Validation of Biogenics Research Chamber for Elicitation of Symptoms to Dust Mite Antigen

Abstract #766

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Introduction

The major cause of indoor perennial allergic disorders, particularly asthma, allergic rhinoconjunctivitis (AR), and atopic dermatitis, is allergy to house dust mites (HDM). Those conditions affect up to 25% of the US population. Treatment modalities have included intense efforts to avoid mites, immunotherapy and others with mixed success, invoking the need for more rigorous clinical studies 1. There are many barriers to the evaluation of existing or novel therapies for HDM in the natural setting. Recent studies have demonstrated that exposure to aeroallergens in an Allergen Challenge Chamber (ACC) represents a sensitive, specific and reproducible methodology for elicitation of AR symptomatology secondary to aeroallergens 2, 3. Most of these ACC studies, including ours, have focused on pollen exposures 4, 5. These studies highlight the utility of using ACCs as a physiologically relevant model to monitor individual responses. Highlighting this, a recent NIH workshop recognized the ACC as a potential tool for proving the efficacy of novel products for allergen immunotherapy 6. However, there are only a few studies that have used ACC for elicitation of symptoms following challenge with HDM 7, 8, partly due to the difficulty of the delivery of HDM and the low reproducibility.

Objectives

The objectives of this study were to establish the conditions that would recapitulate AR symptomatology in HDM sensitive patients in our ACC (Biogenics Research Chamber) and to determine the extent of reproducibility of symptomatology elicited during and between repeated exposures to HDM.

Methods

- Participants of both genders, 18 to 70 years were enrolled, and classified as HDM+ or HDM- according to a positive versus negative response, respectively, to skin prick test (SPT) to D. pteronyssinus (≥ 5 mm). There were no differences between HDM+ and HDM- participants by age, gender and ethnicity.
- The study comprised 4 consecutive phases (Figure 2A): (i) a run-in phase in the natural setting comprised 4 days prior to first of series of HDM challenges in the ACC (ACC-I); (ii) ACC-I comprised exposure for 3 hours each on four consecutive days (exposures 1 to 4) to a milled, purified mite body powder of Dermatophagoides pteronyssinus; (iii) Observation phase in the natural setting of 38 days prior to ACC-II; and (iv) ACC-II comprised exposure to HDM using identical conditions as those employed for ACC-I. Twenty-one HDM+ and 14 HDM- participants completed all 4 study phases.
- Total symptom score (TSS, scale 0-28) were monitored at baseline and 30 minute intervals during ACC-I and ACC-II. TSS was also recorded in the morning and evening during the run-in and observation phases. Nasal symptoms comprised nasal congestion, nasal itching, sneezing, and runny nose and ocular symptoms comprised itching, tearing, and redness. Nasal and ocular symptoms were recorded on a scale of 0 (absent) to 4 (very severe).
- Airborne samples were collected from 5 stations for 10 minutes at hourly intervals through a nylon filter for measurement of Der p1 by ELISA, and an Allergenco cassette sampler for microscopic evaluation of mite particles.

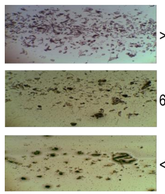


Fig. 1: Visualization of the HDM powder collected in relationship to amount of HDM Der p1 antigen delivered

The top, middle, and lower panels represent the microscopic pictures of the collected HDM powder in the ACC after delivery of Der p1 antigen quantified as >100, >60-100, and <60 ng/M3 (Optics 100X).

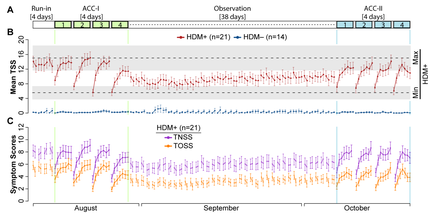
Study Results

Table 1: Distribution of HDM powder in ACC-I

Time	Exposures				Mean	*P*
	1	2	3	5		
10'	78.3	69.8	122.0	96.1	91.5	0.162
60'	71.1	81.2	116.0	83.0	87.8	0.015
120'	80.0	75.9	103.8	99.6	89.8	0.321
180'	93.9	83.7	97.2	126.7	100.4	0.444
Mean	80.8	77.6	109.7	101.3	**92.4**	
***P*-value**	0.055	0.422	0.796	0.429		

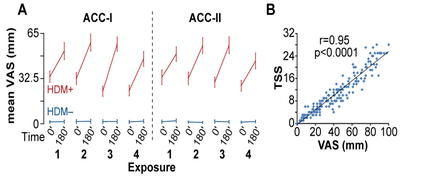
Shown are the mean Der p1 levels (ng/M^3) assayed by ELISA from samples collected from 5 stations at the indicated time points post exposure. Significance values are by ANOVA.

Fig. 2: Study Design and TSS during four study phases



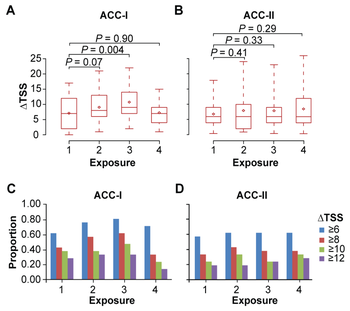
(A) Study phases. **(B, C)** 21 HDM+ and 14 HDM- individuals completed all four phases and depicted are the mean (SD) of the TSS (in B) and Total Nasal Symptom Scores (TNSS) and Total Ocular Symptom Scores (TOSS) (in C). The minimum and maximum mean (with 95% confidence interval) TSS observed in HDM+ individuals throughout the study are shown as dashed lines with grey bands in panel B.

Fig. 3: High correlation between symptom scores recorded on Visual Analog Scale (VAS) and by TSS



(A) VAS recordings at baseline and at 180 min. **(B)** Data from ACC-I showing correlations for values recorded at baseline and 180 min from four exposures.

Fig. 4: Responsiveness to HDM exposure in HDM+ participants during ACC-I and ACC-II



(A, B) Responsiveness (ΔTSS) was calculated as change from the baseline (pre exposure value) to the maximum TSS during each exposure in ACC-I and ACC-II. **(C, D)** Proportion of HDM+ participants that achieved the indicated ΔTSS during each exposure.

Fig. 5: Correlations between the maximum TSS recorded in each of the 4 study phases in 21 HDM+ participants

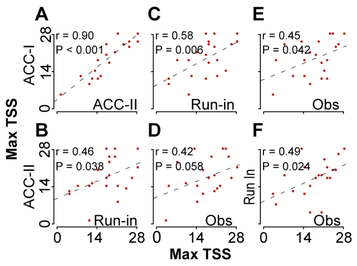
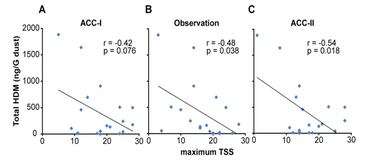


Table 2. Concentration of HDM antigens collected from the mattress dust in the homes of the study participants

Antigen	HDM- participants (n=11)	HDM+ participants (n=20)	P-value*
	Median (IQR)	Median (IQR)	
Total HDM#	1.08 (0.85-2.66)	2.16 (1.16-2.71)	0.36
Der p 1	0.00 (0.00-2.31)	0.39 (0.00-2.29)	0.64
Der f 1	0.00 (0.00-2.23)	0.00 (0.00-1.44)	0.53
Der 2	0.85 (0.48-1.78)	1.22 (0.78-1.98)	0.55

Data are the median (inter quartile range) of the indicated house dust antigens [Log_{10} (ng/G)]; *P-values by Wilcoxon-Mann-Whitney test. #Total HDM antigen load was estimated as the cumulative antigen content of Der p 1, Der f 1, and Der 2 in log_{10} (ng/G), assayed by ELISA.

Fig. 6: Correlations between the total HDM load collected from mattresses of the HDM+ participants and maximum TSS



Data are from 19 HDM+ participants. Total HDM was measured by an ELISA.

Adverse Responses

- There were no significant adverse responses other than bronchospasm in 5 HDM+ participants. They developed 11 episodes of bronchospasm manifested by cough, chest tightness, and wheezing. Bronchospasm was confirmed by physical examination and spirometry. Three participants showed >15% improvement and 1 improved 7% in FEV1 after treatment with albuterol by nebulizer and returned to the ACC for continued exposure without exacerbations.
- One in-chamber bronchospastic participant and 1 other participant required treatment for asthma signs and symptoms approximately 8 hours after the chamber exposure suggesting late phase responses.

Conclusion and Summary

- Exposure to HDM in the ACC induced AR symptomatology in HDM+ but not HDM- participants.
- There is a robust degree of responsiveness to HDM challenge, as nearly 50% of HDM+ participants exhibited an increase in TSS ≥ 6 from baseline symptom levels present before the start of each exposure.
- There is a high degree of concordance in the symptomatology elicited between the two series of HDM exposures as well as during individual exposure, whereas the correlation between the extent of symptoms elicited in the ACCs and those in the natural settings were much lower.
- Clinical trials conducted in the ACC can mitigate confounding by variable exposure to HDM. Highlighting this, among HDM+ participants, there was a negative correlation between the total HDM antigen levels in the mattress dust collected from the homes of the participants and the TSS recorded in the study phases. This suggested that patients with higher compared with lower symptomatology maintained a cleaner home environment.
- Our ACC – the Biogenics Research Chamber -- operated, technically and mechanically, to deliver and disperse HDM allergen at levels to effectively cause symptomatology adequate to study effects of interventions and the underpinning mechanisms of the allergic response.
- The stimulation of significant asthma and the response to treatment suggests that mild asthmatic participants can be safely studied in the chamber setting utilizing HDM allergen.

References

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