Uncontrolled Oxygen Administration and Respiratory Failure in Acute Asthma*

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Study objectives: **To determine if 100% oxygen administration adversely influences gas exchange in acutely ill asthmatic subjects.**
Design: **Prospective preinterventional and postinterventional comparison.**
Setting: **University hospital emergency department.**
Patients: **Thirty-seven asthmatic subjects seeking care for symptomatic exacerbations.**
Interventions: **Twenty minutes of 100% oxygen administration by face mask.**
Measurements and results: **Arterial blood gases and FEV_1 were measured before and during the last minute of oxygen administration. On presentation, the subjects had moderately severe airway obstruction (FEV_1, 49.1 ± 3.6% of predicted); hypocarbia ($Paco_2$, 36.8 ± 1.1 mm Hg); hypoxemia (Pao_2, 70.2 ± 2.5 mm Hg); and respiratory alkalosis (pH, 7.43 ± 0.01). During oxygen breathing, 25 patients (67.6%) experienced elevations in $Paco_2$ ranging from 1 to 10 mm Hg (mean, 4.1 ± 0.6 mm Hg; p = 0.0003). The increase was considered to be a physiologic manifestation of the Haldane effect (*ie*, ≤ 2 mm Hg) in 10 subjects, but in the remaining 15 subjects (40.5% of the total studied), the elevation represented worsening gas exchange. In seven of these patients (46.7%), hypercapnic respiratory failure developed ($Paco_2$ before oxygen, 39.6 ± 0.6; during oxygen, 44.7 ± 0.7 mm Hg; p = 0.005), and in six patients (40%), it worsened ($Paco_2$ before oxygen, 46.8 ± 1.9; during oxygen, 52.0 ± 3.1 mm Hg; p = 0.03). In general, the tendency toward hypercarbia was the greatest in the participants with the most severe airway obstructions.**
Conclusions: **Our data demonstrate that the administration of 100% oxygen to acutely ill asthmatics may adversely influence carbon dioxide elimination.**

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Key words: acute asthma; carbon dioxide retention; gas exchange; respiratory failure; uncontrolled oxygen administration

Supplemental oxygen is a standard form of treatment for COPD syndromes.[1] When given in carefully titrated amounts to patients with chronic bronchitis or emphysema, it improves hypoxemia, lowers pulmonary artery pressures, and reduces morbidity.[1–3] Uncontrolled oxygen administration to patients with severe COPD, however, may cause alveolar hypoventilation, respiratory acidosis, and obtundation.[2–4] Bronchial asthma has been thought to be the exception to this rule, and high-flow oxygen has been assumed to be without hazard in acutely ill individuals with severe obstruction.[5,6] Unfortunately, this may not be the case. While treating several asthmatic subjects with hypercapnic respiratory failure, we noted that a reduction in the fractional concentration of oxygen from 100 to 24% quickly lowered the carbon dioxide tensions to the point that the patients avoided intubation. These findings prompted us to undertake a prospective evaluation of the influence of uncontrolled oxygen breathing on gas exchange during symptomatic destabilizations of this disease. Our observations form the basis of this report.

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Materials and Methods

Asthmatic patients ≥ 18 years of age who presented to the emergency department of University Hospitals of Cleveland with an acute exacerbation of their illness were eligible for participation. This study was performed as part of a resident research program. Asthma was defined according to the guidelines of the National Institutes of Health,[7] and patients with this diagnosis who sought care when the first author was on duty were screened for possible inclusion. Every attempt was made to include all qualified subjects. Anyone receiving central depressants or sedatives, or who had a history of smoking ≥ 10 pack-years, a documented component of COPD in their medical records, a productive cough with purulent sputum, and/or an infiltrate on chest roentgenogram, was excluded.

Initial evaluations included measurements of respiratory rate, pulse, arterial blood gases, and spirometry while the patients were breathing room air. Anyone receiving supplemental oxygen had it removed for 20 min prior to initiating the trial. Arterial saturations were monitored during this period by pulse oximetry. Arterial blood was drawn via puncture of the radial artery (Micro Arterial Blood Gas Custom kit 9025112; Marguest Medical Products; Englewood, CO). The specimens were immediately placed on ice, and Pa_{O_2}, Pa_{CO_2}, and pH were measured with a blood gas analyzer using routine techniques (ABL 505 system; Radiometer America; Westlake, OH). Forced exhalations were recorded in triplicate with a waterless spirometer (Survey Tach/PLUS; Warren E. Collins; Braintree, MA), and the curve with the largest FEV_1 was used for analysis. The data were expressed in absolute terms and as a percentage of predicted normal.[8]

After baseline values were obtained, 100% oxygen was administered for 20 min via a standard nonrebreathing face mask (Model 1060; Hudson RCI; Temecula, CA) and the above measurements were repeated. In this fashion, each patient served as his/her own control. Bronchodilators were withheld during the oxygen trial. Following this period, all participants were treated with a standard previously published protocol featuring the aggressive use of albuterol.[9,10] The Committee on Human Investigations of University Hospitals of Cleveland approved the study, and informed consent was obtained from each participant.

The data were expressed as mean ± SEM and were analyzed by paired *t* tests, two-way analysis of variance, and regression analysis.[11] All statistical tests were two tailed, and p values ≤ 0.05 were considered significant.

Results

Thirty-seven patients (5 men, 32 women) with a mean age of 43.0 ± 2.7 years served as our subjects (Table 1). Our patients had an average 22.7-year history of asthma and presented with signs and symptoms of acute bronchospasm. All of them had dyspnea, tachypnea, and tachycardia. Over 90% were wheezing, and 30% were using their accessory muscles. No one had diaphoresis or cyanosis.

As a group, they had moderate airway obstruction (FEV_1, 49.1 ± 3.6% predicted); a respiratory alkalosis (pH, 7.43 ± 0.01); hypocarbia (Pa_{CO_2}, 36.8 ± 1.1 mm Hg); and hypoxemia (Pa_{O_2}, 70.2 ± 2.5 mm Hg; Table 2). With oxygen administration, FEV_1 fell 4.3% ($p = 0.05$), pH decreased by 0.02 ($p = 0.03$); and Pa_{CO_2} rose by 2.3 mm Hg ($p = 0.0004$). As expected, Pa_{O_2} increased substantially (final mean value, 303.5 ± 15.1 mm Hg; $p < 0.0001$).

Table 1—*Presenting Demographics and Clinical Data

Characteristics	Values
Patients, No.	37
Age, yr	43 ± 2.7
Gender, No.	
Male	5
Female	32
Race, No.	
Black	29
White	8
Duration of asthma, yr	22.7 ± 3.1
Respiratory rate, breaths/min	23.9 ± 0.9
Pulse, beats/min	94.4 ± 3.1
Dyspnea	100
Wheezing	91.3
Accessory muscle use	30.4
Diaphoresis	0
Cyanosis	0

*Data are presented as mean ± SEM or as percent of population unless otherwise indicated.

Figure 1 presents the individual Pa_{CO_2} data before and during the administration of 100% oxygen. *Post hoc* analyses demonstrated that carbon dioxide tensions remained stable in 5 subjects (13.5%), fell in 7 subjects (18.9%), and rose in 25 subjects (67.6%). In the latter, the elevations ranged from 1 to 10 mm Hg (mean, 4.1 ± 0.6 mm Hg; $p < 0.0001$). As can be seen in Table 3, the 12 subjects in whom oxygen did not negatively influence carbon dioxide tensions had less obstruction (FEV_1, 56.5 ± 7.7 vs 43.6 ± 4.2% of predicted; $p = 0.02$). The oxygen and carbon dioxide tensions were not significantly different.

Two patterns of response existed in the subjects in whom Pa_{CO_2} rose (Table 4). In neither group was the deterioration in gas exchange associated with any changes in the FEV_1. In 10 patients with mild to moderate airway obstruction (FEV_1, 58.1 ± 6.5), the increase was slight (*ie*, ≤ 2 mm Hg) and consistent with the physiologic manifestations of the Haldane effect. In the remaining 15 subjects (40.5% of all of the patients studied), carbon dioxide elimination decreased. They had severe airway obstruction (FEV_1, 34 ± 4.0% of predicted; $p = 0.004$), more

Table 2—*Airflow Obstruction and Arterial Blood Gases Before and During Oxygen Administration

Variables	FEV_1	pH	Pa_{CO_2}	Pa_{O_2}
Before	49.1 ± 3.6	7.43 ± 0.01	36.9 ± 1.1	70.2 ± 2.5
During	47.0 ± 3.5	7.41 ± 0.01	39.0 ± 1.5	303.5 ± 15.5
p value	0.05	0.03	0.0003	< 0.0001

*Data are presented as mean ± SEM unless otherwise indicated.

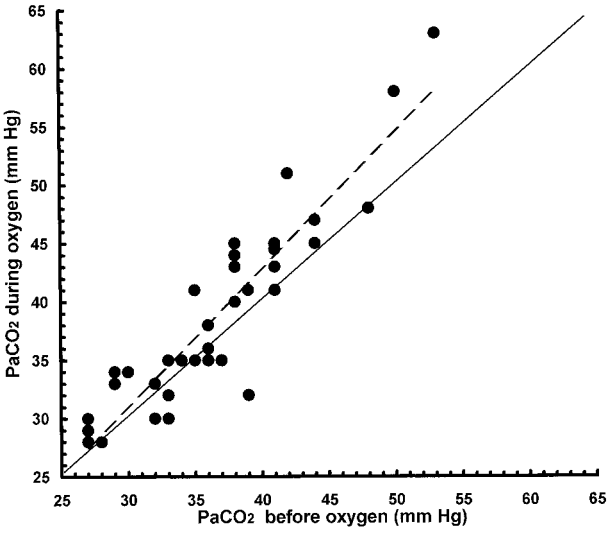

FIGURE 1. The influence of 100% oxygen on $PaCO_2$ in arterial blood. The data points are individual values. The solid and dashed lines represent the line of identity and the regression line during oxygen administration, respectively.

pronounced hypoxemia (PaO_2, 63.7 ± 4.1 mm Hg; p = 0.05), and normocarbia at entrance.

In those patients with nonphysiologic increases in carbon dioxide, hypercapnic respiratory failure (*ie*, $PaCO_2 > 42$ mm Hg) developed *de novo* in seven patients ($PaCO_2$ before oxygen, 39.6 ± 0.6 mm Hg; during oxygen, 44.8 ± 0.7 mm Hg; p = 0.005; Fig 2) and worsened in six patients ($PaCO_2$ before oxygen, 46.8 ± 1.9 mm Hg; during oxygen, 52.0 ± 3.1 mm Hg; p = 0.03; Fig 3). In two subjects, carbon dioxide tensions rose, but did not reach the levels associated with respiratory insufficiency. Once again, there were no changes in the magnitude of the airway obstruction (*de novo* group: FEV_1 before oxygen, 29.9 ± 4.3%, during oxygen 29.0 ± 5.2%; p = 0.71; and preexisting group: FEV_1 before oxygen, 28.0 ± 4%; during oxygen, 24.7 ± 6%; p = 0.20).

Figure 4 displays the relationship between the severity of obstruction and the response to oxygen for all of the participants. There was an inverse association between FEV_1 and $PaCO_2$. As the former fell to < 50% of predicted, the latter tended to increase in response to the oxygen, and the differences between slopes became significant at the p < 0.0001 level.

There were no major fluctuations in respiratory rate or pulse during the experiment (respirations before oxygen, 24 ± 1 breaths/min; during oxygen, 23 ± 1 breaths/min; p = 0.19; and pulse before oxygen, 94 ± 3 beats/min; during oxygen, 97 ± 3 beats/min; p = 0.45).

Table 3—*Distribution of Responses to 100% Oxygen

Variables	FEV_1	pH	$PaCO_2$	PaO_2
No Change or a Fall in $PaCO_2$ (n = 12)				
Before	56.5 ± 7.7	7.45 ± 0.01	35.1 ± 1.3	74.4 ± 4.2
After	55.9 ± 4.7	7.46 ± 0.01	33.7 ± 1.3	331.0 ± 22.1
p value	0.49	0.01	0.08	< 0.001
Increase in $PaCO_2$ (n = 25)				
Before	43.6 ± 4.2	7.43 ± 0.01	37.0 ± 1.4	69.0 ± 3.3
After	42.8 ± 4.3	7.40 ± 0.01	41.1 ± 1.8	296.3 ± 19.8
p value	0.36	< 0.0001	< 0.0001	< 0.0001

*Data are presented as mean ± SEM unless otherwise indicated.

Table 4—*Physiologic and Nonphysiologic Responses to 100% Oxygen

Variables	FEV_1	pH	$PaCO_2$	PaO_2
Increases in $PaCO_2 \leq 2$ mm Hg (Haldane effect; n = 10)				
Before	58.1 ± 6.5	7.43 ± 0.01	35.1 ± 1.9	76.8 ± 4.8
After	57.3 ± 6.2	7.43 ± 0.01	36.7 ± 1.9	318.2 ± 28.1
p value	0.49	0.90	< 0.001	< 0.0001
Increases in $PaCO_2 \geq 2$ mm Hg (n = 15)				
Before	34.0 ± 4.0	7.43 ± 0.01	38.3 ± 2.0	63.7 ± 4.1
After	33.1 ± 4.4	7.38 ± 0.02	44.1 ± 2.4	281.7 ± 28.1
p value	0.53	< 0.0001	< 0.0001	< 0.0001

*Data are presented as mean ± SEM unless otherwise indicated.

DISCUSSION

The results of the present study demonstrate that the administration of 100% oxygen to acutely ill patients with asthma is not as innocuous as formerly thought. In our hands, arterial oxygen tensions uniformly rose, but almost 41% of our subjects experienced elevations in $PaCO_2$ averaging 5.9 mm Hg (Table 4). This finding occurred in those with severe bronchial narrowing (Fig 2, 4), and developed without a deterioration in the underlying airway obstruction (Tables 3, 4).

We recognize that the size of the recorded changes seems relatively small, but their significance does not lie in their magnitude, but rather in their direction. The study was designed only to determine whether 100% oxygen could produce alveolar hypoventilation and not to evoke a maximum response. Based on our experience with COPD,[2,3] had we prolonged administration > 20 min, it is likely that any tendency to develop, or worsen, hypercapnia would have been magnified, as would the size of the effect. Obviously, further experimentation would be required to verify this point, but as it is, approximately, 47% (7/15) of the participants acutely developed carbon dioxide retention, and in another 40% (6/15), elevated levels rose further. Since the inherent risks are that the sickest patients may worsen and that caregivers may be mistakenly led into unneces-

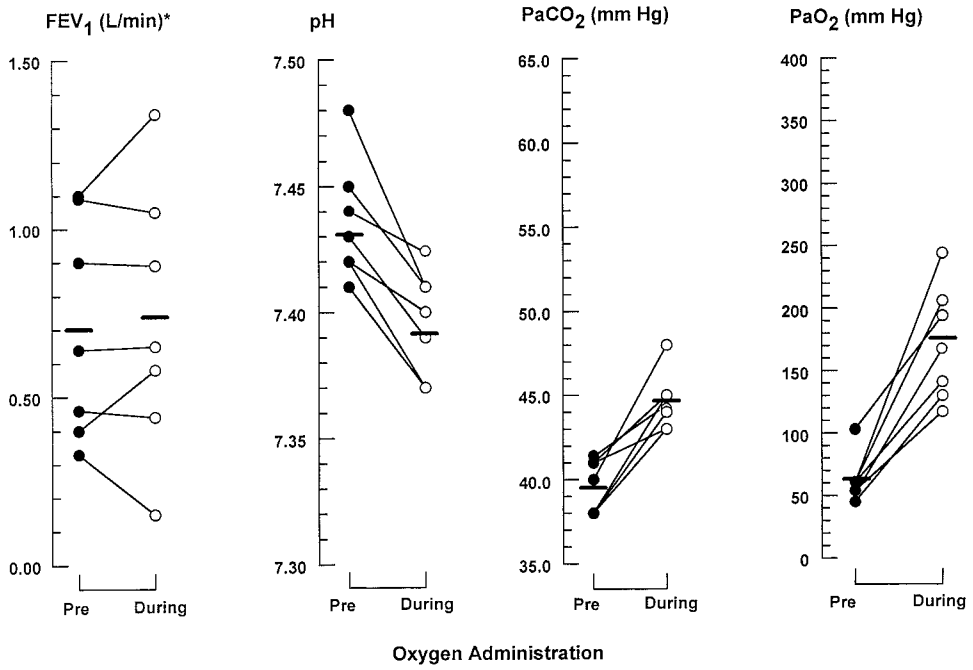

FIGURE 2. Oxygen administration and the development of respiratory failure. The solid and open circles represent the individual values for FEV_1 in liters and the arterial blood gas values before and during oxygen administration, respectively. pH is the negative log of the hydrogen ion concentration; $PaCO_2$ is the partial pressure of carbon dioxide in millimeters of mercury (mm Hg); PaO_2 is the partial pressure of oxygen in millimeters of mercury. The small horizontal lines indicate the mean values.

sary interventions, we believe our data draw attention to physiologic events of potential clinical importance.

If a fractional concentration of oxygen of 100% can adversely impact gas exchange in acute asthma, it seems reasonable to ask why the effect has not been seen previously? Although a number of theoretical possibilities exist, the most likely reason is that any untoward change induced by uncontrolled oxygen would readily be overlooked, unless specifically sought. The influence of oxygen on carbon dioxide elimination has been evaluated in stable patients with mild obstruction,[12] and because little was found, it was assumed to be safe during acute decompensations. For the most part, this supposition is correct; however, our data suggest that when airflow limitation is severe enough to threaten respiratory reserves, even slight reductions in effective alveolar ventilation by 100% oxygen can have untoward effects. If an arterial gas were drawn in such circumstances, any abnormalities in carbon dioxide would be ascribed to the patient's asthma and not to the influence of oxygen. Further, since oxygen is given as a supplement to bronchodilators, and as the latter eliminate the airflow limitation, the influence of the former dissipates. In this instance, the impact of uncontrolled oxygen administration would come to the fore only when the bronchial obstruction is severe and slow to resolve, but again it would likely be attributed to the underlying disease.

Would care suffer if smaller fractional concentrations of oxygen were used? Given all that has been learned about the blood gas abnormalities in acute asthma, the answer seems to be no. Generally speaking, achieving adequate arterial oxygen tensions during episodes of asthma is not a major problem. It is accepted that the need to increase oxygen delivery to the muscles of respiration rises with increasing pulmonary work, and that supplemental oxygen is necessary[13]; however, the factors that dangerously limit energy availability are not typically operational in the vast majority of acute attacks. Unlike other forms of chronic obstructive lung disease, oxygen tensions low enough to interfere with extraction of oxygen at the tissue level have never been reported. Severe hypoxemia (*ie*, a $PaO_2 < 40$ mm Hg) is extremely rare,[14–21] and in studies involving many hundreds of participants, the mean PaO_2 at sea level ranges between 65 and 69 mm Hg with associated saturations of 93 to 96%.[14–17] In one recent work, $< 2\%$ of $> 1{,}500$ acutely ill patients presented with oxygen saturations $< 90\%$, and in these patients, the values were quickly restored to normal by giving 4 L/min of supplemental oxygen.[9] Thus, it appears that controlled oxygen can be safely employed.

While there are no studies in the literature that we

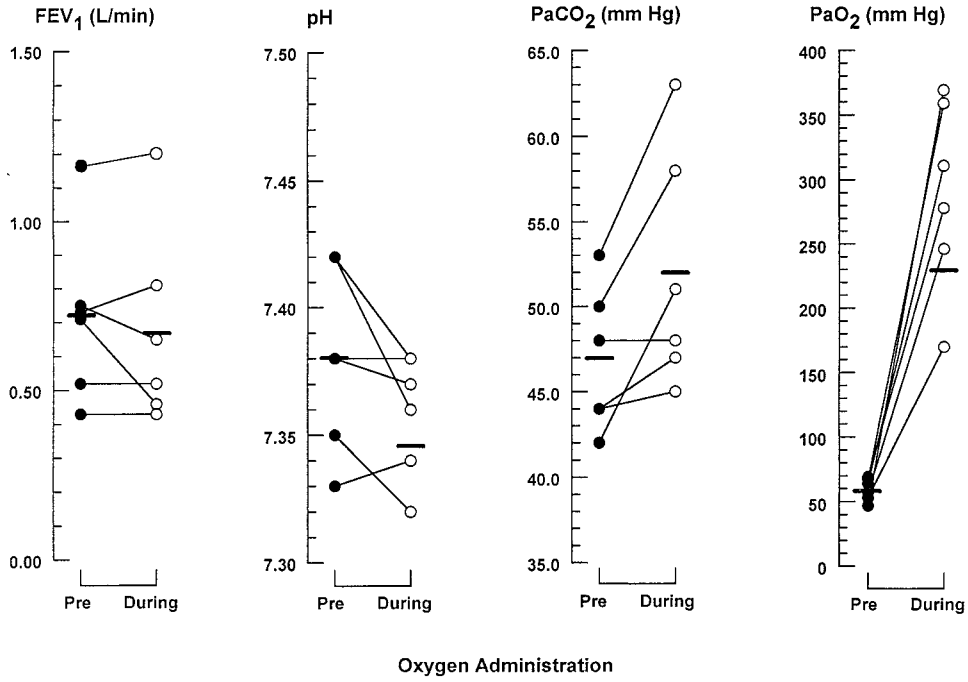

FIGURE 3. The effect of oxygen administration on patients with preexisting carbon dioxide retention. The solid and open circles represent the individual arterial blood gas values before and during oxygen administration, respectively. The format is identical to that of Figure 2.

can specifically draw on for comparison purposes, there are data that offer indirect support for our findings. Arterial carbon dioxide values > 60 mm Hg are uncommon features of acute asthma.[14–17] Yet, in several studies on fatal, or near fatal attacks, admission $PaCO_2$ and PaO_2 levels > 100 mm Hg have been recorded.[22–24] Such a pattern cannot exist without supplemental oxygen administration. According to the alveolar air equation, 80 mm Hg is the highest PCO_2 that can be reached while breathing ambient air at sea level without the individual approaching a degree of hypoxemia incompatible with life.[2] Consequently, it may be that the use of unregulated concentrations of oxygen in combination with marked airflow limitation was partly responsible for the status of these patients. Definitive conclusions will await future investigations; however, this reasoning does not seem far-fetched. In the two patients referred to in the introduction who prompted this prospective study, $PaCO_2$ fell 17 mm Hg (from 56 to 39 mm Hg) and 23 mm Hg (from 62 to 39 mm Hg), respectively, within 10 min of reducing the oxygen concentration from 100 to 28%.

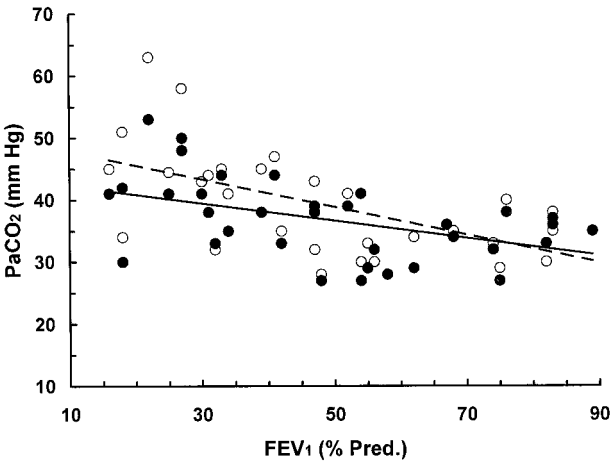

FIGURE 4. Comparison of the relationship between airway obstruction as measured by FEV_1 expressed as a percentage of predicted normal (FEV_1, % Pred.) and arterial carbon dioxide tensions ($PaCO_2$, mm Hg) before (solid circles and line) and during (open circles and dashed line) oxygen administration.

We think it unlikely that our findings resulted from sources other than the administration of 100% oxygen. The 20 min without therapy did not adversely alter lung function. Although the FEV_1 fell a small amount for the entire group, the data in Tables 2–4 and in Figures 2, 3 demonstrate that it did not change in the patients in whom carbon dioxide tensions rose. Our subjects are typical examples of asthmatic patients requesting medical assistance in an urban emergency center. Their ages, durations of asthma, presenting physiologies, racial and gender composition, and degrees of impairment exactly mirror participants in previous studies.[9,10,25] Every one was carefully screened to meet the diagnostic

criteria outlined in current National Institutes of Health consensus reports,[7] and because of the limited availability of the junior investigator (J.C.), patient recruitment was a random process. Most importantly, each subject served as his or her own control, and all had reversible airway narrowing. Thus, our results were not biased by patient selection or by the presence of other forms of obstructive lung disease. Finally, there is nothing to suggest problems with their ventilatory control mechanisms. Although blunted hypoxic drives have been recognized in some asthmatics,[26,27] this abnormality is exceptionally uncommon and invariably is associated with recurrent respiratory failure.[26] None of our subjects possessed such a history.

In summary, the findings of the present work demonstrate that the administration of 100% oxygen to acutely ill asthmatics can result in respiratory depression with carbon dioxide retention, particularly in patients with severe airway obstruction.

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