

Letter

HISTAMINE AND METHACHOLINE CHALLENGE CUT POINTS

Direct bronchoprovocation challenges with histamine or methacholine are, with some caveats, highly sensitive tests for current symptomatic asthma. The original tidal breathing method defined a cut point for the provocation concentration causing a 20% decrease in forced expiratory volume in 1 second (FEV_1) (PC_{20}) as 8 mg/mL.¹ Because the PC_{20} measurement is imprecise, with best-case repeatability of ± 1 doubling concentration, the American Thoracic Society defined 8 mg/mL ± 1 concentration (IE, 4-16 mg/mL) as a *borderline* range, with a cut point of 16 mg/mL defined as the level above which a histamine or methacholine challenge result would be defined as negative.²

We have previously published a population study of the 2-minute tidal breathing histamine inhalation challenge in 500 randomly selected college students (age range, 20-29 years; 51% female; FEV_1 , normal [$>80\%$ predicted] in 499 students).³ The data were analyzed using the 8-mg/mL cut point. We reexamined these data to assess the effect of using a 16-mg/mL cut point. The method involved isotonic saline followed by doubling concentrations of histamine (0.03-8.0 mg/mL) inhaled from a Wright nebulizer (output, 0.13 mL/min) by tidal breathing for 2 minutes at 5-minute intervals. Single measures of FEV_1 were taken at 30 and 90 seconds. The percentage decrease in FEV_1 was calculated from the lowest post saline point to the lowest post histamine point and the PC_{20} calculated from the log concentration vs response curve.¹⁻³ The PC_{20} was extrapolated to between 8 and 16 mg/mL, as has been previously validated, in patients with a 10% to 19% FEV_1 decrease.⁴ We were particularly interested in the prevalence of a positive (or *nonnegative*) test result in individuals without asthma.

The results are summarized in the **Figure**. The 17 patients with current asthma (symptoms within the past week) all had histamine PC_{20} values of 8 mg/mL or less. The 16 patients with asthma on allergen exposure (within the past year but >1 week ago) showed an increased prevalence from 38% to 56% when 8 mg/mL was compared with 16 mg/mL, and the 19 patients with a past diagnosis of asthma (no symptoms in the past year) showed an increased prevalence from 11% to 37% (comparing 8 and 16 mg/mL). There were 158 individuals with rhinitis (49% atopic) but no asthma symptoms. The prevalence of a PC_{20} of 8 mg/mL or less was 16%; this increased to 29% with the 16-mg/mL cut point. There were 290 individuals with neither asthma nor rhinitis; 4.5% of these individuals had a PC_{20} of 8 mg/mL or less, and 21% had a PC_{20} of 16 mg/mL or less.

These results indicate that, as would be expected, increasing the PC_{20} cut point increases the diagnostic sensitivity while reducing the diagnostic specificity. The histamine PC_{20} of 16 mg/mL had a high false-positive rate—in this population, 29% in individuals with rhinitis and no asthma and 21% in individuals

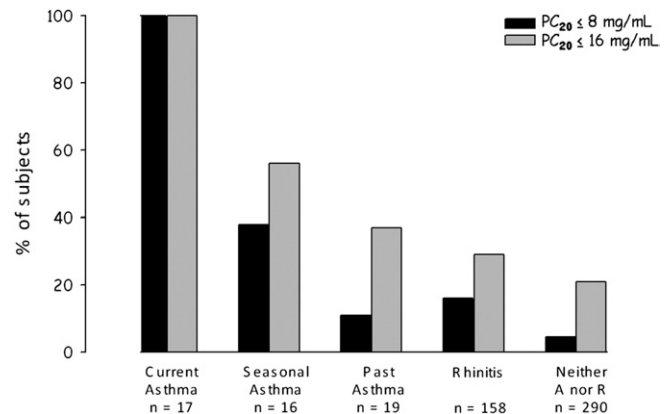


Figure. Prevalence of patients with a histamine provocation concentration causing a 20% decrease in forced expiratory volume in 1 second of 8 mg/mL or less (solid bar) and 16 mg/mL or less (gray bar) in 52 patients with asthma, 150 patients with rhinitis but no asthma, and 290 patients with neither asthma nor rhinitis.

with neither rhinitis nor asthma. By contrast, a lower cut point of 1 mg/mL is highly specific because none of the 448 individuals with no asthma demonstrated a PC_{20} less than 1 mg/mL; however, the sensitivity, at this level, decreased to 41%.³ Although this study was performed with histamine, histamine and methacholine produce comparable results;⁵ therefore, we would anticipate similar results with methacholine.

These data confirm that direct airway responsiveness testing with histamine, and almost certainly with methacholine as well, is highly sensitive. With 2 important caveats, a PC_{20} greater than 16 mg/mL excludes a diagnosis of asthma with reasonable certainty. The first caveat is the requirement for symptoms to be clinically current because airway responsiveness can, sometimes quite rapidly, return to normal in patients with no exposure and no symptoms.⁶ The second caveat is the requirement for the challenge to be performed using an inhalation technique that does not involve deep inhalations because such maneuvers have been shown to counteract the effect of inhaled histamine and methacholine not only in healthy individuals but also in individuals with mild asthma.⁷

In conclusion, a histamine PC_{20} cut point of 16 mg/mL is highly sensitive and valuable in excluding asthma provided symptoms are current and deep inhalations are avoided. This cut point, however, lacks specificity, and a PC_{20} of 16 mg/mL or less cannot be used to confirm a diagnosis. Indirect challenges with physical stimuli (exercise, eucapnic voluntary hyperpnea, nonisotonic aerosols) or chemical stimuli (adenosine monophosphate, mannitol) are highly specific but accordingly less sensitive.⁸ Their sensitivity and specificity are likely similar to a histamine-methacholine cut point of 1 mg/mL (not validated to our knowledge). Therefore, indirect challenges are more appropriate for confirmation of a diagnosis of (current) asthma.

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