The Acute Effects of Oxygen and Carbon Dioxide on Renal Vascular Resistance in Patients With an Acute Exacerbation of COPD*

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Objective: Changes in renal hemodynamics occur in patients with severe COPD, especially during an acute exacerbation. Renal hemodynamics are affected by changes in oxygen and carbon dioxide levels, but these changes have not been well defined, particularly in the acute clinical situation. We wished to determine whether oxygen or carbon dioxide levels have the predominant effect on renal hemodynamics in patients with an acute exacerbation of COPD.

Design: Fourteen patients with an acute exacerbation of COPD and a PaO₂ < 64 mm Hg were studied. Initially, the patients breathed room air (hypoxemia). Then their arterial oxygen saturation was raised to approximately 95% (normoxemia) and then to 98 to 99% (hyperoxemia). Finally, 1 L/min of carbon dioxide was added to the circuit (hyperoxemic hypercapnia). Using duplex ultrasonography, the pulsatility index (PI) of an intrarenal artery was measured after 10 min at each level of oxygenation. The PI is an index of distal renovascular resistance.

Results: The PI fell significantly from room-air values on inducing hyperoxemia (p < 0.05). This suggests decreased renovascular resistance and increased renal blood flow. When hyperoxemic hypercapnia was induced, the PI rose significantly from the hyperoxemia level (p < 0.001).

Conclusions: In hypoxemic patients, renovascular resistance decreased when hyperoxemia was induced. This fall in renovascular resistance was reversed with the addition of carbon dioxide. This suggests that acute changes in carbon dioxide levels might have a more dominant role than oxygen levels in determining renovascular resistance.

(CHEST 1999; 115:1588–1592)

Key words: carbon dioxide; COPD; oxygen; renal vascular resistance

Abbreviations: ETCO₂ = end-tidal CO₂; NO = nitric oxide; PI = pulsatility index; RBF = renal blood flow; SaO₂ = arterial oxygen saturation

Renal hemodynamics are affected by changes in arterial oxygen and carbon dioxide levels. This has been well documented in patients with COPD, especially during an acute exacerbation. Hypercapnia is associated with a decrease in renal blood flow (RBF), although the effect of hypoxemia is less certain. However, because patients with an acute exacerbation of COPD frequently have a combination of hypoxemia and hypercapnia, we wished to determine whether it is changes in oxygen or carbon dioxide levels that have the predominant effect on renal hemodynamics.

In this study, we investigated renal vascular resistance in a group of patients with hypoxemia secondary to COPD. We studied the effects of added oxygen and carbon dioxide on their renal vascular resistance, which we measured noninvasively using duplex ultrasonography. Changes in renal vascular resistance reflect alterations in renal vasoconstriction and thus, indirectly, in RBF. We postulated that improved oxygenation would decrease renal vascular resistance and that induced hypercapnia would have the opposite effect.

Materials and Methods

Fourteen patients (6 men, 8 women) hospitalized with an acute exacerbation of COPD were studied within 24 h of admission. Entry criteria for the study were a known diagnosis of COPD, an absence of primary cardiac disease, and a PaO₂ < 64 mm Hg on room air on the study day. The patients met the American Thoracic Society criteria for the diagnosis of COPD, and they were all current or previous cigarette smokers. Current use of diuretics or angiotensin-converting enzyme inhibitors was not an...
exclusion factor, but these medications were not given for at least 6 h prior to the study. Informed consent was obtained from all patients, and approval by the hospital ethics committee was obtained.

Renal Hemodynamics

All studies were performed at the same time each day. A real-time ultrasound scanner (model 128XP; Acuson; Mountain View, CA) with color flow and pulsed-scanning facility was used for the Doppler ultrasound examinations. With the patient in the seated position, the right kidney was scanned with a 2-MHz probe via the transclavicular route. A renal interlobar artery was selected near the renal hilum. The angle of the ultrasound beam was adjusted until the maximum Doppler frequency shift was obtained. From the sonogram that was produced, the integrated computer software (Graphpad Prism, version 2.0; Graphpad Software Inc; San Diego, CA) calculated the pulsatility index (PI). The PI is an index of resistance to flow distal to the point of sampling; therefore, it is an indirect index of the degree of vasoconstriction, rather than a direct measurement of RBF. The lower the PI, the less the resistance to flow and, therefore, the greater the rate of flow. The PI results presented are each the mean of three measurements.

Validation

The PI has been validated in healthy volunteers. Using dopamine and dobutamine to vary renovascular resistance, the changes in renal vascular resistance, as measured using classical methodology, correlated strongly with changes in the PI. A further study showed that both the PI and resistive index correlated significantly with effective renal plasma flow, renal vascular resistance, filtration fraction, and creatinine clearance. In a study of renal hemodynamics in COPD, the PI and the mean of the maximum instantaneous flow were used. All of the subjects increased their mean of the maximum instantaneous flow and had a simultaneous decrease in their PI in response to inhaled oxygen, suggesting that both parameters are equally sensitive to changes in renal hemodynamics in COPD. In our center, the coefficient of variation of PI is 2.05%.

Circuit

A circuit incorporating a two-way tap was constructed, allowing the patient to breathe room air to which oxygen and carbon dioxide at varying flow rates could be added. The patient breathed through a one-way valve attached to a tightly fitting face mask. The arterial oxygen saturation (SaO₂) was monitored by means of a pulse oximeter with an ear probe ( Critikon Oxy- shuttle; SensorMedics; Anaheim, CA). End-tidal CO₂ (ETCO₂) was monitored by a capnometer (model M1016A; Hewlett Packard; Waltham, MA), with the carbon dioxide sensor attached to the expiratory port. The capnometer was calibrated before each study, and air leaks were excluded with the device in use. We measured ETCO₂ rather than transcutaneous carbon dioxide levels because transcutaneous measurements take longer to equilibrate. The gradient between Paco₂ and ETCO₂ is usually small (< –5.25 mm Hg) in normal subjects. We accept that ETCO₂ measurements may not be accurate in patients with pulmonary disease, especially COPD, as such patients have an uneven distribution of ventilation and the arterial/ETCO₂ gradient widens from 9.8 to 20.3 mm Hg. However, we were not concerned with the absolute values of ETCO₂, but rather we wished to monitor changing trends in ETCO₂ with the addition of oxygen and carbon dioxide.

Our aim was to study the renal vascular resistance in each patient at standardized levels of SaO₂ and ETCO₂. Each patient was studied at baseline (room air), and then with an SaO₂ of approximately 95% (normoxemia), and then 98 to 99% (hyperoxemia). The fraction of inspired oxygen was titrated in each case to achieve the desired SaO₂. Each level of SaO₂ was maintained for at least 10 min after stabilization, and the renal vascular resistance was remeasured. There were no intervening rest periods. After 10 min of hyperoxemia, 1 L/min of carbon dioxide was added to the circuit for 10 min, or until the ETCO₂ stabilized, and the renal vascular resistance was remeasured. We aimed to achieve an increase in the ETCO₂ level of approximately 15 mm Hg from the hyperoxic value. We used a 10-min period of exposure to the different gas inhalations because a pilot study found that more prolonged exposure in similar patients resulted in respiratory distress and dizziness. We recorded both the pulse rate and the arterial BP throughout the study.

Data Analysis

The PI measurements during the inhalation of different gas mixtures were compared using the Kruskal-Wallis test for nonparametric data. The Dunn multiple comparison test was used, where appropriate, to determine the levels at which the changes in PI were significant. Numeric variables were compared between the different subgroups by the Mann-Whitney test for nonparametric data. Variables were also compared by means of least squares regression analysis. The results are given as mean (± SD), and p < 0.05 was considered significant.

RESULTS

Fourteen patients with a mean (± SD) age of 65.9 ± 9.3 years old were studied. All patients were hypoxic on room air, with a mean Paco₂ of 51.8 ± 8.8 mm Hg and a mean PaO₂ of 54.8 ± 8.8 mm Hg (Table 1). Six patients were receiving domiciliary oxygen therapy. All patients were receiving nebulized bronchodilator treatment, diuretic therapy, an angiotensin-converting enzyme inhibitor, and IV steroids and antibiotics, but no patients were receiving theophylline therapy. Six of the patients had edema at the time of the study.

All of the patients reached an SaO₂ of 95% after at least 10 min inspired oxygen, at varying flow rates, without any change in ETCO₂ (Table 2). All except one patient reached an SaO₂ of at least 98%, again

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**Table 1—Demographic Data**

<table>
<thead>
<tr>
<th>Demographic Information</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>65.9 (9.30)</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>0.60 (0.11)</td>
</tr>
<tr>
<td>FVC, L</td>
<td>1.60 (0.62)</td>
</tr>
<tr>
<td>KCO, % predicted</td>
<td>41.6 (25.9)</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>51.8 (8.8)</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>54.8 (8.8)</td>
</tr>
</tbody>
</table>

*All data are mean (SD). KCO = lung diffusion capacity corrected for alveolar ventilation.*

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without an increase in ETCO₂. The PI responses to changes in the levels of fraction of inspired oxygen and the inspired carbon dioxide concentration were rapid, and they stabilized within minutes of altering the flow rates.

The PI changed significantly in response to changes in inspired gases (p < 0.0001 by Kruskal-Wallis testing; Table 2). The PI fell by 10% from the room air values when the subjects were given sufficient oxygen to raise their SaO₂ to approximately 95% (normoxemia), but this was not significant (Table 2). The PI fell further from room air values when the SaO₂ was increased to 98 to 99% (hyperoxemia; p < 0.05; Table 2), while the ETCO₂ did not change significantly. This suggests that renal vascular resistance decreased with improved oxygenation. However, there was no significant difference in PI values between normoxemia and hyperoxemia. The decrease in PI secondary to improved oxygenation was reversed by the addition of carbon dioxide, despite hyperoxemia being maintained. When inspired carbon dioxide was added, the PI rose from the hyperoxic level of 0.95 ± 0.18 to 1.21 ± 0.18 (p < 0.01).

Ten patients had a room-air PaCO₂ > 45 mm Hg, and we compared these patients to the patients without hypercapnia. Contrary to our expectations, the room-air PI was similar for the hypercapnia group and the normocapnia group, respectively: 1.14 ± 0.15 vs 1.20 ± 0.11. The baseline SaO₂ was similar for the hypercapnia group and the normocapnia group, respectively: 87.7 ± 4.7% vs 88.3 ± 5.7%. The difference in ETCO₂ between the hypercapnia group and the normocapnia group was significant: 35.0 ± 4.1 vs 27.7 ± 2.1 mm Hg, respectively (p < 0.05). There was no significant difference between the hypercapnia and normocapnia patients in their PI responses to variations in inspired gases. We also found similar mean PI results when comparing patients with edema to patients without edema, respectively: 1.10 ± 0.15 vs 1.08 ± 0.18 (not significant). There was no significant change in the pulse rate and BP at the various stages of the study.

### Table 2—SaO₂, ETCO₂, and PI in Response to Variations in Oxygen and Carbon Dioxide Levels*

<table>
<thead>
<tr>
<th>Condition</th>
<th>SaO₂ (%)</th>
<th>ETCO₂ (mm Hg)</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline SaO₂</td>
<td>87.8 (4.76)</td>
<td>34.0 (5.1)</td>
<td>1.09 (0.16)</td>
</tr>
<tr>
<td>Normoxemia</td>
<td>95.3 (0.9)†</td>
<td>32.0 (6.3)</td>
<td>1.0 (0.18)</td>
</tr>
<tr>
<td>Hyperoxemia</td>
<td>98.1 (0.93)‡</td>
<td>31.0 (5.9)</td>
<td>0.95 (0.15)‡</td>
</tr>
<tr>
<td>Hyperoxemia + CO₂</td>
<td>97.7 (1.86)‡</td>
<td>46.0 (7.7)†</td>
<td>1.21 (0.18)†</td>
</tr>
</tbody>
</table>

*All data are mean (SD).
†p < 0.05 when compared to baseline (room air) variable.
‡p < 0.001 when compared to baseline (room air) variable.
§p < 0.01 when compared to baseline (room air) variable.

### Discussion
In this study, we found that when hypoxemic COPD patients were given sufficient oxygen to raise their SaO₂ to 98 to 99%, their distal renovascular resistance decreased. This suggests that RBF increased with improved oxygenation. This decrease in renovascular resistance was reversed by the addition of inhaled carbon dioxide, despite maintaining hyperoxemia. This suggests that, in the acute phase, changes in carbon dioxide levels play a pivotal role in determining the renal hemodynamic response to changes in arterial blood gases. However, the hypercapnic subjects had a baseline renovascular resistance similar to that of the normocapnic subjects, suggesting a differential renovascular response to acute and chronic hypercapnia.

Studies carried out on COPD patients during an acute exacerbation have shown decreased RBF in the presence of hypercapnia.4,6,7 The most recent of these studies7 showed that COPD patients with hypercapnic respiratory failure had a lower RBF than the normocapnic, hypoxemic patients. However, in the current study, as in one of our previous studies, we found no significant difference between the baseline RBF of our normocapnic and hypercapnic subjects. A possible explanation for the discrepancy in these findings is that while the level of hypercapnia was similar in both this study and that of Howes et al,7 our hypercapnic subjects were slightly less hypoxemic than the subjects of Howes et al. However, all of our subjects, whether normocapnic or hypercapnic at baseline, had a rapid and marked rise in renovascular resistance when they inhaled additional carbon dioxide. These findings support a differential renal hemodynamic response to acute and chronic hypercapnia. Chronic hypercapnia, unlike acute hypercapnia, is associated with changes in hydrogen ion concentration, and this may play a role in influencing renal hemodynamics. While an animal study17 has shown that the reduction in RBF with hypercapnia is independent of the hydrogen ion concentration, to our knowledge, there are no equivalent human studies.

Hypercapnia can influence renal hemodynamics by direct and indirect mechanisms. Hypercapnia can cause direct renal vasoconstriction, and hypercapnia also stimulates noradrenaline release by direct action on the sympathetic nervous system.18 Indirectly, hypercapnia causes systemic vasodilation, inactivating the baroreceptors with a subsequent release of noradrenaline, leading to a fall in RBF.1,2,18 Neurogenic control of RBF in response to hypercapnia may also be important, as an animal study17 has shown that this response is abolished by renal denervation.

The effect of hypoxemia on renal hemodynamics is
less clear. The majority of previous studies on COPD patients showed decreased RBF in the presence of hypoxemia. In an early study, RBF increased in response to moderate hypoxemia, and it was only in the presence of severe hypoxemia (a PaO₂ < 40 mm Hg) that RBF decreased. Recent studies of COPD patients with moderate hypoxemia have found reduced RBF. Our study supports these findings, as our patients (with comparable hypoxemia) also had decreased renovascular resistance with improved oxygenation, although this only reached significance when the SaO₂ reached 98 to 99%. It is possible that our patients could have had a significant improvement in PI if the SaO₂ had been maintained at 95% for > 10 min.

The mechanism whereby hypoxemia affects renal hemodynamics is not fully understood. In animal studies, changes in RBF secondary to hypoxemia are abolished by the denervation of the peripheral chemoreceptors, and are attenuated by renal denervation but not influenced by adrenal-peripheral chemoreceptors, and are attenuated by hypoxemia are abolished by the denervation of the animal studies, changes in RBF secondary to chemoreceptor stimulation. We previously studied a group of normal and renal transplant subjects (with denervated kidneys) and measured their renal vascular resistance in response to hypoxemia. We found that renal denervation does not completely abolish the renovascular responses to hypoxemia. Nitric oxide (NO) may also have a role in the renal hemodynamic response to hypoxemia. Howes et al found that hypoxic COPD patients were unresponsive to L-arginine, a NO precursor, while L-arginine caused renal vasodilation in normal subjects; therefore, the researchers concluded that the disturbance in renovascular tone seen in hypoxic COPD patients may be due to a disturbance of the NO pathway.

Clinical experience suggests that renal function in COPD patients improves with increased oxygenation. We investigated the effect of hypoxemia on renal hemodynamics to determine whether maximum vasodilation occurred at physiologic levels of oxygenation (a SaO₂ of 95%), or whether further vasodilatation occurred with hyperoxemia. We found that the maximum renal vasodilatation occurred during hyperoxemia. The mechanism whereby hypoxemia influences renal hemodynamics is unknown, but it may be due to inhibition of the chemoreceptors by hyperoxemia. Contrary to our expectations, in this study, the ETCO₂ did not rise with increasing levels of inhaled oxygen. A possible explanation for the failure of ETCO₂ to rise might be that the duration of hyperoxemia was too short to allow the ETCO₂ levels to increase.

In summary, we found that in patients with hypoxemia, renovascular resistance decreased when hyperoxemia was induced. This improvement in renovascular resistance was reversed by elevating carbon dioxide levels, suggesting that acute changes in carbon dioxide may play a more dominant role than oxygen in determining RBF. This emphasizes the importance of controlled oxygen therapy and the prevention of progressive hypercapnia in patients with an acute exacerbation of COPD.

References
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