

Letter to the Editor

Allergen challenge dose-response slope

To the Editor:

The dose-response curve for methacholine using doubling doses at 5-minute intervals is, on average, approximately linear; that is, double the dose causes double (or slightly more) the response. We have observed that the dose response to doubling doses of allergen administered at 12-minute intervals is frequently steep. This retrospective review was done to compare the dose-response slopes of the last 2 doses of methacholine and allergen in the same individuals.

We reviewed allergen and methacholine inhalation tests performed in our laboratory over the past 25 years. Allergen inhalation is done by administering doubling concentrations (ie, doses) for 2 minutes of tidal breathing at 12-minute intervals between the start of one and the start of the next concentration.¹ Methacholine is inhaled in doubling concentrations for 2 minutes of tidal breathing at 5-minute intervals.² We selected allergen challenge tests in which the FEV₁ decrease 10 minutes after the last concentration was 19% or more. We examined screening or placebo (ie, unmedicated) allergen challenges, and for subjects with multiple studies, we selected the first study meeting the criterion to avoid any selection bias. We also examined an unmedicated methacholine challenge done within a 1-week period and also the first we identified with a 19% or more FEV₁ decrease at the last concentration. The primary comparison was the percentage FEV₁ decrease at the second-to-last concentrations of allergen and methacholine and the ratio between the last and second-to-last response; these were compared by using the paired *t* test.³

We identified 54 subjects (32 female subjects; 26.1 ± 7.9 [SD] years old) whose challenges met the selection criteria. Mean

FEV₁ was 3.46 ± 0.77 L or $93.7\% \pm 12.8\%$ predicted. The mean FEV₁ decrease at the last concentration was $25.3\% \pm 5.0\%$ and $25.4\% \pm 4.4\%$ for allergen and methacholine, respectively (Fig 1, panels 1 and 2, respectively; $P = .87$). The mean FEV₁ decrease at the second-to-last concentration of allergen was $8.9\% \pm 3.1\%$, which was significantly lower than that seen for the second-to-last concentration of methacholine (ie, $12.2\% \pm 3.2\%$; Fig 1; $P < .0001$). The ratio of the last to second-to-last response was 3.2 ± 1.5 for allergen compared with 2.3 ± 0.8 for methacholine (Fig 1, $P < .0001$).

These data indicate that the dose-response curve for doubling doses of allergen administered at 12-minute intervals is steeper than that for doubling doses of methacholine administered at 5-minute intervals. The response at the threshold ($\geq 19\%$) was more than 3-fold that of the response at the second-to-last (ie, half) concentration for allergen compared with slightly more than 2-fold for methacholine. The most plausible explanation would be differences in the duration of effect and corresponding differences in the cumulative effect of allergen and methacholine. Methacholine has only a slight cumulative effect when doubling doses/concentrations are administered at 5-minute intervals.⁴ Although we are not aware of comparative data for allergen challenges, the maximal response occurs, on average, at 20 or 30 minutes after challenge.⁵ Therefore it is probable that there is a greater cumulative effect of allergen inhaled at 12-minute intervals, and this would likely explain our results.

These data have practical value in the performance of allergen inhalation tests, which are exclusively a research tool. One should strive to avoid severe airflow obstruction and the added possibility of severe late asthmatic responses, which might not be as responsive to bronchodilator reversal compared with both the

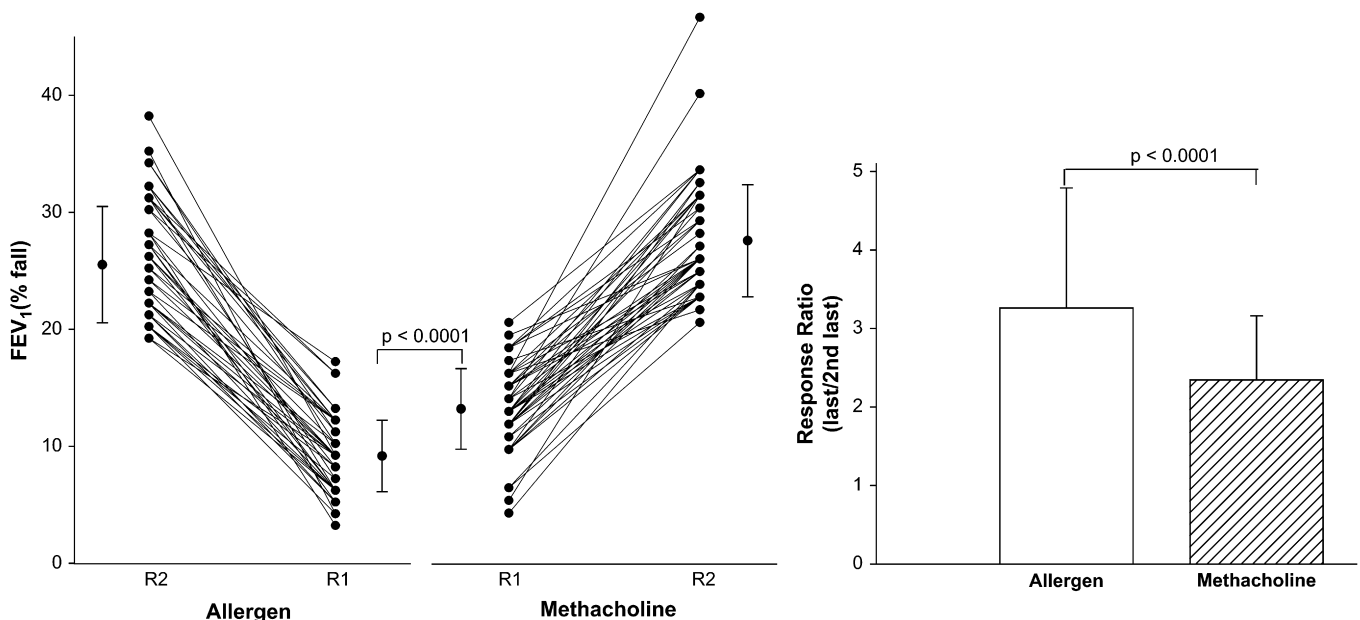


FIG 1. Individual terminal dose-response slopes (with mean and SD) to allergen (right) and methacholine (center). The left panel shows the mean ratios defined as the response to the last concentration (mean approximately 25%) divided by the response to the second-to-last concentration of allergen and methacholine, respectively.

allergen-induced early response and the methacholine response. Investigators should be aware of the potential for a steep dose-response curve and take appropriate precautions.

First, we would suggest that allergen concentrations should not be increased by any more than doubling; some protocols use tripling, half-log (approximately 3.3-fold), and even 10-fold dose steps.

Second, the timing between allergen inhalations can be increased. Increasing the interval between allergen dose step-ups to 20 or 30 minutes over the entire challenge would not be practical because of time concerns. For safety reasons, we often administer 5 or more allergen concentrations; this already requires in excess of 1 hour with the current 12-minute interval. However, our more recent protocols have often modified so that after a threshold 10% FEV₁ decrease, we wait 10 minutes and repeat the FEV₁ measurement before proceeding. This helps avoid excessively large early asthmatic responses, without prolonging the allergen challenge procedure too much.

In summary, we have confirmed that the dose-response curve for allergen is significantly steeper than that for methacholine. Appropriate precautions and protocol modifications should be undertaken when performing allergen inhalation tests.

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