Hypoxic Pulmonary Vasoconstriction in Nonventilated Lung Areas Contributes to Differences in Hemodynamic and Gas Exchange Responses to Inhalation of Nitric Oxide

Albert Benzing, M.D.,* Georg Mols, M.D.,† Thomas Brieschal, M.D.,‡ Klaus Geiger, M.D.§

Background: Enhancement of hypoxic pulmonary vasoconstriction (HPV) in nonventilated lung areas by almitrine increases the respiratory response to inhaled nitric oxide (NO) in patients with acute respiratory distress syndrome (ARDS). Therefore the authors hypothesized that inhibition of HPV in nonventilated lung areas decreases the respiratory effects of NO.

Methods: Eleven patients with severe ARDS treated by venovenous extracorporeal lung assist were studied. Patients' lungs were ventilated at a fraction of inspired oxygen (F\text{\textsubscript{O}\text{2}}) of 1.0. By varying extracorporeal blood flow, mixed venous oxygen tension (P\text{\textsubscript{vO}\text{2}}), partial oxygen pressure in mixed venous blood (P\text{\textsubscript{aO}\text{2}}), was adjusted randomly to four levels (means, 47, 54, 64 and 84 mmHg). Extracorporeal gas flow was adjusted to prevent changes in mixed venous carbon dioxide tension (P\text{\textsubscript{vCO}\text{2}}). Hemodynamic and gas exchange variables were measured at each level before, during, and after 15 ppm NO.

Results: Increasing P\text{\textsubscript{vO}\text{2}} from 47 to 84 mmHg resulted in a progressive decrease in lung perfusion pressure (PAP-PWPD; P < 0.05) and pulmonary vascular resistance index (PVR; P < 0.05) and in an increase in intrapulmonary shunt (Q\text{\textsubscript{sh}}/Q\text{\textsubscript{T}}; P < 0.05). P\text{\textsubscript{vCO}} and cardiac index did not change. Whereas the NO-induced reduction in PAP-PWPD was smaller at high P\text{\textsubscript{vO}}. NO-induced decrease in Q\text{\textsubscript{sh}}/Q\text{\textsubscript{T}} was independent of baseline P\text{\textsubscript{vO}}. In response to NO, arterial P\text{\textsubscript{a}} increased more and arterial oxygen saturation increased less at high compared with low P\text{\textsubscript{vO}}.

Conclusion: In patients with ARDS, HPV in nonventilated lung areas modifies the hemodynamic and respiratory response to NO. The stronger the HPV in nonventilated lung areas the more pronounced is the NO-induced decrease in PAP-PWPD. In contrast, the NO-induced decrease in Q\text{\textsubscript{sh}}/Q\text{\textsubscript{T}} is independent of P\text{\textsubscript{vO}}, over a wide range of P\text{\textsubscript{vO}} levels. The effect of NO on the arterial oxygen tension varies with the level of P\text{\textsubscript{vO}}, by virtue of its location on the oxygen dissociation curve. (Key words: Gases, nitric oxide. Lung: acute respiratory distress syndrome; extracorporeal lung assist; hypoxic pulmonary vasoconstriction.)

IN patients with the acute respiratory distress syndrome (ARDS), inhalation of nitric oxide (NO) decreases pulmonary artery pressure and decreases intrapulmonary right-to-left shunt (Q\text{\textsubscript{sh}}/Q\text{\textsubscript{T}}). Inhaled NO dilates vessels of ventilated lung areas, thereby redistributing blood flow from nonventilated to ventilated lung regions. As a consequence ventilation-perfusion (V\text{\textsubscript{v}}/Q\text{\textsubscript{v}}) matching improves. A physiologic mechanism of improvement in V\text{\textsubscript{v}}/Q match is hypoxic pulmonary vasoconstriction (HPV) in lung areas with low ventilation/perfusion ratios.

 Whereas in ventilated alveoli low alveolar oxygen tension is primarily responsible for eliciting HPV, in nonventilated alveoli mixed venous oxygen tension (P\text{\textsubscript{vO}}) becomes the decisive stimulus. Enhancement of HPV by almitrine has been shown to decrease Q\text{\textsubscript{sh}}/Q\text{\textsubscript{T}}, to improve oxygenation, and to increase pulmonary artery pressure in patients with acute lung injury and ARDS. Further, almitrine increases the respiratory response to inhaled NO, suggesting that redistribution of blood flow toward ventilated lung units during administration of NO is increased by HPV in nonventilated lung areas. Therefore we hypothesized that attenuation of HPV in nonventilated lung areas decreases the respiratory response to inhaled NO.
INHALED NO AND NONVENTILATED LUNG AREAS

Table 1. Patient Clinical Characteristics at Time of Study

<table>
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<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Underlying Disease</th>
<th>Days of Mechanism Ventilation</th>
<th>Days on ECLA</th>
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<td>Urosepsis</td>
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<td>10</td>
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ECLA = extra corporeal lung assist; PEEP = positive end-expiratory pressure.

Materials and Methods

After obtaining approval from the local ethics committee and informed consent from patients' next of kin, 11 consecutive patients with severe ARDS treated by venovenous extracorporeal lung assist were studied. Table 1 summarizes patients' clinical characteristics. For extracorporeal lung assist, the inferior vena cava was cannulated percutaneously with a heparin-coated 25-French catheter (Medtronic, Düsseldorf, Germany) via a femoral vein. The superior vena cava was cannulated with a 23-French catheter via the right internal jugular vein. Blood was drained from the inferior vena cava into a reservoir and returned to the superior vena cava through two heparin-coated hollow fiber oxygenators (Maxima; Medtronic, Düsseldorf, Germany) by two roller pumps (Stöckert, Munich, Germany) in parallel. A continuous flow of oxygen was delivered to the gas port of the oxygenator. Whereas extracorporeal oxygen supply to the patient depends on extracorporeal blood flow, extracorporeal elimination of carbon dioxide depends mainly on the ventilation:perfusion ratio of the membrane oxygenators. To prevent recirculation in the extracorporeal circuit, the tip of the drainage catheter was placed approximately 5 cm below the diaphragm.

Patients were included in the study when arterial oxygen tension (P_{\text{aO}_{2}}) was 60–65 mmHg at an extracorporeal blood flow of 2–3 l/min and a fraction of inspired oxygen (F_{\text{I}_{2}}) of 0.4. All patients had a radial artery catheter and fiberoptic pulmonary artery catheter (Opticath P7110-EP8, Abbott, Wiesbaden, Germany) in place, the latter for continuous measurement of mixed venous oxygen saturation (S_{\text{vO}_{2}}).

The patients were sedated with flunitrazepam and paralyzed with pancuronium. The lungs were ventilated with pressure control (peak airway pressure, 25–38 cm H₂O) and a positive end-expiratory pressure of 6–12 cm H₂O (Servo 900C; Siemens Elema, Lund, Sweden). Respiratory rates ranged from 7 to 10 breaths per minute. During the study period, F_{\text{I}_{2}} was maintained at 1. P_{\text{aCO}_{2}} was aimed at 45, 55, 65, and 85 mmHg in random order by changing extracorporeal blood flow. Extracorporeal gas flow was adjusted to keep mixed venous carbon dioxide tension (P_{\text{vCO}_{2}}) unchanged. At each level of P_{\text{vO}_{2}}, hemodynamic and gas exchange variables were measured before, during, and after inhalation of NO at a concentration of 15 ppm. Each test period lasted 20 min, and measurements were made at the end of each period.

Heart rate; systolic, diastolic and mean arterial pressure; systolic, diastolic and mean pulmonary artery pressure (PAP); and pulmonary artery wedge pressure (PAWP) were recorded on a monitoring system (Sirecust 1281; Siemens, Erlangen, Germany). All pressure measurements were made at end-expiration with the patient supine and the transducers (Medex Novotrans II MX 860, Hilliard, OH) zeroed to ambient pressure at the mid-axillary line. Cardiac output was determined as the mean of three thermodilution measurements randomly made during the respiratory cycle using 10 ml saline at room temperature and a cardiac output computer (Sirecust 1281). Blood gas tensions, hemoglobin oxygen saturations (S_{\text{aO}_{2}} and S_{\text{vO}_{2}}), and total hemoglobin concentration were determined in arterial and mixed venous blood samples (ABL 510; Radiometer, Copenhagen, Denmark). Cardiac index, Q_{\text{O}}/Q_{\text{A}}, oxygen transfer by the patients' lungs (V_{\text{O}}_{2\text{LUNG}}), and pulmonary vascular resistance index (PVRI) were calculated using standard formulas.
Nitric oxide was administered as described previously. Nitric oxide and NO$_2$ concentrations were monitored continuously by electrochemical sensors (GS 8641 NO and GS 8650 NO$_3$; Bieler & Lang, Achern, Germany). Methemoglobin was measured photometrically.

Data are expressed as means ± SEM. Data before, during, and after NO inhalation at different levels of PV$_{O_2}$ were analyzed using two-way analysis of variance for repeated measures followed by a Student-Newman-Keuls test for multiple comparisons. Nitric oxide–induced changes in PAP, PAWP, PVRI, Q$_I$/Q$_T$, PAo$_2$, and SaO$_2$ at the four levels of PV$_{O_2}$ were compared using a one-way analysis of variance for repeated measures followed by a Dunnett test for multiple comparisons. A probability value less than 0.05 was considered significant.

Results

Increases in extracorporeal blood flow increased PV$_{O_2}$ without changes in PV$_{CO_2}$ and cardiac index (table 2, fig. 1). The increase in PV$_{O_2}$ was associated with a decrease in mean PAP, pulmonary perfusion pressure (PAP-PAWP), and PVRI (P < 0.05; table 2, figs. 2A and B), and with an increase in intrapulmonary right-to-left shunt (P < 0.05; table 2, fig. 2C) and SaO$_2$ (P < 0.05; table 2). Inhaled NO decreased PAP, PAWP, PVRI, and Q$_I$/Q$_T$, and increased SaO$_2$, arterial oxygen content, and PAo$_2$ (figs. 3A–C, 4A–C). The NO-induced decrease in PAP-PAWP and PVRI was smaller at high shunt with low PV$_{CO_2}$ levels (figs. 3A and B). In contrast, the decrease in Q$_I$/Q$_T$ was independent of the underlying PV$_{O_2}$ (fig. 3C). Except for the second level of PV$_{O_2}$ (i.e., mean 54 mmHg), inhaled NO increased PV$_{O_2}$ from all other baseline PV$_{O_2}$ levels (table 2). The increase in SaO$_2$ and arterial oxygen content was smaller (P < 0.05; fig. 4A and 4B), and the increase in PAo$_2$ was greater (P < 0.05; fig. 4C) at high compared to low PV$_{O_2}$. Values before and after NO were not different. Methemoglobin concentration never exceeded 1.4%, and NO$_2$ concentration did not exceed 1 ppm.

Discussion

The main result of this study is that hypoxic pulmonary vasoconstriction in nonventilated lung areas is an important factor in determining the hemodynamic and respiratory response to NO inhalation in patients with ARDS. Further, the increase in PAo$_2$ during NO breathing is influenced by PV$_{O_2}$.

Table 2. Hemodynamic and Respiratory Responses to Inhaled NO at Increasing Levels of PV$_{O_2}$

<table>
<thead>
<tr>
<th>NO</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV$_{O_2}$</td>
<td>15 ppm</td>
<td>15 ppm</td>
</tr>
<tr>
<td>25</td>
<td>15.8 ± 0.2</td>
<td>15.8 ± 0.2</td>
</tr>
<tr>
<td>30</td>
<td>15.8 ± 0.2</td>
<td>15.8 ± 0.2</td>
</tr>
<tr>
<td>40</td>
<td>15.8 ± 0.2</td>
<td>15.8 ± 0.2</td>
</tr>
<tr>
<td>50</td>
<td>15.8 ± 0.2</td>
<td>15.8 ± 0.2</td>
</tr>
</tbody>
</table>

Values are means ± SEM. EBF = extracorporeal blood flow; PV$_{O_2}$ = mixed venous oxygen tension; PAP = mean pulmonary artery pressure; PAWP = pulmonary arteriolar wedge pressure; PVRI = pulmonary vascular resistance index; Q$_I$/Q$_T$ = intrapulmonary right-to-left shunt; VO$_2$ = oxygen uptake by the patient; F$_{O_2}$ = inspired oxygen fraction; PAo$_2$ = arterial oxygen content; SaO$_2$ = arterial oxygen saturation; PAo$_2$ = arterial oxygen content; PV$_{CO_2}$ = central venous pressure; HR = heart rate; Patients were ventilated at a constant tidal volume of 10 mL/kg and an inspiratory:expiratory time ratio of 1:2.

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![Graph showing the effect of varying extracorporeal blood flow on mixed venous P_O2 (PvO2), mixed venous P_CO2 (PvCO2), and cardiac index in 11 patients treated by venovenous extracorporeal lung assist. P_O2 increased from 47 mmHg to 84 mmHg, whereas (PvCO2 and cardiac index remained constant. #P < 0.05 vs. P_O2 at lowest extracorporeal blood flow.]

Fig. 1. Effect of varying extracorporeal blood flow with concomitant adjustment of extracorporeal gas flow on mixed venous P_O2 (PvO2), mixed venous P_CO2 (PvCO2), and cardiac index in 11 patients treated by venovenous extracorporeal lung assist. P_O2 increased from 47 mmHg to 84 mmHg, whereas (PvCO2 and cardiac index remained constant. #P < 0.05 vs. P_O2 at lowest extracorporeal blood flow.

Hypoxic pulmonary vasoconstriction increases pulmonary artery pressure and improves V_A/Q matching by diverting blood flow toward ventilated alveoli in the diseased lung. Usually alveolar tension is the primary determinant of hypoxic pulmonary vasoconstriction. However, in nonventilated alveoli P_O2 becomes the determining factor for HPV. In late ARDS, as in our patients, the pulmonary V_A/Q pattern is characterized by nonventilated and well-ventilated lung units rather than by a broad spectrum of V_A/Q imbalances. During ventilation at 1.0, alveolar P_O2 in ventilated lung areas is high enough to inhibit HPV even in alveoli with low V_A/Q ratios. Moreover, at a P_FiO2 of 1.0 alveoli with low V_A/Q ratios tend to collapse and become atelectatic. Thus, at P_FiO2 1.0 HPV is present only in nonventilated lung areas, and a decrease in PAP and PVRI in response to an increased P_Vo2 reflects attenuation of HPV in nonventilated lung areas.

In acute lung injury and ARDS, hypoxic pulmonary vasoconstriction is modulated by several factors. In animals with oleic acid-induced lung injury, pretreatment with indomethacin or aspirin restored the blunted HPV, suggesting that a vasodilating prostaglandin may interfere with HPV. In isolated rat lungs, endothelium-derived relaxing factor attenuates the pressure response to alveolar hypoxia. Increased left atrial pressure has been reported to inhibit HPV in piglets but not in dogs. A high PAP may abolish HPV. Endotoxin and platelet-activating factor reduce, whereas metabolic acidosis enhances the pulmonary pressure response to hypoxia in animals.

![Graph showing the effect of increasing mixed venous P_O2 (PvO2) on pulmonary perfusion pressure (PAP-PWP) (A), pulmonary vascular resistance index (PVRI) (B), and intrapulmonary shunt (Q_s/Q_T) (C) before (closed circles) and during inhalation of 15 ppm NO (open circles). The PAP-PWP and PVRI decreased and Q_s/Q_T increased with increasing PvO2. At high PvO2 (mean 64 and 84 mmHg), NO did not decrease PAP-PWP and PVRI, whereas Q_s/Q_T decreased at each PvO2. #P < 0.05 vs. value at lowest PvO2. *P < 0.05 vs. value before NO.]

Fig. 2. Effect of increasing mixed venous P_O2 (PvO2) on pulmonary perfusion pressure (PAP-PWP) (A), pulmonary vascular resistance index (PVRI) (B), and intrapulmonary shunt (Q_s/Q_T) (C) before (closed circles) and during inhalation of 15 ppm NO (open circles). The PAP-PWP and PVRI decreased and Q_s/Q_T increased with increasing PvO2. At high PvO2 (mean 64 and 84 mmHg), NO did not decrease PAP-PWP and PVRI, whereas Q_s/Q_T decreased at each PvO2. #P < 0.05 vs. value at lowest PvO2. *P < 0.05 vs. value before NO.
Changes in $P_{CO_2}$ and acid-base status modulate pulmonary vascular tone in animals\textsuperscript{22-24} and in humans.\textsuperscript{24,25} Because cardiac index, $P_{O_2}$, and acid-base status were kept constant in our patients, the observed changes in pulmonary perfusion pressure, PVRI and $Q_s/Q_t$ (fig. 2

**Fig. 3.** Nitric oxide–induced changes in pulmonary perfusion pressure (PAP-PAWP) (A), pulmonary vascular resistance index (PVRI) (B), and intrapulmonary shunt ($Q_s/Q_t$) (C) at different levels of mixed venous $P_{O_2}$ ($P_{O_2}$). At high $P_{O_2}$, the changes in PAP-PAWP and PVRI were smaller than at low $P_{O_2}$, whereas changes in $Q_s/Q_t$ were independent of baseline $P_{O_2}$, *P* < 0.05 vs. value at $P_{O_2}$ 47 mmHg.

**Fig. 4.** Nitric oxide–induced changes in $Sa_o$ (A), arterial oxygen content (B), and in arterial oxygen tension ($Pa_o$) (C) at different levels of mixed venous $P_{O_2}$ ($P_{O_2}$). *P* < 0.05 vs. value at $P_{O_2}$ 47 mmHg.
and table 2) must be the result of changes in \(P_{\text{V}O_2}\). Rossaint et al.\textsuperscript{26} did not observe a significant change in PAP in patients with ARDS treated by extracorporeal lung assist when \(P_{\text{V}O_2}\) was decreased. However, the decrease in \(P_{\text{V}O_2}\) was only 20 mmHg, whereas in our patients \(P_{\text{V}O_2}\) varied by 37 mmHg (between 47 and 84 mmHg). Moreover, their patients had been ventilated for a longer period, and Pa\(_{\text{a}}\)/Fi\(_{\text{O}_2}\) was higher than in our patients (309 vs. 101 mmHg) at a similar level of \(P_{\text{V}O_2}\) (approximately 55 mmHg).

Inhaled NO administered to patients with ARDS produces vasodilation in ventilated lung areas and increases blood flow to those regions.\textsuperscript{2} As a result, intrapulmonary shunt and pulmonary artery pressure decrease. Changes in \(Q_s/Q_t\) do not correlate with changes in PAP or PVR\(_t\).\textsuperscript{1,27-29} Pulmonary perfusion pressure and pulmonary vascular resistance are determined by cardiac output and vasoconstriction in ventilated and in nonventilated lung areas. At constant cardiac output, the pulmonary vascular bed may be considered a resistor consisting of two circuits with different resistances in parallel. When vascular resistance in ventilated lung areas is high, total pulmonary vascular resistance and pulmonary perfusion pressure depend increasingly on vascular resistance in ventilated lung areas, and total PVR will finally approach vascular resistance of ventilated lung areas. In that case, a decrease in vascular resistance of ventilated lung areas by inhaled NO will result in a relatively large decrease in total PVR and PAP-PAWP. In contrast, when vascular resistance in the nonventilated lung is low, the percentage of NO-induced decrease in PVR and pulmonary perfusion pressure will be relatively small. Findings in our patients would support such underlying mechanisms. At low \(P_{\text{V}O_2}\), PVR and PAP-PAWP were high (suggesting high vascular resistance in nonventilated lung areas) and subsequent NO inhalation caused a relatively large decrease in these parameters (figs. 2A and B, figs. 3A and B). Consequently, when \(P_{\text{V}O_2}\) was high (suggesting low vascular resistance in nonventilated lung areas), inhaled NO had no significant effect on total PVR and PAP-PAWP (figs. 2A and B, figs. 3A and B).

Several investigators have shown that in ARDS the NO-induced decrease in PVR is more pronounced when baseline PVR is high.\textsuperscript{1,27,28,30} This effect can be attributed, at least in part, to the extent of hypoxic vasoconstriction in nonventilated lung areas. Inhaled NO dilates only preconstricted pulmonary vessels and does not affect pulmonary vessels with normal tone.\textsuperscript{31}

If vascular tone in ventilated lung areas is high, total PVRI and the NO-induced change in total PVRI will also be high. In that case, the change in \(Q_s/Q_t\) should correlate with the change in PVRI. In patients with ARDS, however, the changes in PVRI and PAP do not correlate with changes in \(Q_s/Q_t\) during NO inhalation.\textsuperscript{1,27-29}

In our patients, \(Q_s/Q_t\) increased with rising \(P_{\text{V}O_2}\) levels. Administration of NO decreased \(Q_s/Q_t\) consistently by 4% regardless of the magnitude of (figs. 2C and 3C). Blood flow to nonventilated lung areas depends on the size of the injured lung segment, the hypoxic vasoconstriction, and the total flow.\textsuperscript{32-35} Because cardiac index did not change and because it is unlikely that the size of injured lung segments changed during the study period, the increase in \(Q_s/Q_t\) with increasing \(P_{\text{V}O_2}\) must be attributed to the inhibition of HPV at higher levels. The increase in \(P_{\text{V}O_2}\) coincided with the decrease in pulmonary perfusion pressure at high \(P_{\text{V}O_2}\). The finding that intrapulmonary shunt increased with increasing \(P_{\text{V}O_2}\) is consistent with similar observations in animal studies and in segmental atelectasis.\textsuperscript{5} Viewing the pulmonary vascular bed as a resistor consisting of two circuits with different resistances in parallel (i.e., ventilated and nonventilated lung areas), resistance of nonventilated areas has little effect on redistribution of flow toward ventilated lung areas when resistance of those areas decreases. Thus vascular resistance in nonventilated lung areas which is modulated by \(P_{\text{V}O_2}\), has a marked influence on the NO-induced reduction in pulmonary perfusion pressure but a negligible one on the decrease in intrapulmonary shunt over a wide range of vascular resistances.

In this study, \(Q_s/Q_t\) at different \(P_{\text{V}O_2}\) levels was calculated using the standard shunt equation.\textsuperscript{36} In contrast to the inert gas elimination technique,\textsuperscript{39,40} calculated intrapulmonary shunt theoretically could be influenced by the oxygen uptake in the lungs and by the arteriovenous oxygen content difference (\(\Delta \text{vD}_{\text{O}_2}\)). Several authors have compared oxygen shunt to inert gas shunt at \(\text{Fi}_{\text{O}_2}\) 1.0.\textsuperscript{40-45} Wagner et al.\textsuperscript{40} found an excellent correlation between both methods of shunt determination in dog lungs under various experimental conditions (normal, oleic acid injury, pulmonary embolism, and pneumonia). In their animals, intrapulmonary shunt ranged from 0 to 40%. Values of \(P_{\text{V}O_2}\), were not reported. Hlastala et al.\textsuperscript{41} found in dog lungs with atelectasis and after oleic acid injury a notable correlation of both methods when the shunt was between 20% and 80%. However, \(P_{\text{V}O_2}\) values were not reported. At lower shunt levels, oxygen shunt was systematically higher than in-
ert gas shunt. This difference was attributed to the fact that in contrast to inert gas shunt, oxygen shunt includes shunts from the bronchial circulation. An additional source of error in calculated shunt may come from the properties of oxygen electrode. Sato et al. compared oxygen shunt and inert gas shunt in dog lobes with varying degrees of intrapulmonary shunt, ranging from 0% to 66%. They found a good correlation between both methods, although at low shunt levels (less than 12%), oxygen shunt was higher than inert gas shunt whereas at higher shunt levels oxygen shunt was lower than inert gas shunt. The main reason for these differences was the properties of the electrode. \( \text{PvO}_2 \) ranged from 22 to 48 mmHg. Bresn et al. compared inert gas shunt and oxygen shunt in dog lungs and in the left lower lobe after oleic acid injury of the left lower lobe. Cardiac output was varied by arteriogenous fistulas. Opening the arteriogenous fistulas not only increased cardiac output, but it also increased \( \text{PvO}_2 \) from 48 to 62 mmHg and decreased the arteriogenous oxygen content difference (\( \Delta \text{Do}_2 \)). Despite the increase in \( \text{PvO}_2 \) and the decrease in \( \Delta \text{Do}_2 \), calculated shunt and inert gas shunt in left lower lobes and in the whole lung did not differ for a range of inert gas shunts.

Oxygen consumption by lung tissue results in a systematic error in calculated shunt. However, this potential error was not relevant under various experimental conditions. When oxygen uptake by the lungs is zero (i.e., all oxygen is transferred by the extracorporeal circuit), the shunt equation should not be used because dividing a term by zero is impossible. In all our patients oxygen uptake by the lungs was greater than zero even at high \( \text{PvO}_2 \) (table 2). Thus in our patients calculated shunt represents real shunt, although a small systematic error may be inherent.

The consistent decrease in intrapulmonary shunt during NO administration at each level of \( \text{PvO}_2 \) coincided with varying increases in arterial oxygen tension (fig. 4C). As a consequence of the shape of the oxygen dissociation curve, the decrease in \( \dot{Q}/\dot{Q}_{\text{T}} \) at low \( \text{SvO}_2 \), resulted in a relatively large increase in \( \text{SaO}_2 \) and arterial oxygen content (figs. 4A and B) but in a relatively small increase in \( \text{PaO}_2 \). In contrast, the same decrease in \( \dot{Q}/\dot{Q}_{\text{T}} \) at high \( \text{SvO}_2 \), resulted in a relatively large increase in \( \text{PaO}_2 \) with only a small increase in \( \text{SaO}_2 \) and arterial oxygen content (figs. 4A and B). Thus the assessment of the beneficial effect of NO purely on the basis of an increase in \( \text{PaO}_2 \) may be misleading.

In patients with ARDS, the NO-induced increase in \( \text{PaO}_2 \) was more pronounced during administration of almitrine, a substance that enhances HPV in nonventilated lung areas. Although initial arterial oxygen saturation was higher during almitrine administration, subsequent NO application decreased venous admixture similarly in the presence or absence of almitrine. Thus the larger increase in \( \text{PvO}_2 \) during NO and almitrine can be attributed to the location of the \( \text{PvO}_2 \) in the oxygen dissociation curve.

In conclusion, our data suggest that hypoxic pulmonary vasoconstriction in nonventilated lung areas contributes to the hemodynamic and respiratory responses during nitric oxide inhalation. The stronger the HPV in nonventilated lung areas the more pronounced is the NO-induced decrease in PAP-PAWP and PVRI. The increase in \( \text{PaO}_2 \) during NO breathing is greater at high compared with low mixed venous oxygen tension.

References

11. West JB, Wagner PD. Ventilation-perfusion relationships, The
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32. Dantzker DR, Lynch JP, Weg JG. Depression of cardiac output is a mechanism of shunt reduction in the therapy of acute respiratory failure. Chest 1980; 77:636–12


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