lt; 0.4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 min</td>
<td>30 min</td>
<td>60 min</td>
</tr>
<tr>
<td>HR, b/min</td>
<td>99 ± 26</td>
<td>103 ± 20</td>
<td>103 ± 21</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>87 ± 12</td>
<td>88 ± 11</td>
<td>85 ± 11</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>13 ± 5</td>
<td>12 ± 3</td>
<td>12 ± 4</td>
</tr>
<tr>
<td>CI, L/min·m⁻²</td>
<td>4.0 ± 1.2</td>
<td>4.0 ± 1.1</td>
<td>3.9 ± 1.2</td>
</tr>
<tr>
<td>LVSWI, gm·m⁻²⁻¹</td>
<td>52 ± 60</td>
<td>43 ± 18</td>
<td>39 ± 16</td>
</tr>
<tr>
<td>SVR, dyne·cm⁻¹·m⁻²</td>
<td>958 ± 405</td>
<td>960 ± 349</td>
<td>990 ± 510</td>
</tr>
<tr>
<td>PVR, dyne·cm⁻¹·m⁻²</td>
<td>177 ± 108</td>
<td>180 ± 80</td>
<td>193 ± 121</td>
</tr>
</tbody>
</table>

*All values are mean ± SD. HR = heart rate; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; CI = cardiac index; LVSWI = left ventricular stroke work index; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance.

†p<0.05
‡p<0.001 between adjacent values.

myocardial VO₂ in humans, dogs, and isolated rabbit hearts; (3) to decrease cerebral VO₂; (4) to decrease renal blood flow and function; and (5) to decrease hepatic blood flow.

In contrast to earlier works and to our previous findings in nonseptic presurgical patients, cardiac output did not decrease, nor systemic vascular resistance increase, with hyperoxia in these patients. A possible reason for the blunted effect at the resistance vessel level is that more than half these patients suffered from sepsis or pneumonia which are known to lower vascular resistance and to diminish vascular reactivity. With return to baseline FIO₂ in the recovery period, however, a decrease in vascular resistance and an increase in cardiac output did indicate some release of constriction of the resistance vessels.

The decrease in VO₂ in hyperoxia without a fall in O₂ delivery suggests maldistribution of blood flow in the microcirculation and increased functional O₂ shunting. This is consistent with an increase in Pvo₂ and a decrease in O₂ extraction similar to that seen by others. In recovery, an increase in VO₂ and fall of Pvo₂ to baseline levels suggested improvement of blood flow at the distribution vessels. In thin muscle preparations, increased PaO₂ caused vasoconstriction, reduction of capillary density, and development of regions with no capillary flow. Widening of intercapillary distances has been shown to occur in rat heart after moderate hyperoxia (PaO₂ > 150 mm Hg) with maximum distances observed at PaO₂ near 300 mm Hg. If microcirculatory controls act to protect tissue from unphysiologically high PO₂ in hyperoxia, overshooting of such responses might lead to some areas of relative hypoxia. There are several reports about left-shifted PO₂ histograms (increases in low tissue PO₂ values) in skeletal muscle during hyperoxia.

We conclude that impaired tissue O₂ delivery on the tissue level may be one possible mechanism responsible for depression of cellular respiration and/or organ dysfunction in short-term hyperoxia. Canine limb VO₂ was reversibly reduced by local hyperoxic perfusion when flow decreased as vascular resistance increased. Similar O₂ delivery-dependence has been reported for canine myocardial performance. Those findings along with the immediate recovery of VO₂ that we observed when FIO₂ was returned to baseline make O₂ toxicity an unlikely cause of the reduction in VO₂. Reduced ventilatory and cardiac work due to increased FIO₂ may have contributed to a reduction in whole body VO₂ in spontaneously breathing subjects. In this study, however, only patients receiving continuous positive pressure ventilation and optimized patient-ventilator match by deep sedation were investigated; they also exhibited no significant changes in cardiac output or left ventricular stroke work during hyperoxia. It is unlikely, therefore, that the decrease in VO₂ can be explained by a hyperoxia-induced decrease in respiratory drive and concomitant decrease in cardiorespiratory work. Other possibilities for the decrease in VO₂ would include systemic cellular O₂ toxicity and a facultative decrease in O₂ demand.

Methodologic Validity

The validity of O₂ consumption measurement by thermodilution and cardiac output and arteriovenous oxygen content difference has been confirmed by direct comparison with that measured by respiratory gas exchange and considered even more accurate.
under hyperoxic conditions than the respiratory method.\textsuperscript{40,41} Calculation of the arterial and venous O\textsubscript{2} content from measurement of O\textsubscript{2} saturation using the co-oximeter was shown to be in good agreement with direct measurements of O\textsubscript{2} content by the classic Van Slyke vacuum extraction and manometric procedure or the use of an O\textsubscript{2}-consuming cell.\textsuperscript{42} Lodato,\textsuperscript{12} applying the same method for calculation of O\textsubscript{2} consumption as \( V_{O_2} = CI \times (CaO_2 - C\bar{V}O_2) \), very carefully ruled out a systematic underestimation of \( V_{O_2} \) during hyperoxia.

**POSSIBLE CLINICAL IMPLICATIONS**

The current practice of short-term O\textsubscript{2} administration in procedures such as intubation, bronchoscopy, or other situations that may result in hypoxemia is undoubtedly advisable to increase alveolar \( P_o_2 \) and the modest \( O_2 \) stores that are available. Our findings, however, suggest that increasing the \( FIO_2 \) may temporarily disturb tissue oxygenation and \( O_2 \) consumption in critically ill patients whose whole body \( O_2 \) delivery can be maintained by adequate conventional intensive care therapy. Within the limits of this study, that is in hemodynamically stable patients, typically with sepsis or pneumonia and \( PaO_2 \) of about 100 mm Hg, ventilation with 100 percent \( O_2 \) did not improve whole body oxygenation over a time span of 90 minutes. On the contrary, \( PaO_2 \) at unphysiologically high levels reduced \( V_{O_2} \).

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