

Provocation of nonallergic rhinitis subjects in response to simulated weather conditions using an environmental exposure chamber model

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ABSTRACT

Nonallergic rhinitis (NAR) subjects present clinically with similar symptoms to subjects with allergic rhinitis, but which mechanistically are not IgE-mediated. NAR is difficult to study because of multiple, as yet unknown, disease mechanisms and lack of biomarkers and diagnostic tests. The purpose of this proof of concept pilot study was to develop an environmental exposure chamber (EEC) model to simulate weather conditions in a controlled setting to objectively diagnose NAR subjects and ultimately to investigate novel NAR therapies. Thirty-seven subjects with a history of NAR confirmed by negative skin-prick test to a panel of aeroallergens were tested with cold dry air (CDA) and temperature change challenges. Objective (acoustic rhinometry [AcR] and nasal secretions) and subjective measures (total nasal symptom scores [TNSSs]: congestion, rhinorrhea, and postnasal drip [0–3]) were collected. Data was presented as mean $\pm$ SEM and statistical significance was assessed by paired t-test. The NAR EEC AcR responders to CDA had a significant decrease in mean minimal cross-sectional area (MCA; a measure of nasal patency) of $22.2 \pm 2.43\%$ ($p < 0.0001$) and $6.7 \pm 7.22\%$ (not statistically significant) at 30 and 60 minutes, respectively, with a concomitant increase in TNSS of 1.0 ± 0.24 U and 1.4 ± 0.30 U, respectively. AcR responders to temperature change showed a significant decrease in mean MCA to warm air of $16.0 \pm 3.82\%$ ($p < 0.001$) and $19.4 \pm 3.88\%$ ($p < 0.0001$) at 30 and 60 minutes, respectively, with an increase of TNSS of 0.4 ± 0.25 U and 0.4 ± 0.27 U, respectively. With rapid conversion to cold air, further decrease in mean MCA accompanied by an increase in TNSS was observed at 30 and 60 minutes. Increase in rhinorrhea was highest for CDA and the cold air phase of the temperature change challenge. Using the NAR EEC model, significant symptoms were induced in response to simulated weather changes in NAR patient responders. This proof of concept pilot study shows that the EEC model provides a consistent and reliable method to phenotype weather-induced NAR subjects that could be used to investigate disease mechanisms and novel therapies for NAR.

(Allergy Asthma Proc 33:333–340, 2012; doi: 10.2500/aap.2012.33.3579)

Nonallergic rhinitis (NAR) is a non-IgE-mediated rhinopathy of unknown etiology.¹ NAR encompasses a number of clinical conditions including vasomotor rhinitis, occupational rhinitis, drug-induced rhinitis, hormonal-induced rhinitis, NAR with eosinophilia syndrome, gustatory rhinitis, and emotion-induced rhinitis.¹ A diagnosis requires negative skin-prick testing to aeroallergens in conjunction with persistent nasal symptoms (>9 months/year) consisting of rhinorrhea, nasal congestion, sneezing, or postnasal drip.¹ Subjects often have symptoms in response to nonallergic triggers such as

noxious odorants and chemical fumes or temperature and/or barometric pressure changes.¹ Within the rhinitis population, it has been estimated that $\sim 23\%$ have pure NAR (characterized by nasal symptoms but a negative skin-prick test) and 34% have mixed rhinitis (a combination of allergic and nonallergic).^{2,3} Although not life-threatening, the impact of NAR on quality of life can be quite significant.⁴ Currently, treatment of NAR focuses on avoidance of triggers and nonspecific pharmacotherapy because the mechanism(s) of NAR are currently unknown. Although a number of topical corticosteroids (fluticasone propionate, budesonide and beclomethasone) and topical antihistamines (azelastine) have been approved by the Food and Drug Administration for the treatment of NAR or vasomotor rhinitis, their mechanism of action for this idiopathic disorder remains elusive.⁵ Development of specific novel treatments for NAR has been impeded by the inability to objectively measure end organ responses to non-specific NAR triggers in a clinical setting.

The primary objective of this proof of concept pilot study was to better characterize NAR subjects by measuring their objective and subjective end organ re-

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Funded by Cetero Research and GlaxoSmithKline

R. Murdoch is an employee of GlaxoSmithKline, the remaining authors have no conflicts of interest to declare pertaining to this article

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Table 1 Summary of subject demographics

Parameters	CDA DC Responder (n = 25)	CDA AcR Responder (n = 19)	Temperature Change DC Responder (n = 19)	Temperature Change AcR Responder (n = 26)
Race (n [%])				
Asian	1 (4%)	2 (11%)	1 (5%)	1 (4%)
Black or African American	2 (8%)	3 (16%)	3 (16%)	4 (15%)
White	20 (80%)	11 (58%)	15 (79%)	19 (73%)
Multiracial/other*	2 (8%)	3 (16%)	0 (0%)	2 (8%)
Ethnicity (n [%])				
Hispanic or Latino	2 (8%)	3 (16%)	1 (5%)	2 (8%)
Not Hispanic or Latino	23 (92%)	16 (84%)	18 (95%)	24 (92%)
Gender (n [%])				
Male	12 (48%)	9 (47%)	6 (32%)	10 (38%)
Female	13 (52%)	10 (53%)	13 (68%)	16 (62%)
Age (yr $\pm$ SE)	47 $\pm$ 1.7	46 $\pm$ 2.1	49 $\pm$ 7.2	47 $\pm$ 9.0
Minimum, Maximum	33, 62	33, 62	38, 62	33, 63

Note: Age was calculated using the informed consent date; n is the number of subjects.

% is the percentage based on n.

*Subjects who checked two or more races were classified as multiracial.

AcR = acoustic rhinometry; CDA = cold dry air; DC = diary card.

sponses induced by simulated weather conditions using a novel NAR environmental exposure chamber (EEC) model.

METHODS

This study was approved by the appropriate institutional review boards and regulatory agencies and conducted in accordance with the principles of Good Clinical Practice. Written informed consent was obtained from subjects before any study-related activities were initiated.

Fifty-seven male and female subjects between the ages of 18 and 65 years who had a negative skin-prick testing to a panel of allergens (cat and dog dander, dust mite, cockroach, mold, tree, grass, and ragweed) were screened for a history of chronic NAR symptoms to at least one trigger (pollution, weather changes, perfumes, or cleaning products). Women were required to allow sufficient time to be nonpregnant, nonlactating, or postmenopausal and those of childbearing potential were required to have a confirmed negative urine pregnancy test and to use appropriate birth control methods. Subjects enrolled were generally in good health based on medical history and physical examination. Subjects were excluded if they had a history of uncontrolled asthma, rhinitis medicamentosa secondary to intranasal vasoconstrictors, or any clinically significant uncontrolled medical problem. Subjects were not permitted to use systemic or intranasal corticosteroids, intranasal antihistamines, inhaled cromoglycates, or nedocromil sodium within 30 days or during the study. Subjects unable to stop taking nasal medi-

cations (e.g., xylometazoline) or those who participated in an investigational drug study within 30 days before study start were also excluded. Other exclusionary criteria included any nasal surgery within 3 months of the first visit, presence or history of nasal polyps, nasal or paranasal sinus infection in the past 30 days, and significant anatomic abnormalities affecting nasal function.

Subjects who passed the screening criteria (20 female and 17 male subjects) returned at a minimum of 3 days later for the first temperature challenge visit (Table 1). At each challenge visit, they were exposed to either a cold dry air (CDA) challenge or a temperature change challenge (warm air followed by cold air), scheduled at least 3 days apart, to allow for sufficient time for resolution of any symptoms related to the challenges. Ambient temperature stabilization was previously validated to occur over a maximum time period of 30 minutes before challenges.

Nonallergic Rhinitis Environmental Exposure Chamber

The NAR EEC is a state-of-the-art facility that was designed and built for the purpose of studying NAR and facilitates the challenging and close monitoring of four subjects at a time (Fig. 1). The air handling system in the EEC is equipped with large desiccating capacity to rapidly remove moisture from the chamber air and recirculate dry air back into the chamber through custom-designed air velocity tubes and discharges. The chamber and air velocity tubes are equipped with custom adjustable controls that allow air to be conditioned to specified temperature, relative humidity (RH), and

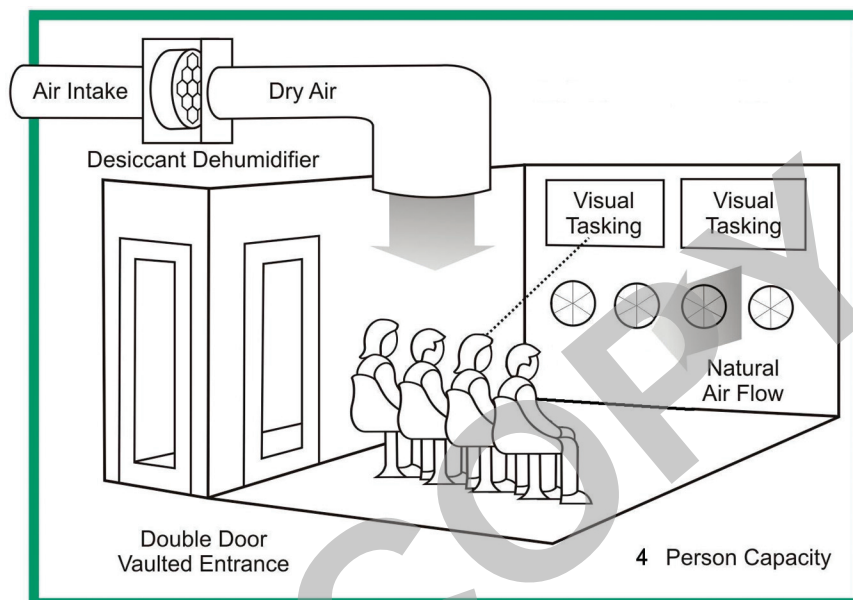


Figure 1. Schematic diagram of nonallergic rhinitis (NAR) chamber: temperature, relative humidity (RH), barometric pressure, and air velocity can be controlled through a state-of-the-art system.

velocity and to allow for barometric pressure control in the chamber.

CDA: A Static Challenge

The CDA challenge consisted of exposing subjects to a $14 \pm 5^\circ\text{C}$ temperature with $<15\%$ RH over 1 hour. The CDA was directed at the level of the subjects' faces (maximum exposure diameter, 2ft) at a velocity of 5 ± 3 ft/s for the duration of the challenge.

Temperature Change: A Dynamic Challenge

The temperature change challenge was a 2-hour challenge that involved initially exposing subjects to warm air conditions of $35 \pm 5^\circ\text{C}$ for 1 hour. The conditions were then rapidly converted to cold air ($14 \pm 5^\circ\text{C}$) to which subjects were exposed for an additional 1 hour. Both the warm and the cold air were directed at the subjects' faces at a moderate velocity of 5 ± 3 ft/s with an RH of $\sim 20\%$.

Symptom Assessments

During the exposure challenges, subjects were subjectively assessed for rhinitis symptoms using diary cards (DCs) that measure total nasal symptom scores (TNSSs). Nasal congestion, rhinorrhea and postnasal drainage were rated on a 4-point scale (0–3), where 0 = none (no sign/symptom evident), 1 = mild (sign/symptoms clearly present but minimal awareness, easily tolerated), 2 = moderate (definite awareness of sign/symptom, which was bothersome but tolerable), 3 = severe (sign/symptom was hard to tolerate). Objective measurements of nasal patency were determined using acoustic rhinometry (AcR) performed with the RhinoScan system (Interacoustics USA, Eden Prairie, MN). The minimal cross-sectional area (MCA)

was measured in either the left or the right nostril at each time point before, during, and after each exposure. The amount of nasal secretion by each patient was estimated by calculating the difference between nasal secretions on tissues collected and weighed after all temperature challenges and the preweights of the unused tissue paper. The primary efficacy variables assessed were mean change from baseline (MCFB) in TNSS, MCFB in individual symptom severity, MCFB in nasal patency as measured by AcR, and mean nasal secretion weight collected during the challenges. Safety assessments included monitoring of any occurrences of adverse events throughout the study.

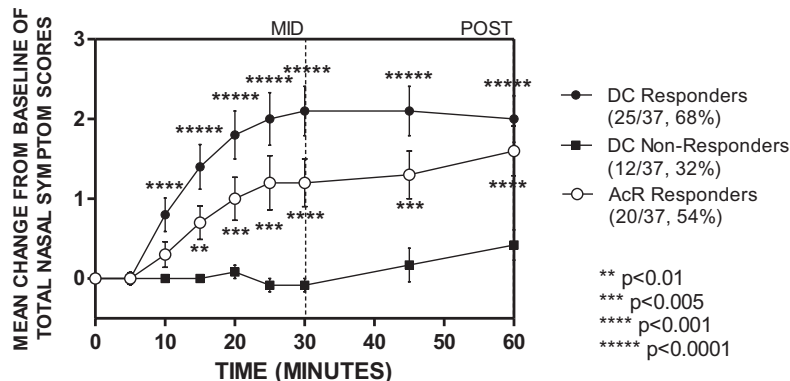
Responders versus Nonresponders

To minimize the blunting of responses by nonresponders, criteria were set before analyzing the data to remove nonresponders from the analyses. Both subjective (DC) and objective (AcR) criteria were considered to identify responders to the simulated weather condition challenges. DC nonresponders were defined as subjects who scored "0" or "negative" MCFB on $\geq 80\%$ of their TNSS DCs during a particular challenge. Responders were defined as the remaining subjects who scored "0" or "negative" MCFB on $< 20\%$ of their TNSS on DCs (and were classed as "DC responders") during a particular challenge. "AcR responders" were defined as those subjects who had a $\geq 10\%$ decrease in nasal patency with challenge condition exposure.

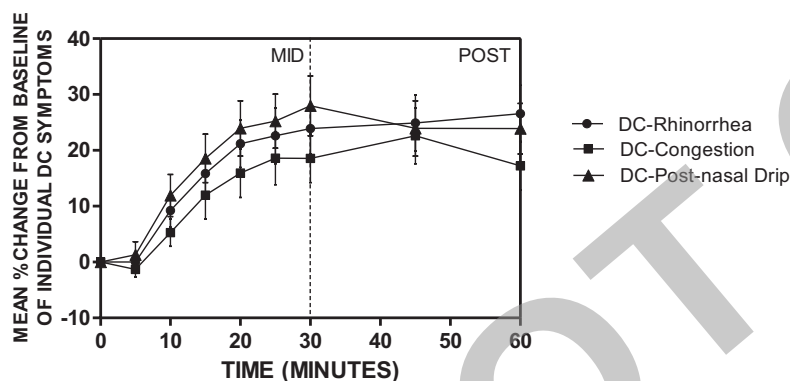
Statistical Analyses

All statistical analyses were performed using GraphPad Prism V5 software (GraphPad, Inc., San Diego, CA). Descriptive analyses measured means $\pm$ SEM for all objective and subjective outcomes. Changes in nasal

A.



B.



C.



Figure 2. Cold dry air (CDA) challenge. (A) Mean change from baseline of total nasal symptom score (TNSS) during CDA challenge (60 minutes). There was statistically significant increase of mean change from baseline (MCFB) of TNSS in diary card (DC) and acoustic rhinometry (AcR) responders with minimal response in DC nonresponders. (B) Mean percent change from baseline of individual symptoms using DC in DC responders ($n = 25/37$; 68%). (C) Nasal patency at mid-CDA (30 minutes) and post-CDA (60 minutes) challenges. Decrease in nasal patency at mid-point of CDA challenge was statistically significant for both DC responders ($p = 0.0035$) and AcR responders ($p < 0.0001$).

patency observed using AcR were tested for significance using a standard paired *t*-test.

RESULTS

Of the 57 subjects medically screened, 37 subjects were qualified to be tested with the NAR EEC challenges of CDA and temperature change. As shown in Table 1, some subjects did not respond to either of the challenges. Subjects were classified as DC and/or AcR responders based on their subjective DC symptom responses and/or objective change in nasal patency. As outlined in Table 1, subjects were primarily Caucasian with an average age of 48 years and a nearly equal distribution of male and female subjects. For the CDA challenge among either the DC or the AcR responders, male and female subjects were similar. For

the temperature change challenge, there were more female than male responders.

CDA Challenge

MCFB of TNSSs. CDA was an effective trigger inducing NAR symptoms in many of the NAR subjects when measured subjectively with DC as well as objectively with AcR and nasal secretions. A distinct patient population responded to the CDA trigger subjectively and objectively. Twenty-five of 37 subjects exposed to CDA were considered to be DC responders (68%). A pronounced increase in the MCFB of TNSS was observed with an initial increase from 0.00 ± 0.08 U (not statistically significant [NS]) at 5 minutes to 0.80 ± 0.21 U

($p < 0.001$) at 10 minutes (Fig. 2 A). A further increase was observed from baseline of 1.40 ± 0.28 U ($p < 0.0001$) and 2.10 ± 0.31 U ($p < 0.0001$) at 15 and 30 minutes, respectively. Between 30 and 60 minutes, there was a plateau of the MCFB of TNSS with a total increase from baseline of 2.00 ± 0.29 U ($p < 0.0001$) at 60 minutes. DC nonresponders had a MCFB of TNSS ranging from -0.08 to 0.42 , indicating the specificity of responses by a subset of NAR subjects.

Nineteen of 37 (54%) subjects were identified as objective responders by AcR defined criteria of a $\geq 10\%$ decrease in MCA. Among these subjects, the MCFB of TNSS was 0.00 ± 0.07 U (NS) at 5 minutes, 0.32 ± 0.17 U (NS) at 10 minutes, and 0.63 ± 0.21 U at 15 minutes ($p < 0.01$). The increases at 20, 30, and 60 minutes were 0.84 ± 0.23 U ($p < 0.005$), 1.00 ± 0.24 U ($p < 0.001$), and 1.42 ± 0.30 U ($p < 0.001$), respectively (Fig. 2 A).

Individual Symptom Scores—Congestion, Runny Nose, and Postnasal Drip. When subjective DC responders were evaluated for individual symptom scores (Fig. 2 B), rhinorrhea increased from baseline by $15.84 \pm 3.37\%$ at 15 minutes (Fig. 2 B) and further increased to $23.88 \pm 4.52\%$ at 30 minutes before plateauing at 45–60 minutes. Postnasal drip showed a similar pattern with increases of $18.56 \pm 4.33\%$ at 15 minutes and $27.96 \pm 5.35\%$ at 30 minutes before plateauing at 45 and 60 minutes. Nasal congestion scores were lower than rhinorrhea or postnasal drip scores, initially increasing by $11.96 \pm 4.25\%$ at 15 minutes and further increasing to $18.56 \pm 4.33\%$, $22.60 \pm 5.00\%$, and $17.24 \pm 4.35\%$ at 30, 45, and 60 minutes, respectively.

Nasal Patency Using AcR. When nasal patency was assessed using AcR, there was a $10.12 \pm 4.09\%$ decrease in mean percent change in MCA at 30 minutes in the DC responders (Fig. 2 C) at the midpoint of the CDA challenge ($p = 0.0035$). A $3.36 \pm 5.51\%$ (NS) increase in MCA was observed by 60 minutes, which may reflect accommodation by subjects to the chamber conditions over time. Using $\geq 10\%$ in MCA to define responders, a significant decrease of $22.20 \pm 2.43\%$ at 30 minutes ($p < 0.0001$) was observed, which remained decreased by $6.65 \pm 7.22\%$ at 60 minutes (NS).

Nasal Secretions. The mean volume of nasal secretions collected from the 25 DC responders was 0.53 ± 0.17 g. The mean nasal secretion weight from the AcR responders defined as a $\geq 10\%$ decrease in MCA who were more congested was lower at 0.31 ± 0.10 g (Fig. 3).

Temperature Change Challenge

MCFB of TNSSs. The temperature change challenge also revealed responders and nonresponders as defined by both subjective and objective measures. Using

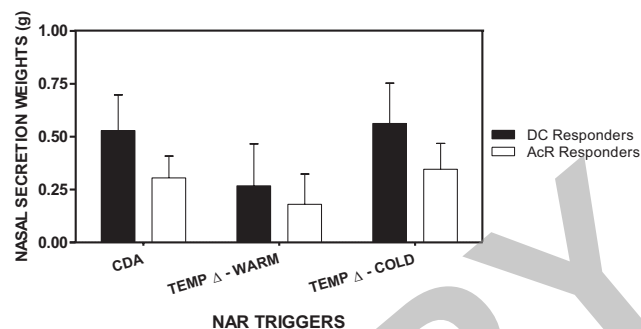


Figure 3. Mean weight of nasal secretions (g). Amount of nasal secretions collections from subjects after various nonallergic rhinitis (NAR) challenges, analyzed as diary card (DC) responders and acoustic rhinometry (AcR) responders. The reproducibility of the cold temperature challenge was seen between the cold dry air (CDA) and the cold air component of the temperature change challenge.

the DC responder criteria, 19 of 37 subjects (51%) qualified. Analysis of DC responders only (Fig. 4 A) revealed an increase in MCFB of TNSS over the course of the 1st hour during the warm air phase, which further increased after transitioning to the cold air phase. The DC responders manifested a 0.68 ± 0.27 U ($p < 0.05$) change by 10 minutes, which increased to 1.10 ± 0.31 U ($p < 0.005$) by 20 minutes. This stabilized and was maintained at ~ 0.95 U at 30 ($p < 0.005$), 45 ($p < 0.01$), and 60 ($p < 0.01$) minutes during the warm air phase. After switching to cold air, there was a further increase in MCFB of TNSS of 1.40 ± 0.26 U ($p < 0.0001$) at 10 minutes, 1.80 ± 0.39 U ($p < 0.001$) at 20 minutes, and 2.10 ± 0.31 U ($p < 0.0001$) at 30 minutes. Thereafter, the MCFB of TNSS stabilized and remained between 2.10 and 2.20 U at 30–60 minutes during the remainder of the cold air phase ($p < 0.0001$).

The MCFB of TNSS for the DC nonresponders was also analyzed to show the specificity of the trigger (Fig. 4 A). Throughout the 1st hour during the warm air phase, there was no increase in MCFB of TNSS for the nonresponders. An increase in nasal symptoms (~ 0.44 U) was observed during the 2nd hour with cold air at 45–60 minutes.

Twenty-six subjects (70%) qualified as AcR responders when the criteria of a $\geq 10\%$ decrease in MCA was used (Fig. 4 A). These individuals manifested a 0.31 ± 0.25 U (NS) increase in MCFB of TNSS with exposure to warm air by 10 minutes, which further increased to 0.58 ± 0.28 U by 20 minutes (NS). The subjects appeared to accommodate to the warm air conditions as increases in MCFB of TNSS plateaued between 0.35 and 0.42 at 30–60 minutes, respectively (NS). After switching to the cold air phase, an increase in the MCFB of TNSS of 0.58 ± 0.27 U ($p < 0.05$) at 10 minutes and of 0.96 ± 0.33 U ($p < 0.01$) at 20 minutes was observed. The MCFB of TNSS eventually stabilized (between 1.10 and 1.20 at 30–60 minutes; $p < 0.005$),

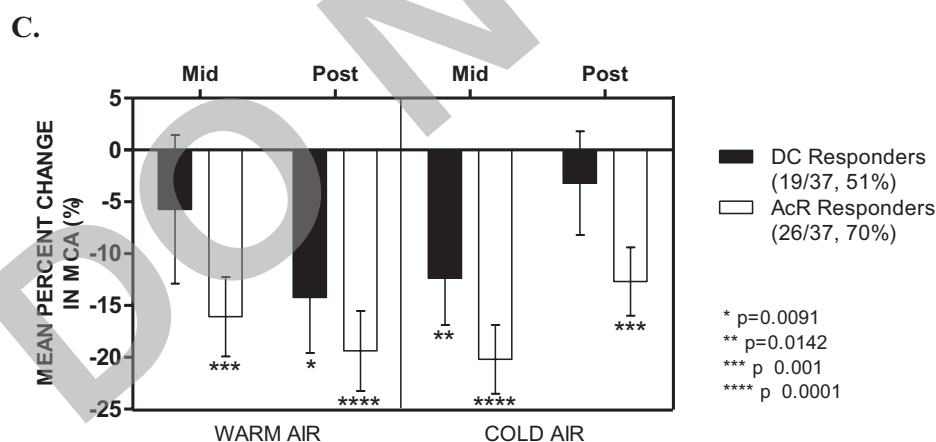
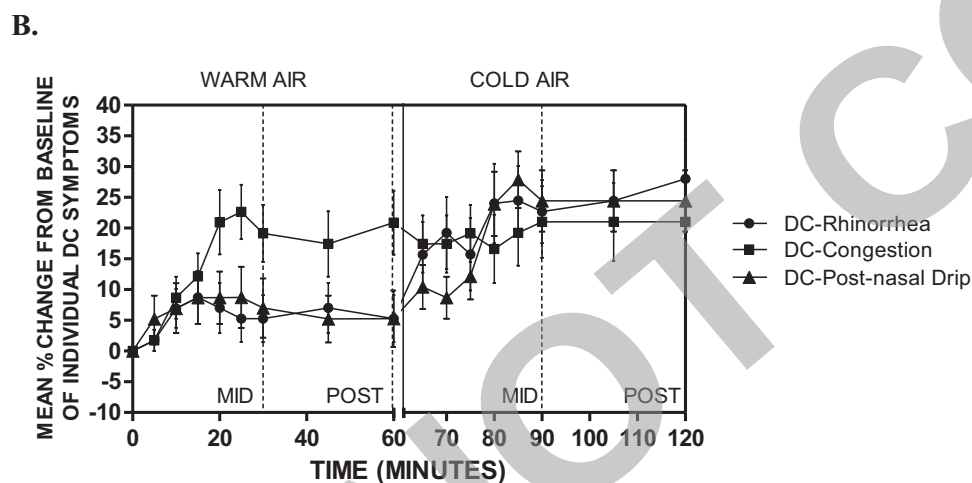
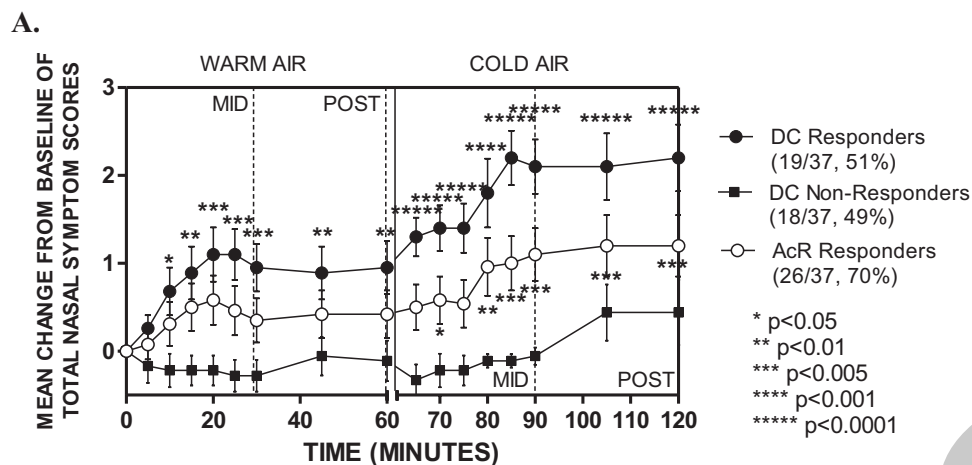


Figure 4. Temperature change challenge. (A) Mean change from baseline of total nasal symptom score (TNSS) during temperature change challenge (2 hours). Warm air induced ~1 U of change from baseline with an increase by 2 U with cold air. (B) Mean percent change from baseline of individual symptoms using the diary card (DC) in DC responders ($n = 19/37$; 51%). Congestion was higher during the warm air component of the challenge with runny nose and postnasal drip being higher during cold air. (C) Nasal patency at the middle (30 minutes) and end (60 minutes) of both warm air and cold air phases of the temperature change challenge. The greatest change in nasal patency was observed at the warm air post-time point ($p = 0.0091$, DC responders; $p \leq 0.0001$, acoustic rhinometry [AcR] responders) and cold air mid-time point ($p = 0.0142$, DC responders; $p \leq 0.0001$, AcR responders).

perhaps, as subjects accommodated to the cold air conditions. There were three subjects who were responders only to the warm air and six who were responders specifically to the cold air phase using the objective AcR criteria. However, most of the subjects were responders during both warm and cold phases of the challenge. Of note, the cold air component of the temperature change challenge resulted in very similar responses compared with the CDA challenge, indicating the reproducibility of these two challenges. Of the

19 subjects who were AcR responders during the CDA challenge, 10 (53%) were also responders during the temperature change challenge. Using DC responder criterion, 13 of 25 subjects (52%) who qualified as a DC responder during the CDA challenge were also responders during the temperature change challenge.

Individual Symptom Scores—Congestion, Runny Nose, and Postnasal Drip. Individual symptom score responses by DC responders to the temperature change

challenge were more noticeable (Fig. 4 B). At 15 minutes into the warm air phase, there was an $8.74 \pm 4.29\%$ increase in rhinorrhea, $8.68 \pm 4.25\%$ in postnasal drip, and $12.16 \pm 3.75\%$ in nasal congestion. At 30 minutes with warm air, rhinorrhea only increased by $5.26 \pm 3.84\%$ and postnasal drip by $7.00 \pm 4.81\%$ but nasal congestion increased by $19.16 \pm 4.63\%$. After 45 minutes, rhinorrhea and postnasal drip increased by $7.00 \pm 4.10\%$ and $5.21 \pm 3.80\%$, respectively whereas nasal congestion increased by $17.42 \pm 5.30\%$. After 60 minutes of warm air exposure, there was a $5.26 \pm 3.84\%$ increase in rhinorrhea, $5.26 \pm 4.60\%$ in postnasal drip, and $20.89 \pm 5.20\%$ in congestion.

After a rapid change to cold air conditions, the reversal of the symptoms was quite evident. After 5 minutes, there was a $15.68 \pm 5.30\%$ increase in rhinorrhea, an increase in postnasal drip of $10.42 \pm 3.62\%$ and a $17.42 \pm 4.66\%$ increase in nasal congestion. By 20 minutes, there was a $24.00 \pm 6.49\%$ and $23.94 \pm 5.26\%$ increase of rhinorrhea and postnasal drip, respectively, and nasal congestion increased by $16.61 \pm 5.60\%$ from baseline. Nasal congestion and postnasal drip stabilized at ~ 21.00 and 24.42% , respectively, between 30 and 60 minutes. Rhinorrhea increased further by $22.68 \pm 5.13\%$, $24.42 \pm 5.00\%$, and $28.00 \pm 6.39\%$ at 30, 45, and 60 minutes, respectively.

Nasal Patency Using AcR. With the inclusion of only those subjects that met the criteria of DC responders, the mean percent change in nasal patency by AcR decreased by $5.74 \pm 7.15\%$ (NS) at 30 minutes during the warm air phase and further decreased by $14.21 \pm 5.37\%$ ($p = 0.009$) at 60 minutes (Fig. 4 C). After switching to cold air, a significant decrease in nasal patency by $12.37 \pm 4.50\%$ ($p = 0.014$) was observed at 30 minutes. A smaller decrease in nasal patency of $3.21 \pm 5.00\%$ (NS) was observed at 60 minutes.

The results from the 26 AcR responders ($\geq 10\%$ decrease in MCA) showed an initial decrease in nasal patency of $16.08 \pm 3.82\%$ at 30 minutes ($p = 0.0003$) during warm air exposure, which further decreased by $19.38 \pm 3.87\%$ at 60 minutes ($p < 0.0001$; Fig. 4 C). The mean change in MCA at 30 minutes during cold air exposure in the temperature change challenge ($-20.19 \pm 3.32\%$; $p < 0.0001$) was similar in magnitude to the decrease observed at 60 minutes during the warm air exposure. More significantly, the mean change in MCA was also similar to that observed at 30 minutes during the CDA challenge, indicating reproducibility of the cold temperature trigger in the NAR EEC. At the end of the temperature change challenge (60 minutes of cold air), there was a significant but smaller decrease in MCA of $12.69 \pm 3.30\%$ ($p = 0.0009$).

Nasal Secretion. Considering only the DC responders (Fig. 3), the mean quantity of nasal secretions was

0.27 ± 0.20 g during the warm air phase and 0.56 ± 0.19 g during the cold air phase. Almost twice the amount of nasal secretions were collected when subjects were exposed to the cold air component of the challenge compared with the warm air phase, showing that the cold air may be a more effective trigger, especially for inducing rhinorrhea. Similarly, there were differences in symptoms triggered by different temperatures. With warm air, there was a greater increase in nasal congestion compared with rhinorrhea or postnasal drip. In contrast, for the cold air component, rhinorrhea was the predominant symptom compared with nasal congestion.

Among AcR responding subjects ($\geq 10\%$ decrease in MCA; Fig. 3), the mean nasal secretion collected was 0.18 ± 0.14 g with warm air and 0.35 ± 0.12 g with cold air. More nasal secretions were collected during the cold air component of the challenge than during the warm air, regardless of whether DC or AcR responders were used.

Safety Analysis

Subjects were monitored for changes in health throughout their study participation. As anticipated, there were no adverse events reported.

DISCUSSION

This study is novel because it was the first to use an NAR chamber model to characterize NAR subjects by eliciting objective and subjective changes in response to simulated weather conditions that are common NAR triggers. Both the CDA and the temperature change challenges show differences in the magnitude of change depending on the temperature of the air in the EEC. For example, nasal congestion was more prevalent in response to warm air whereas rhinorrhea was more prevalent in response to cold air. These distinct responses were confirmed subjectively by increases in TNSSs and objectively by decreased nasal patency using AcR and increased nasal secretion collection. Assessment of AcR and DC scores at 0, 30, and 60 minutes revealed that 42% of subjects responded to CDA and 58% responded to the temperature change challenge (Table 2). Of note, the maximum change in symptoms was consistently observed at the midpoint of the cold air challenges. The plateau of symptoms toward the end of the cold air challenges likely represents subjects acclimatizing to the environment. The results of our study are consistent with previous reports showing a good correlation between a subjective cold hyperresponsiveness scale and objective changes in nasal response induced by cold air provocation as measured by AcR.^{6,7} These observations are not altogether surprising when one considers the potential mechanistic role of transient response potential (TRP) receptors in NAR. For example, it is known that TRPA1 and TRPM8 are acti-

Table 2 Comparison of NAR questionnaire and CDA and temperature change challenges

	CDA	Temperature Change
Number of subjects who responded "yes" to the NAR Questionnaire*	94%	94%
Responder with both AcR and DC (at times when both AcR and DC were collected)	42%	58%
Agreement between NAR history and NAR clinical study (whether they answered "yes" or "no" on NAR Questionnaire*)	47%	64%
Percent of subjects who reported "yes" on the NAR Questionnaire and actually responded (DC and/or AcR)	44%	62%

*Ref. 9.

AcR = acoustic rhinometry; CDA = cold dry air; DC = diary card; NAR = nonallergic rhinitis.

vated at cold temperatures <18°C and between 8°C and <23–28°C, respectively.⁸

As shown in Table 2, the questionnaire used to screen subjects for NAR developed and validated by Brandt and Bernstein⁹ revealed a high percentage of subjects reporting symptoms in response to CDA (94%) and sudden weather change (94%). However, of the subjects who reported "yes" on the questionnaire, only 44% actually responded to the CDA challenge and 62% to the temperature change challenge. Incorporating a more objective instrument such as the Irritant Index Questionnaire score may be a better way to characterize NAR subjects in the future and improve the specificity of the rhinitis screening questionnaire.^{10,11} Our data indicate that NAR subjects have a heterogeneous response to nonallergic triggers. Although CDA was the most consistent trigger subjects responded to, 22% of NAR subjects did not respond to either challenge whereas the remainder responded to one or both temperature related challenges. However, the discordance between subjective and objective responses emphasizes the importance of incorporating provocation into the phenotypic characterization of NAR patients.

The advantages of conducting chamber studies for NAR subjects include the ability to precisely regulate environmental conditions year round irrespective of confounding outdoor conditions while investigating novel

therapeutics and that data generated from chamber studies has been accepted by regulatory agencies in the United States, Canada, United Kingdom, and Europe.

There are several limitations of this study that should be mentioned. First, the definition of "responder" to the various challenges needs to be further refined as to whether it should be based on subjective (TNSS) and/or objective scores (AcR and nasal secretion collection) and what magnitude of response should be considered clinically significant. Second, this study was not repeated on the same individuals to establish reproducible clinical outcomes. Finally, no control groups (*i.e.*, allergic rhinitis, normal healthy individuals, or mixed rhinitis subjects) were incorporated in this pilot study for comparison with the NAR subjects. Future studies should address these limitations.

In summary, this proof of concept NAR chamber model study was found to be feasible for phenotyping NAR subjects whose symptoms are induced by CDA and temperature changes. Additional clinical studies are needed to confirm the reproducibility of these findings and to extend this investigation to other nonallergic triggers such as fragrances, chemical irritants, and pollutants. However, the preliminary data generated thus far indicates that using an NAR chamber model is feasible for future investigation of novel NAR therapies in well-characterized NAR subjects.

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