



## opinions/hypotheses

# Hypocapnia and Asthma\*

## A Mechanism for Breathing Retraining?

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There is some evidence that breathing retraining may be beneficial for patients with asthma, but the mechanism behind this benefit is still unknown. One hypothesis is that individuals can be trained to raise carbon dioxide levels and thereby reverse the bronchoconstrictive effects of hypocapnia and utilize the bronchodilatory effects of hypercapnia. This theory presupposes that individuals with asthma have lower carbon dioxide levels than the healthy population. This article reviews the available evidence supporting the hypothesis and concludes that although attractive, there is currently insufficient evidence to attribute the benefits of breathing retraining to this mechanism. (CHEST 2005; 127:1808–1811)

**Key words:** asthma; breathing retraining; carbon dioxide; hypocapnia

**Abbreviations:** ASM = airway smooth muscle;  $\text{ETCO}_2$  = end-tidal carbon dioxide

Although pharmacologic therapy remains the primary mode of treatment for patients with asthma, many people also use complementary or alternative therapies. In a recent US study<sup>1</sup> of inner-city children with asthma, 89% of parents questioned reported giving their child some form of complementary therapy, yet only 18% had informed their physician about this. Various forms of breathing retraining have been used as a therapy for patients with asthma in the United States, Europe, and Australia, with some reported benefits,<sup>2–4</sup> although such benefits have yet to be definitively confirmed. The mechanism behind the reported benefits is currently not known, but one physiologic hypothesis relates to carbon dioxide. The purpose of this article is to draw attention to a theory related to the possible role of carbon dioxide in asthma, and to review the available evidence supporting it.

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### SEARCH STRATEGY

Multiple strategies were incorporated to maximize identification of suitable studies. We searched MEDLINE, EMBASE, Cochrane library, CINAHL, and reference lists of original and review articles. Authors of relevant abstracts were contacted to seek additional information.

### HYPOCAPNIA

The  $\text{PaCO}_2$  reflects the balance between the production and elimination of carbon dioxide. Under normal conditions, the  $\text{PaCO}_2$  is maintained at approximately 39 to 41 mm Hg by alveolar ventilation under the control of respiratory centers in the pons and medulla.<sup>5</sup> Changes in the production of carbon dioxide are usually accompanied by corresponding alterations in alveolar ventilation with little or no change in  $\text{PaCO}_2$ . The main physiologic causes for hypocapnia are related to hyperventilation. Mild hypocapnia is not generally associated with any serious effects in healthy individuals, but Laffey and Kavanagh<sup>6</sup> have proposed that hypocapnia may have a pathogenic role in the development of systemic diseases. However, this suggestion is not new, as it can be found in early writings from the late Russian physiologist, Konstantin Buteyko, during the 1950s.<sup>7</sup>

## HYPOCAPNIA AND BRONCHOCONSTRICTION

Although hypocapnia is a consistent finding in acute asthma, it is not certain whether it has any clinically relevant pathogenic role. Proponents of the Buteyko breathing technique<sup>7</sup> would suggest that this is the case. Also, in 1968 it was hypothesized in the *New England Journal of Medicine*<sup>8</sup> that hypocapnia during an asthma attack could perpetuate bronchospasm and lead to a cycle of progressive hypocapnia and increasing bronchospasm. There is a body of experimental evidence that supports this hypothesis. There is *in vitro* animal evidence suggesting that low alveolar PCO<sub>2</sub> causes bronchoconstriction,<sup>9</sup> while a high PCO<sub>2</sub> acts directly on the airway smooth muscle to cause bronchodilatation.<sup>10</sup> There is also *in vivo* animal evidence that hypocapnia increases airway resistance.<sup>11–13</sup>

In addition, there is support for the association between hypocapnia and bronchoconstriction from experimental evidence from humans.<sup>14–19</sup> Fisher et al<sup>20</sup> and McFadden et al<sup>21</sup> have shown that a low alveolar carbon dioxide in patients with asthma was associated with increases in airway tone. Van den Elshout et al<sup>19</sup> studied the effects of hypercapnia and hypocapnia on respiratory resistance in both normal and asthmatic subjects. They found that a reduction in end-tidal PCO<sub>2</sub> of only 7.5 mm Hg caused an increase in resistance by 13% and a fall in reactance by 45% in asthmatics, while the same reduction in PCO<sub>2</sub> had no effect on healthy subjects. Conversely an increase in end-tidal PCO<sub>2</sub> of only 7.5 mm Hg resulted in a significant fall in airway resistance in both asthmatic and normal subjects. Bayindir et al<sup>22</sup> reported on the adverse effects of hypocapnia during cardiopulmonary bypass, which led to a significant increase in airway resistance and a reduction in lung compliance.

Airway smooth muscle (ASM) is now recognized as being the major end-effector of acute airway narrowing in asthma.<sup>23</sup> The primary function of ASM is to regulate the bronchomotor tone in response to contractile agonists. ASM responsiveness is influenced by both internal and external stimuli; however, it is still unclear whether the airway hyperresponsiveness seen in asthma is primarily due to changes within the smooth muscle itself, or to changes external to the muscle. Possible mechanisms for hypocapnia inducing bronchoconstriction may be through neural reflexes, through increasing blood vessel caliber, through the provocation of mediator release, or through a direct effect on the ASM. A study by Lindeman et al<sup>13</sup> suggests that hypocapnia has a direct effect on ASM cells, possibly via the effect of intracellular alkalosis on intracellular free calcium concentration. Reynolds and McEvoy<sup>9</sup> suggested

that in the guinea pig lung, a reduction in alveolar PCO<sub>2</sub> produced an increase in airway resistance by inducing bronchospasm and increasing the permeability of microvessels in the airway, and that this effect was mediated by the release of tachykinins from C-afferent nerves in the airways. However, the mechanism for the bronchoconstriction is still uncertain and may relate to the degree of hypocapnia. Sterling<sup>14</sup> found that when end-tidal PCO<sub>2</sub> was approximately < 30 mm Hg, the bronchoconstriction was mediated via the autonomic nervous system (through the vagus nerve), but that when end-tidal PCO<sub>2</sub> was < 15 mm Hg it was mediated by direct effect on the ASM.

## HYPOCAPNIA AND ASTHMA

In 1952, Buteyko theorized that “hidden” hyperventilation is the basic cause of asthma,<sup>7</sup> linked to the inflammatory and structural changes characteristic of the disease. During acute episodes of asthma, hyperventilation leading to hypocapnia is well documented,<sup>6,24,25</sup> but very few studies<sup>19,26,27</sup> have suggested that patients with asthma are hypocapnic when their asthma is stable. In 1988, Hormbrey et al<sup>27</sup> compared carbon dioxide response and breathing pattern in patients with asthma, patients with symptomatic hyperventilation, and healthy subjects. The asthmatic group had a significantly higher resting respiratory frequency and minute ventilation, and had lower mean end-tidal carbon dioxide (ETCO<sub>2</sub>) [37 mm Hg] than the other two groups (40 mm Hg and 41 mm Hg, respectively). However, there were only six subjects in each group. Van den Elshout et al<sup>19</sup> studied 30 asthmatic and 15 healthy volunteers and also found that the asthmatic group had lower mean resting ETCO<sub>2</sub> when compared to the healthy subjects (36 mm Hg vs 40 mm Hg). Neither of these two studies used matched control subjects. However, more recently, Osborne et al<sup>26</sup> studied a group of 23 patients with mild, stable asthma and compared them with a matched control group. Both arterial carbon dioxide and ETCO<sub>2</sub> were found to be significantly lower in the patients with asthma (ETCO<sub>2</sub>, 37 mm Hg vs 40 mm Hg). Concomitant evidence for clinically significant hyperventilation in such subjects is not available. Thomas et al<sup>28</sup> reported that one third of women and one fifth of men treated for asthma in a single general practice had symptoms suggestive of hyperventilation or “dysfunctional breathing.” However, they used the Nijmegen questionnaire to assess dysfunctional breathing, and some authors<sup>29,30</sup> have questioned the validity of this questionnaire in identification of hyperventilation in an

asthmatic population because of the potential overlap between the symptoms of anxiety and those of asthma.

If one assumes that the observed hypocapnia in stable asthmatics is due to hyperventilation, it is an attractive proposition that retraining breathing patterns to reduce hyperventilation in such individuals should make it possible to raise carbon dioxide levels. This should theoretically reverse any bronchoconstrictive effects of hypocapnia, and possibly make use of the bronchodilatory effects of hypercapnia. There is some evidence that various forms of breathing retraining (eg, physiotherapy, yoga, and Buteyko) have had some beneficial effects on asthma patients. However, at present it is uncertain what mechanism produces these effects over and above any placebo effect. Apart from the carbon dioxide hypothesis, another potential physiologic mechanism behind breathing retraining is the effect of rhythmic stretching on the ASM.<sup>31,32</sup> A number of psychological mechanisms are also possible such as increasing feelings of mastery or control, induction of relaxation/meditation, or nonspecific attention effects. A recent randomized controlled trial of the Buteyko breathing technique by Cooper et al<sup>4</sup> found that Buteyko breathing improved asthma symptoms and reduced bronchodilator use, but without affecting airway caliber or responsiveness. Thomas et al<sup>2</sup> reported on a study of physiotherapy breathing retraining for asthma patients and found improved quality-of-life scores. However, neither of these studies shed any light on the mechanism producing the improvements generated. Buteyko, physiotherapy, and yoga therapies share very similar breathing techniques that encourage slowing the rate of breathing, and the use of breath holding. Very few studies of breathing therapy have included measures of carbon dioxide in their outcomes. One exception is the randomized controlled trial of Buteyko by Bowler et al,<sup>33</sup> who found no significant differences in means between the intervention and control groups after intervention, but unfortunately do not report any within subject changes. In a controlled trial currently only published in abstract form, Abramson et al<sup>34</sup> reported no changes in lung function, but did find some increase in ET<sub>CO<sub>2</sub></sub> in one group and some reduction in response to carbon dioxide in another. They employed a factorial design involving four groups, one receiving "full" Buteyko (Buteyko practitioner plus Buteyko video), two receiving "partial" Buteyko (Buteyko practitioner plus placebo video, or Buteyko video plus placebo educator), and one receiving no Buteyko (placebo video plus placebo educator). Their findings are interesting, but the complexity of their design makes interpretation difficult.

## FUTURE RESEARCH

Although breathing control and breathing training are common interventions for respiratory conditions, there is a paucity of randomized clinical trials examining their effectiveness or the mechanism for any effect. A recent Cochrane review stated that "no reliable conclusions can currently be drawn concerning the use of breathing exercises for asthma in clinical practice."<sup>35</sup> However, trends for improvement are encouraging; further large-scale trials, including full descriptions of treatment methods and outcome measurements, are required to establish effectiveness. To establish if the carbon dioxide mechanism plays a role, researchers need first to establish if people with asthma do have significant differences in either absolute level of carbon dioxide or sensitivity to carbon dioxide. There is also a need for some well-designed clinical trials of breathing retraining with carbon dioxide as the primary outcome measure.

## CONCLUSION

There is now some evidence that asthmatic individuals have lower levels of carbon dioxide than the healthy population, even when they are stable and asymptomatic. There is also some indirect evidence that a significant proportion of the stable asthmatic population have symptoms of hyperventilation. Physiotherapists and others regularly use breathing retraining techniques to alleviate these symptoms, with some reported benefits. While these may be related to raising an individual's carbon dioxide levels, as has been hypothesized, as yet there is no convincing evidence that this occurs, or that such a goal is either desirable or achievable.

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