Communications to the Editor

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Heliox Effect or Rapid-Onset Acute Severe Asthma

To the Editor:

We read with great interest the article by Kass and Terregino that appeared in the August 1999 issue of CHEST.1 In this article, the authors conducted a randomized controlled study to evaluate the effect of heliox on airflow obstruction and dyspnea in adult patients with acute severe asthma. The authors concluded that “heliox rapidly improves airflow obstruction and dyspnea in patients with acute severe asthma and may be useful as a therapeutic bridge until the corticosteroid effect occurs.” Through a close inspection of the entry data, we found that the heliox group presented an important (statistically nonsignificant) difference in the mean duration of attack prior to emergency department presentation (32.6 vs 51.1 h). Accordingly, the heliox group is composed of patients with a more rapid-onset asthma than the control group. Additionally, it is well known that rapid-onset asthmatic patients exhibit a more severe asthma at presentation and a quick recovery compared with slow-onset asthma patients.2–5 The study data are congruent with this idea. Thus, heliox group patients appear more severe at presentation (peak expiratory flow, 120.9 vs 140.0 L/min; dyspnea score, 6.18 vs 4.04; respiratory rate, 30.1 vs 24.3 breaths/min; heart rate, 115.4 vs 104.6 beats/min), and had a faster recovery. Because the authors did not remove the bias introduced by that difference at the initial level, their conclusions appear doubtful. Consequently, the patient’s improvement could be due to that factor.

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Heliox for Acute Severe Asthma

To the Editor:

The study by Kass and Terregino (CHEST; August 1999)1 adds to the growing body of evidence that heliox is effective in improving airflow obstruction and dyspnea in patients treated in the emergency department (ED) for acute, severe asthma. However, in the first paragraph of their discussion the authors state that “similar objective improvements have been demonstrated in children” and reference two studies, one of which was performed by my colleagues and myself.2 Using a double-blind cross-over design, we found that heliox had absolutely no effect on either FEV1 or dyspnea in 11 children who were admitted to the hospital with acute asthma. We concluded that heliox was not beneficial in our study population. While we did find that the children with less severe asthma had some improvement in peak expiratory flow rate (PEFR), though not in FEV1, with heliox, those with the most severe asthma had essentially the same values for PEFR and FEV1 during air and heliox breathing. PEFR is the spirometric value that is most likely to be associated with turbulent flow and, thus, is the most susceptible to improvement with heliox. I wonder whether the patients in the study by Kass and Terregino had any significant change in FEV1? As Kass and Terregino did not calibrate the peak flowmeters with heliox, we really do not know whether their two patient groups started from the same baseline. Moreover, how can we be sure that a change in PEFR with heliox using an uncalibrated peak flowmeter is equivalent to the same change in PEFR while breathing air? Nevertheless, there is substantial evidence that heliox can benefit patients presenting to the ED with acute, severe asthma. However, there are few data that confirm the benefit from heliox in the inpatient setting. Our study in children hospitalized with acute asthma found no benefit from heliox and does not support the findings by Kass and Terregino.

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To the Editor:

Drs. Rodrigo and Rodrigo in their letter suggest that the heliox group had a more rapid onset than the oxygen group. In our study (CHEST, August 1999),\textsuperscript{1} there was a considerable overlap in duration of symptoms between the groups, which was not statistically significant (p = 0.30). Previously it had been demonstrated that patients with a duration of symptoms < 72 h had a better chance of responding successfully to heliox.\textsuperscript{2} Almost all of the oxygen group patients had a duration of symptoms < 72 h, and yet only 17% had a 20% increase in peak expiratory flow (PEF) and percent predicted PEF (%PEF), while 100% of the heliox group did. They also suggest that the heliox group had more severe asthma at presentation than the oxygen group, which could have accounted for the differences found between the groups in response to the treatments. Since the intrinsic variation in PEF is large, the mean differences in PEF and %PEF between the groups of 19.1 L/min and 4.4%, respectively, are small and were not statistically significant (p = 0.27).\textsuperscript{3} There were trends for the heliox group to have higher dyspnea scores and vital signs. Since both groups had severe airflow obstruction with a %PEF < 31% that was not statistically significant, it is highly unlikely that these small differences in PEF and trends in dyspnea scores and vital signs between the groups biased the data such that all of the heliox group had a rapid response to treatment while only a few of the oxygen group did.

Dr. Carter alludes to the statement in our discussion that “similar objective findings have been demonstrated in children.”\textsuperscript{4} He takes exception to our reference to his study supporting this statement. The objective findings that we referred to were PEF and dyspnea and not FEV\textsubscript{1}. In fact, his study did show a significant (p = 0.04) difference in %PEF between heliox and air (control) treatment arms.\textsuperscript{5} He is correct in that there were no statistically significant differences in dyspnea scores between the groups, but this may have been due to the very low baseline scores (mean 2.5 on a 0 to 10 scale). While his study did not show a significant difference between the treatments for percent predicted FEV\textsubscript{1}, there was a difference in %PEF and percent predicted PEF\textsubscript{25–75} (midexpiratory flow rate). There was also a trend (p = 0.07) for improvement in %FEV\textsubscript{1} for heliox when compared to baseline. It is also more common to look for an improvement in FEV\textsubscript{1} by using percent change in actual value from baseline than change in percent predicted.\textsuperscript{6} This may have improved the analysis of the response to heliox. There is also a second reference supporting the alluded-to statement, which shows a 69.4% increase in PEF and decrease in dyspnea score from 5.7 to 1.9.\textsuperscript{7} Both of these values are highly statistically significant. Dr. Carter also questions the effect of heliox on PEF with uncalibrated peak flowmeters. As we referenced in our discussion, it has been shown that heliox causes a large underestimation of PEF\textsuperscript{8} and that correcting for heliox greatly increases the improvement in PEF with heliox.

Inhaled Indomethacin in Bronchorrhea in Bronchioloalveolar Carcinoma

Role of Cyclooxygenase

To the Editor:

In patients with bronchioloalveolar carcinoma, airway obstruction by a copious amount of sputum provides a risk for respiratory failure and even death.\textsuperscript{1} Homma et al (CHEST, May 1999)\textsuperscript{2} have shown that inhaled indomethacin reduces refractory bronchorrhea in bronchioloalveolar carcinoma, suggesting a role of cyclooxygenase in airway hypersecretion in this disease.

We thus studied the effect of inhaled indomethacin on sputum production and the expression of cyclooxygenase-2 (COX-2) messenger RNA (mRNA) in seven patients with bronchioloalveolar carcinoma having bronchorrhea. A transbronchial lung biopsy was taken from the most affected area, and the gene expression was assessed by Northern blotting. The COX-2 primers were 5’-TTCGATGATGATGAGGAGGAATTG-3’ (sense) and 5’-GATCCCGTATGAGGGTTAAGTTTA-3’ (antisense), giving rise to a 276-base pair polymerase chain reaction product.\textsuperscript{3} Then, each patient received inhaled indomethacin, 75 mg/d, for 4 weeks, while the sputum expectorated was collected and weighed daily, and the values were reduced to weekly averages. A comparison between two groups, one showing positive for COX-2 mRNA expression and another negative, was made by analysis of variance and Scheffé’s test.

The expression of COX-2 mRNA was detected in four patients. During the baseline period, a mean sputum production was greater in the COX-2 messenger RNA-positive group (570 g/d) than in the COX-2 mRNA-negative group (165 g/d; p = 0.033, Fig 1). After the 4-week treatment, daily production of sputum decreased in the COX-2 mRNA-positive group by a mean ± SD of 49 ± 17% (p = 0.025), but it remained unchanged in the COX-2 mRNA-negative group. With respect to the change from baseline value, there was a significant difference between the two groups (p = 0.029). Therefore, upregulation of COX-2 in carcinoma cells and the resultant synthesis of cyclooxygenase products of arachidonic acid may be involved in the pathogenesis of

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