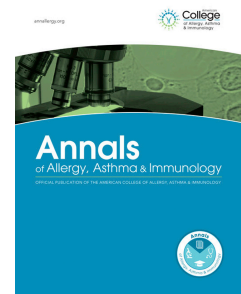


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Characterising the Early and Late Asthmatic Response in the Allergen Inhalation Challenge

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Title: Characterising the Early and Late Asthmatic Response in the Allergen Inhalation Challenge

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Allergen Inhalation Challenges (AICs) are widely used in research to assess airway responses to allergen exposure and predict therapeutic effectiveness of various medications.¹ Characteristics of early (EAR) and late (LAR) asthmatic responses are often described in general terms.²⁻⁴ Original research findings focus on mean data. We are not aware of any data objectively documenting responses of individual participants and it is important to acknowledge that mean data does not accurately reflect the range of individual responses and the relevant safety implications of performing AICs. We therefore sought to directly characterize the timing, magnitude and recovery characteristics of the EAR and LAR with an emphasis on individual responses.

Through retrospective analysis of allergen challenge data we selected challenges performed in treatment naïve asthmatics, where the FEV₁ fall 10 minutes post inhalation was at least 20% below baseline FEV₁ and the response was followed, untreated, for at least 3 hours. Data from individuals who participated in multiple studies were included only once at first identification. All challenges were performed using standardized 2-minute tidal breathing methodology utilizing a Wright[®] jet nebulizer and a Hans Rudolph[®] two-way-valve,⁵ and all participants met standard AIC clinical trial inclusion/exclusion criteria.⁴ Allergen dosing met standardized protocols.³

We identified 65 AICs meeting our predefined conditions. Participant demographics, mean (SD): age 29 (+/-10) years, height 171 (+/-9) cm, baseline FEV₁ 3.57 (+/-0.73) L (90 (+/-11) % predicted). Twenty-nine participants were female. Allergens used for inhalation challenges were cat (n=27; 27 EARs, 12 LARs), grass pollen (n=15; 15 EARs, 5 LARs), house dust mite (n=15; 15 EARs, 5 LARs), horse (n=7; 7 EARs, 1 LAR) and birch pollen (n=1,1 EAR, 0 LAR).

In the 65, the maximum EAR occurred at 10 and 20 minutes in 26 and 28 participants respectively, demonstrating that maximum EAR after AIC occurs within 20 minutes in 83% of cases. Eight participants reached maximal bronchoconstriction at 30 minutes and bronchoconstriction was maximal at 45 minutes in 3 participants (Figure 1). Of the eleven participants with maximal fall in FEV₁ beyond 20 minutes, only 1 was 5% (6.9%) greater than the fall at 20 minutes. Following the initial 10-minute assessment, 15 participants experienced a further fall in FEV₁ of $\geq 5\%$ at 20 minutes (range 5.0-17.6%). Of these, 10 were between 5 and 9.9% and 5 were $> 10\%$. The potential progression of obstruction between the first (10 minute) and second (20 minute) measurements is an important consideration when the 10 minute fall in FEV₁ is greater than 15% but less than the target 20%: this requires a safety decision whether and when to administer additional allergen. With respect to magnitude of individual EAR responses, maximal decreases in FEV₁ ranged from 20.0 to 45.4% (Figure 1); 33 participants had maximal decreases in FEV₁ between 20 and 30%, 26 participants experienced maximal falls between 30 and 40% and 6 participants experienced EAR bronchoconstriction greater than 40% indicating that relatively large and potentially uncomfortable responses do occur.

There were 42 (64.6%) isolated early responders; 90% of these showed maximal improvement in FEV₁ by ≤ 3 hours. All 42 participants had recovered to $>90\%$ of baseline FEV₁ within 3 hours, and 33 of these had recovered by 90 minutes. In general, recovery did not seem to relate to magnitude of response.

The LAR is defined as a fall in FEV₁ of 15% or more during the 3 to ≥ 7 hours following allergen inhalation.²⁻⁴ Dual responders, those with an EAR followed by an LAR, accounted for 23 of the 65 AIC's reviewed (35.4%), considerably less than the estimated 50% prevalence previously reported.²⁻⁴ In our relatively small sample, four dual responders had maximal

responses at 5 hours, 6 at 6 hours, and 13 at 7 hours (Figure 1). Notably, 83% of dual responders still had bronchoconstriction beyond 15% at 7 hours. The observation of maximal constriction at 7 hours is clearly limited in that measurement of the response ceased at that time point. This lends support to late responses being potentially maximal, and of large magnitude, beyond 7 hours and also emphasizes the importance of having a plan in place to manage the participant at the end of the day when they leave the laboratory, which is important for both participant safety and data integrity. The range in magnitude of late responses was 16.4 – 45.8%; the range of percent fall in FEV₁ over the defined timeframe of the LAR (i.e. 3-7 hours) was -6.7 – 45.8% (Figure 1). In terms of recovery prior to the development of a late response, 1 had their maximum EAR recovery at 90 minutes, 8 at 2 hours, 11 at 3 hours, 1 at 4 hours, and 2 at 5 hours, suggesting the majority of late responses begin to develop at 3 – 4 hours, consistent with published mean data.²⁻⁴ Most dual responders showed improvement in FEV₁ to within 90% of baseline by 4 hours post allergen inhalation however two failed to recover to less than 10% bronchoconstriction at any time point.

Through retrospective review of AIC data, we were able to objectively support some of the characteristics of allergen challenges routinely described in generalized terms including the timing of peak early responses and onset of late responses. In addition, we have highlighted a number of safety aspects, including the potential for significant early and late responses, the need to carefully assess the administration of additional allergen when the response at 10 minutes is close to but below target and the reality that many dual responders are still experiencing significant bronchoconstriction at the end of the day. It is worth noting that these data from a Western Canadian province may under-represent other regions, especially where allergen avoidance is not possible and dual responses are more prevalent (e.g. house dust mite and higher

humidity). Importantly, individual characteristics following AIC may not be appreciated from mean data and have the potential to occur despite the use of highly standardized methods; this underscores the recommendation that allergen inhalation challenges be performed by those with extensive knowledge and experience.

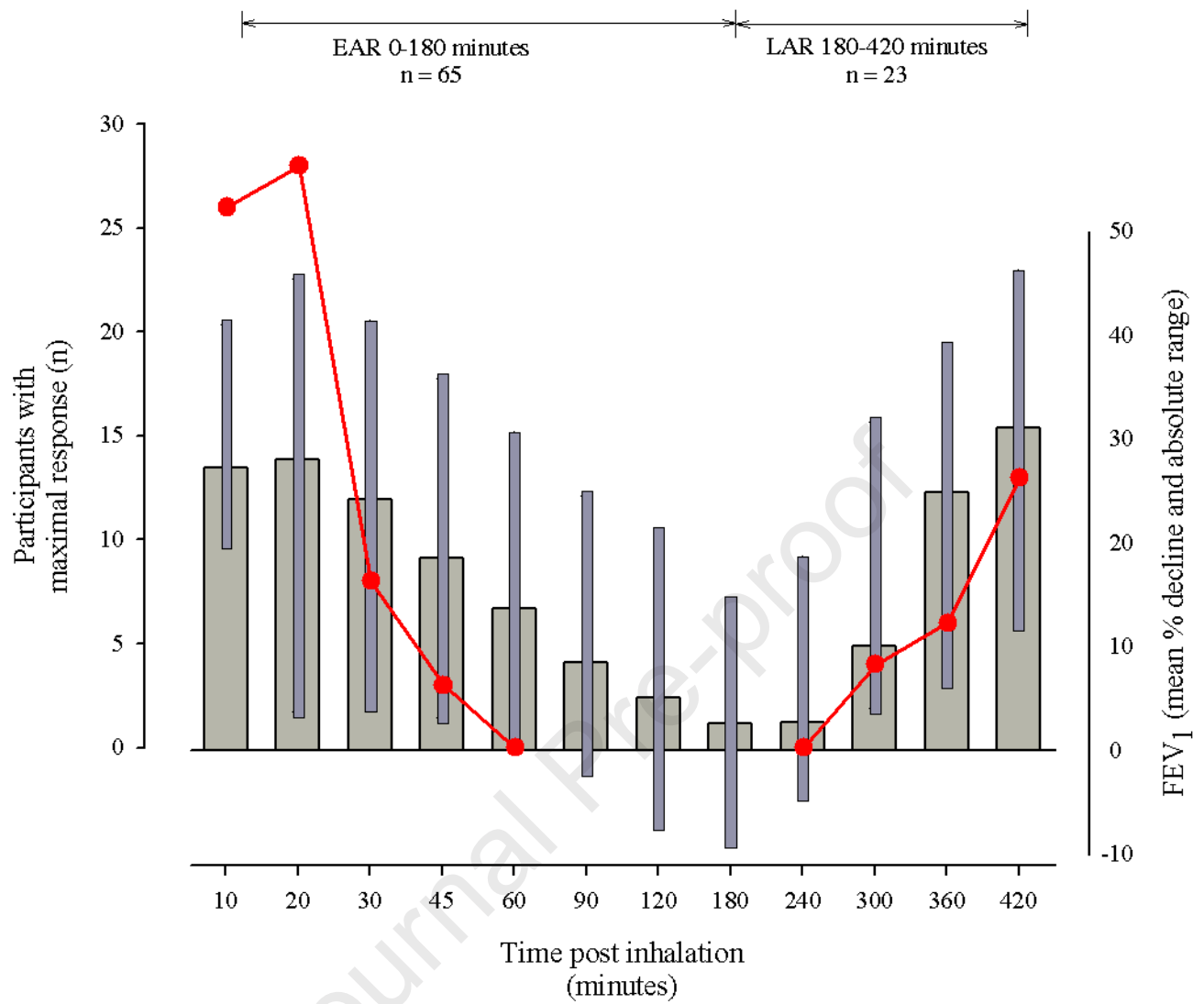
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Figure 1

The thick bars represent the mean percent decrease in FEV_1 (range of individual responses, thin bars), in both EAR and LAR at time intervals post-allergen inhalation. The overlying red circles represent the number of participants with a maximal response in both EAR and LAR at time intervals post-allergen inhalation.



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