

Ganesh Shanmugam, MD^a
Lawrence B. Schwartz, MD, PhD^b
David A. Khan, MD^{a,c}

From ^athe Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9030; ^bthe Department of Internal Medicine, Division of Rheumatology, Allergy and Immunology, Medical College of Virginia, Virginia Commonwealth University, Richmond, Va; and ^cthe Division of Allergy and Immunology, University of Texas Southwestern Medical Center, Dallas, Tex.

Disclosure of potential conflict of interest: No Conflict of Interest disclosure statements were received from the authors.

REFERENCES

1. Lenchner K, Grammer LC. A current review of idiopathic anaphylaxis. *Curr Opin Allergy Clin Immunol* 2003;3:305-11.
2. Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T. Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. *N Engl J Med* 1987;316:1622-6.
3. Tanus T, Mines D, Atkins PC, Levinson AI. Serum tryptase in idiopathic anaphylaxis: a case report and review of the literature. *Ann Emerg Med* 1994;24:104-7.
4. Schwartz LB, Yunginger JL, Miller J, Bokhari R, Dull D. Time course of appearance and disappearance of human mast cell tryptase in the circulation after anaphylaxis. *J Clin Invest* 1989;83:1551-5.
5. Schwartz LB. Effector cells of anaphylaxis: mast cells and basophils. *Novartis Found Symp* 2004;257:65-74.

doi:10.1016/j.jaci.2005.12.1356

Deep inhalation bronchoprotection in asthma: Correlation with airway responsiveness

To the Editor:

Deep inhalation to total lung capacity (TLC) before methacholine challenge provides marked protection against methacholine-induced bronchoconstriction in normal subjects.¹ This is said not to occur in subjects with asthma,¹ but a close look at the data shows that although this may be true when one looks at mean data, examination of individual data demonstrates significant bronchoprotection in some subjects with asthma.^{2,3} We have recently demonstrated that 5 TLC inhalations during methacholine challenge, administered either by dosimeter or by tidal breathing methods, significantly reduced airway responsiveness in several subjects with asthma, generally at the milder end of the airway responsiveness spectrum.⁴⁻⁶ In this brief report, we reanalyze data from 2 of these studies^{5,6} to look for correlations between the degree of bronchoprotection of these 5 deep inspirations and both the level of the underlying airway responsiveness to methacholine and the baseline airway caliber.

A total of 32 subjects with asthma participated in trials in which methacholine PC₂₀ was determined by the same inhalation method on 1 occasion with 5 TLC inhalations and on 1 occasion without. The subjects (17 male, 15 female) were 28.8 ± 1.6 (SEM) years old and had FEV₁ of 90.6% ± 2.4% predicted. Medication requirements included as-needed β₂-agonists in 28 and regular inhaled corticosteroids in 10. Four subjects were using no treatment, 2 had seasonal asthma and were tested in the fall, and 2 had diagnosed asthma with mild exercise-induced symptoms that went untreated. There were 15 subjects

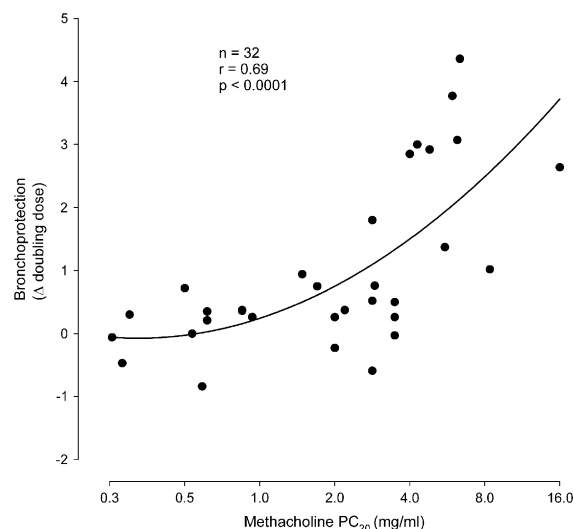


FIG 1. Correlation of bronchoprotection and methacholine PC₂₀. Bronchoprotection in doubling doses is on the vertical axis and the methacholine PC₂₀ (log scale) in mg/mL on the horizontal axis. The curve of best fit is the quadratic equation $y = mx + px^2 + b$.

who performed the standardized 5-breath dosimeter method with the identical methacholine dose inhaled by 5 TLC inhalations on 1 occasion (the standard method⁷) and 5 half-inspiratory capacity inhalations on the second occasion.⁵ The other 17 subjects performed tidal breathing determinations of methacholine PC₂₀ with the identical dose on 1 occasion with 2 minutes tidal breathing and no deep inhalations (the standard method⁷) and, on the second occasion, with 5 TLC inhalations and breatholds taken over the course of the 2 minutes of methacholine inhalation.⁶ The degree of bronchoprotection was determined by the number of doubling dose changes in the PC₂₀; this is a standard technique used to assess the effect of pharmacologic agents on airway responsiveness. The formula for the calculation of degree of bronchoprotection (doubling dose) is $\Delta \log PC_{20} \div 0.3$ (ie, $\log_{10} 2$).⁸

Underlying airway responsiveness was assessed by the standardized 2-minute tidal breathing methacholine^{7,9} PC₂₀ performed within 2 weeks of the bronchoprotection study in the first 15 subjects and as part of the bronchoprotection study in the other 17 subjects. The methacholine PC₂₀ data were log-transformed. Various regression analyses were performed with log PC₂₀ and bronchoprotection in doubling doses.

The magnitude of bronchoprotection ranged from -0.84 to +4.4 doubling doses. Linear regression showed a highly significant positive correlation with log PC₂₀ ($r = 0.65$). The correlation was improved using a quadratic regression ($y = mx + px^2 + b$); this is shown in Fig 1 ($n = 32$; $r = 0.69$; $P < .0001$). In the most responsive half of the population (16 subjects with PC₂₀ ≤ 2 mg/mL), the deep inhalations had no effect on the PC₂₀ ($P = .09$), and the bronchoprotection ranged from -0.84 to +0.94 doubling concentrations, indicating that the 2 values for PC₂₀

were all within ± 1 doubling concentration. By contrast, in the 16 subjects with borderline to mild airway hyperresponsiveness (AHR; $PC_{20} > 2$ mg/mL), the range of bronchoprotection was between -0.6 and $+4.4$ doubling doses, and the difference between the methacholine PC_{20} values with and without deep inspirations averaged 1.8 concentrations and was highly significant ($P = .0003$). Although there was a significant relationship between $FEV_1\%$ predicted and log PC_{20} ($r = 0.36$; $P = .05$), there was no relationship between FEV_1 and bronchoprotection ($r = 0.18$; $P = .34$).

Recently, inhaled corticosteroids have been shown to restore deep inhalation bronchoprotection in patients with asthma and mild AHR.¹⁰ We compared the bronchoprotective effect of TLC inhalations in the 10 subjects using inhaled corticosteroids and the 22 subjects not using them. In this cross-sectional analysis, there was no statistical difference in bronchoprotection (1.27 ± 0.45 SEM vs 0.85 ± 0.28 doubling concentrations; $t = 0.79$; $P > .2$). The 4 subjects using no medications showed more bronchoprotection (1.7 ± 0.62 vs 0.9 ± 1.3 doubling concentrations), but the small numbers made this not significant ($t = 1.23$; $P > .2$).

These data confirm what is evident from the publications from which these data were derived,^{5,6} namely that 5 deep TLC inhalations taken during methacholine inhalation provide bronchoprotection in many subjects with asthma. They extend our observations by demonstrating the marked correlation ($P < .0001$) with the degree of airway responsiveness and by showing that this bronchoprotection appears limited to subjects with mild or very mild AHR (methacholine $PC_{20} > 2$ mg/mL). These data are not inconsistent with other studies that have failed to demonstrate any deep inhalation bronchoprotection in subjects with asthma. The failure to see bronchoprotection almost certainly would relate to subject selection. It is likely that in studies such as that by Kapsali et al,¹ the small number of subjects with asthma could well have been selected to have AHR in the range of our subjects with tidal breathing $PC_{20} < 2$ mg/mL.

Perhaps the most important point to note is that the bronchoprotective effect of the deep inhalations was great enough that several of our subjects with asthma had what is recognized as negative (or normal) methacholine challenge tests⁷ with the deep inhalation methods. Based on our 3 studies,⁴⁻⁶ it would appear that the deep inhalation dosimeter method for methacholine challenge has an unacceptable loss of sensitivity. This suggests methacholine

(and possibly other) challenges should be performed using non-TLC inhalation methods.

In summary, deep inhalations to TLC during methacholine challenge result in bronchoprotection in many subjects with asthma. This correlates with the degree of AHR and is limited to subjects with mild or very mild AHR.

We thank Jacquie Bramley for assisting in the preparation of this manuscript.

Donald W. Cockcroft, MD, FRCP(C)

Beth E. Davis, BSc

From the Division of Respiriology, Critical Care and Sleep Medicine, Department of Medicine, Royal University Hospital, University of Saskatchewan, Saskatoon, Saskatchewan, Canada.

Disclosure of potential conflict of interest: D. Cockcroft has consultant arrangements with AstraZeneca, Merck, Methapharm, and Novartis; has received grants from Methapharm, IVAX, Boehringer Ingelheim, Topigen, Merck, and AstraZeneca; and is on the speakers' bureau for GlaxoSmithKline, AstraZeneca, and Merck. The other author has no conflict of interest to disclose.

REFERENCES

1. Kapsali T, Permutt S, Laube B, Scichilone N, Togias A. Potent bronchoprotective effect of deep inspiration and its absence in asthma. *J Appl Physiol* 2000;89:711-20.
2. Schichilone N, Kapsali J, Pyrgos G, Anderlind C, Permutt S, Togias A. The distribution of deep inspiration (DI)-induced bronchoprotection (BP). *Am J Respir Crit Care Med* 2001;163:A829.
3. Schichilone N, Pyrgos G, Kapsali T, Anderlind C, Brown R, Permutt S, et al. Airways hyperresponsiveness and the effects of lung inflation. *Int Arch Allergy Immunol* 2001;124:262-6.
4. Cockcroft DW, Davis BE, Todd DC, Smycniuk AJ. Methacholine challenge: comparison of two methods. *Chest* 2005;127:839-44.
5. Todd DC, Davis BE, Hurst TS, Cockcroft DW. Dosimeter methacholine challenge: comparison of maximal versus submaximal inhalations. *J Allergy Clin Immunol* 2004;114:517-9.
6. Allen ND, Davis BE, Hurst TS, Cockcroft DW. Difference between dosimeter and tidal breathing methacholine challenge: contributions of dose and deep inspiration bronchoprotection. *Chest* 2005;128:4018-23.
7. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing—1999: this official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000;161:309-29.
8. O'Connor BJ, Aikman SL, Barnes PJ. Tolerance to the nonbronchodilator effects of inhaled beta₂-agonists in asthma. *N Engl J Med* 1992;327:1204-8.
9. Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977;7:235-43.
10. Scichilone N, Permutt S, Bellia V, Togias A. Inhaled corticosteroids and the beneficial effect of deep inspiration in asthma. *Am J Respir Crit Care Med* 2005;172:693-9.

doi:10.1016/j.jaci.2006.02.007