

- sputum supernatants: validation and detection in asthma. *J Allergy Clin Immunol* 2004;113:657-62.
7. Lemi re C, Chaboillez S, Malo JL, Cartier A. Changes in sputum cell counts after exposure to occupational agents: what do they mean? *J Allergy Clin Immunol* 2001;107:1063-8.
 8. Girard F, Chaboillez S, Cartier A, Cote J, Hargreave FE, Labrecque M, et al. An effective strategy for diagnosing occupational asthma: use of induced sputum. *Am J Respir Crit Care Med* 2004;170:845-50.
 9. Gauvreau GM, Lee JM, Watson RM, Irani AM, Schwartz LB, O'Byrne PM. Increased numbers of both airway basophils and mast cells in sputum after allergen inhalation challenge of atopic asthmatics. *Am J Respir Crit Care Med* 2000;161:1473-8.
 10. Krakowiak A, Krawczyk-Adamus P, Dudek W, Walusiak J, Palczynski C. Changes in cellular and biochemical profiles of induced sputum after allergen-induced asthmatic response: method for studying occupational allergic airway inflammation. *Int J Occup Med Environ Health* 2005;18:27-33.

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Prolonged elevation of serum tryptase in idiopathic anaphylaxis

To the Editor:

Idiopathic anaphylaxis is a well described type of anaphylaxis for which no identifiable provocative agent exists.¹ Serum tryptase levels, a marker of mast cell activation, can be used in the diagnosis of anaphylaxis.² Only 1 known case report exists of elevated tryptase levels in a patient who had a single episode of idiopathic anaphylaxis.³ We describe the case of a patient with idiopathic anaphylaxis and an elevated mature tryptase level ~26 hours after the onset of symptoms.

The patient is a 54-year-old man who presented for office evaluation after having episodes of anaphylaxis for more than 10 years. Symptoms during his episodes included urticaria, pruritus, facial and extremity angioedema, nausea, vomiting, diarrhea, lightheadedness, syncope, and documented hypotension. The severity of his episodes was variable from mild symptoms of angioedema to more severe anaphylaxis with urticaria, angioedema, and hypotension necessitating emergency department admissions. The frequency of his episodes varied between 4 and 18 per year, with an apparent increase in frequency the year before his evaluation. History failed to reveal an inciting factor, including exercise, foods, medications, and insect stings. His past medical history was notable only for hypertension treated with amlodipine. His physical examination while asymptomatic was remarkable only for minimal nasal turbinate edema. Skin prick tests to a panel of 79 foods and spices were negative. Food dye and preservative challenges were also negative. Complete blood count with differential, general chemistries, C1 esterase inhibitor, and complement levels were normal.

Based on his history and laboratory evaluation, a diagnosis of idiopathic anaphylaxis was made. The patient was initially instructed to have a serum tryptase level measured with his next episode. Two months later, approximately 3 hours after eating breakfast, he developed pruritus and urticaria, mild swelling of his hands and feet, and

periorbital and lip edema, followed by throat tightness and severe gastrointestinal distress including nausea, vomiting, and diarrhea. He also experienced lightheadedness that was orthostatic in nature. He received no medical treatment for this episode and simply stayed at home. In the past, the patient had used self-injectable epinephrine, but he found the relief very short-lived and therefore stopped using it.

During this episode, he began a 24-hour urine collection for methylimidazoleacetic acid. His methylimidazoleacetic acid was elevated at 10.1 mg/24 h (normal < 5). Previous baseline 24-hour urine collection for histamine was normal.

The next day, his symptoms had resolved with the exception of a few urticarial lesions. Approximately 26 hours after the initial episode began, a serum tryptase level was measured at 110 ng/mL mature (β) tryptase (normal mature tryptase < 1 ng/mL). All symptoms with the exception of urticaria had resolved by the time this serum sample was obtained. Baseline serum obtained 6 months and 2 years later revealed mature tryptase levels of <1 ng/mL and total tryptase levels of 2 and 3 ng/mL, respectively (normal total tryptase, 1-15 ng/mL). All tryptase assays were performed at Virginia Commonwealth University.

To our knowledge, this is just the second case report of an elevated serum tryptase level in a patient with idiopathic anaphylaxis. In the previous case report, no mention of baseline tryptase levels or follow-up was made.³ The fact that our patient had transient elevations of mature (β) tryptase and a urinary histamine metabolite with an acute episode and normal levels of both mature and total tryptase while asymptomatic strengthens the diagnosis of anaphylaxis involving mast cell activation and makes systemic mastocytosis unlikely. This patient has now been followed for 10 years, and although the frequency of his anaphylactic episodes has decreased substantially, no specific etiology has been determined. The mechanism of idiopathic anaphylaxis has yet to be elucidated, but it is important to make the diagnosis accurately early in the disease course, because the condition is known to recur.¹ Although further investigation is needed, serum tryptase levels obtained during or even after an episode of idiopathic anaphylaxis may aid in making the diagnosis correctly.

Previously, it has been shown that the half-life of serum mature tryptase is about 2 hours, and it has been suggested that tryptase should be checked within 4 hours of an anaphylactic episode.⁴ This case is unique because the elevated tryptase level was drawn ~26 hours after the onset of symptoms and approximately 12 hours after resolution of all symptoms with the exception of a few urticarial lesions. This suggests that in some individuals with anaphylaxis, a serum tryptase may be elevated well beyond this 4-hour interval. In some patients suspected of having anaphylaxis, serum samples may be available only more than 4 hours after the episode. In such cases, determination of periacute and baseline tryptase levels may indeed be useful in securing a diagnosis of anaphylaxis involving mast cells.⁵

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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.

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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

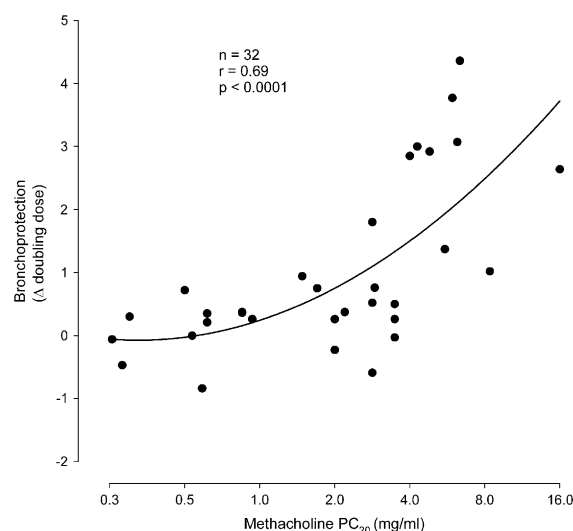


FIG 1. Correlation of bronchoprotection and methacholine PC₂₀. Bronchoprotection in doubling doses is on the vertical axis and the methacholine PC₂₀ (log scale) in mg/mL on the horizontal axis. The curve of best fit is the quadratic equation $y = mx + px^2 + b$.

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