

Short-Time Cold Dry Air Exposure: A Useful Diagnostic Tool for Nasal Hyperresponsiveness

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Objectives/Hypothesis: Demonstration of nasal hyperreactivity (NHR) in allergic and nonallergic rhinitis remains a diagnostic challenge because of the lack of a clinically attractive protocol with high sensitivity and specificity. Our aim was to evaluate the feasibility of a shortened cold dry air (CDA) provocation protocol for the diagnosis of NHR in patients with allergic rhinitis (AR) and idiopathic rhinitis (IR).

Study Design: Twelve AR patients, 12 IR patients, and 12 controls were exposed to air at -10°C and $<10\%$ humidity for 15 minutes.

Methods: Nasal symptoms were subjectively evaluated by visual analogue scale (VAS), and nasal obstruction was objectively measured by peak nasal inspiratory flow (PNIF) before and after CDA exposure. NHR was defined as a drop in PNIF larger than 20% from baseline upon CDA challenge.

Results: Nasal CDA exposure induced nasal obstruction in AR and IR patients but not in controls. The VAS for nasal obstruction increased significantly in IR patients (post-CDA: 9.1 cm [6.9, 9.7] vs. pre-CDA: 5.5 cm [5.0, 8.9], $P = .004$) as well as in AR patients (post-CDA: 5.0 cm [1.3, 6.6] vs. pre-CDA: 0.8 cm [0.0, 1.7], $P = .001$). PNIF values showed a significant decrease in the AR (post-CDA: 50.0 L/min [37.5, 97.5] vs. pre-CDA: 95.0 L/min [52.5, 127.5], $P = .002$) and IR (post-CDA: 75.0 L/min [47.5, 102.5] vs. pre-CDA: 100.0 L/min [67.5, 130.0], $P = .002$) group after CDA provocation, which was not observed in the controls ($P = 1.000$). The sensitivity and specificity of CDA provocation for diagnosis of NHR were 66.7% and 100%, respectively, for both IR and AR. In contrast to nasal obstruction, rhinorrhea and sneezing were not induced by CDA exposure.

Conclusions: This study demonstrates that a short nasal CDA exposure is a reliable method for the diagnosis of NHR in rhinitis patients, with a high sensitivity and specificity.

Key Words: Allergic rhinitis, cold dry air, diagnostic test, idiopathic rhinitis, nasal hyperreactivity, nasal provocation.

Level of Evidence: 4.

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INTRODUCTION

Nasal hyperreactivity (NHR) is defined as an increased sensitivity of the nasal mucosa to commonly encountered environmental stimuli such as smoke, strong odors, sudden change of temperature or humidity, and various chemical pollutants. These aspecific stimuli may give rise to nasal symptoms like obstruction, rhinorrhea, and/or sneezing.¹ Several nasal conditions are

associated with NHR, like allergic rhinitis (AR), infectious rhinitis, and idiopathic rhinitis (IR). IR is a subgroup of noninfectious non-AR (NAR), variously referred to in literature as vasomotor rhinitis or nonallergic noninfectious perennial rhinitis (NANIPER).² The term IR is used to describe patients with complaints of nasal obstruction, sneezing, and/or rhinorrhea for a period of more than 1 year that cannot be attributed to (local) allergy, nasal or paranasal infection, anatomic disorders, pregnancy or lactation, and/or systemic disorders. These patients are nonsmokers and do not use medication affecting nasal function.

Already in 1999, Gerth van Wijk et al. reported NHR as an important feature of AR and NAR.¹ Subsequently, Braat et al. described factors related to pollution and meteorologic events as also being closely related to complaints of NANIPER patients. The authors reported that their group of IR patients experienced primarily chronic, ongoing nasal reactions to these environmental disturbances.³ Shusterman and Tilles also reported nasal physiologic reactivity to cold dry air (CDA) in NAR.⁴

A neurogenic origin is believed to be involved in the development of NHR in AR and IR patients.^{5–7}

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Besides the typical signs of AR (i.e., nasal itch, sneezing, runny nose, and nasal obstruction), patients with AR usually complain of NHR, elicited by nonallergic stimuli. NHR in AR may be part of the inflammatory spectrum of AR and may correlate with bronchial dysfunction.⁸ Indeed, pollen AR patients are affected in their upper airways during the pollen season and also have increased bronchial hyperresponsiveness (BHR).^{8,9} NHR is part of the phenotype of sinonasal infection and may persist for several weeks after resolution of the infection.¹⁰

The mechanisms underlying NHR are not well understood. Extrapolation of insight into mechanisms underlying BHR aids in understanding the potential pathophysiology, involving inflammatory mediators, neural mechanisms, or organ susceptibility. Histologically, NHR in AR has been shown to be associated with hyperinnervation of the nasal mucosa with increased expression of the neuropeptides calcitonin gene-related peptide and substance P in periglandular nerve fibers, which is considered a sign of neuronal hyperactivity.⁵ Interestingly, AR and IR patients show the same level of mucosal hyperinnervation, suggesting a neuroinflammatory involvement in both nasal conditions.⁵

The demonstration of NHR is largely neglected in clinical practice.⁷ The most commonly used diagnostic test for measuring NHR is nasal histamine provocation, which resembles the routinely performed bronchial histamine challenge for BHR.^{11,12} During nasal histamine provocation, increasing doses of histamine (0.125, 0.25, 0.5, 1, 2, and 4 mg/mL) are applied on the nasal mucosa, and measurements of nasal cross-sectional diameter or flow start after 1 minute of provocation and continue for 4 minutes. Other means of provocation, like exposure of the nasal mucosa to capsaicin, have not been thoroughly studied because their diagnostic use is not appealing for the clinician or the patient.¹³

CDA represents a physiologic, safe, tolerable stimulus for the nasal mucosa and has been proven to be a good diagnostic tool in nonspecific hyperreactivity.¹⁴ Building further on the expertise regarding CDA provocation, Braat et al. demonstrated that CDA provocations were superior to nasal histamine provocations in discriminating IR patients from healthy controls, as histamine provocation did not allow discrimination between IR patients and controls.¹⁵ Sensitivity for CDA was 87%, compared with 100% for histamine; specificity was 71% for CDA and 0% for histamine.¹⁵ The protocol used in the latter study is time-consuming, with CDA exposure lasting 30 minutes. At present, more studies on CDA nasal provocation are warranted to confirm the validity of this technique, to find means of shortening the protocol, and to study NHR in different patient populations and controls. However, there is no commercially available CDA device that can be used in clinical practice or for experimental purposes, and the reported studies on CDA have utilized devices that were developed for academic purposes by the research groups. There is now growing consensus about the usefulness of such a technique in daily practice, as NHR often remains undiagnosed and cannot be taken into account

TABLE I.
Patient Characteristics.

Patient Characteristics	IR Patients, n = 12	AR Patients, n = 12	Healthy Controls, n = 12
Age (range), yr	44 (22–60)	32 (20–59)	36 (20–56)
Sex (M/F ratio)	6/6	7/5	4/8
Smoking (%)	1/12 (8)	1/12 (8)	0/12 (0)
Grass pollen allergy (%)	0/12 (0)	12/12 (100)	0/12 (0)
Major nasal complaint			
Rhinorrhea (%)	6/12 (50)	8/12 (67)	
Nasal obstruction (%)	5/12 (42)	3/12 (25)	
Sneezing (%)	1/12 (8)	1/12 (8)	
Itchy nose (%)	0/12 (0)	1/12 (8)	

IR = idiopathic rhinitis; AR = allergic rhinitis; M = male; F = female.

in trials evaluating the effects of current medical treatment of rhinitis.

We aimed to evaluate the feasibility of a shortened CDA-provocation protocol for daily use in an outpatient otorhinolaryngology clinic that could demonstrate NHR in patients with rhinitis. To this purpose, the protocol described by Braat et al.¹⁵ was shortened with a duration of CDA exposure of 15 minutes, comparable with the time needed to perform routine diagnostic tests like nasal flow measurements or skin prick tests (SPTs). We studied three groups of individuals in parallel to evaluate NHR in a control population, a group of grass-pollen AR patients, and a group of well-defined IR patients.

MATERIALS AND METHODS

Patients and Healthy Controls

Twelve AR patients, 12 IR patients, and 12 control subjects were selected on the basis of inclusion and exclusion criteria.

All AR and IR patients were between 18 and 60 years of age and had a minimum of two nasal complaints (nasal obstruction, rhinorrhea, or sneezing) (Table I). Nasal or paranasal infection was excluded by anterior rhinoscopy and nasal endoscopy at the Outpatient Otorhinolaryngology Clinic of the University Hospitals of Leuven. Patients with anatomic disorders affecting nasal function like severe septal deviation, nasal valve dysfunction, and/or septal perforation were excluded from this study, as were patients with rhinosinusitis with or without nasal polyps and pregnant or lactating women. Medication affecting nasal function like β -blockers was not allowed. Local and systemic corticosteroids had to have been stopped 4 weeks before the study. There was no history of past or current xylometazoline or other decongestant nasal spray use or abuse. Antihistamine treatment had to have been stopped for at least 2 weeks before inclusion.

In the IR group, all patients had negative SPT for the 18 most frequent aeroallergens in Belgium (house dust mite, Timothy grass, smooth meadow grass, orchard grass, nettle, *Plantago*, oxeye daisy, mugwort, alder, birch, hazel, horse, cat, dog, rabbit, *Alternaria*, *Aspergillus*, and *Cladosporium* (HAL Allergy, Leiden, the Netherlands). One out of 12 IR patients was an occasional smoker. All IR patients were unresponsive to at least 4 weeks of treatment with a nasal corticosteroid spray

at the recommended dose. In the AR group, all patients had positive SPTs for grass pollen, and all of them were polysensitized. They were all intermittently symptomatic during the pollen season. Eleven of 12 AR patients were nonsmokers.

All healthy volunteers were between the ages of 18 and 60 years and had no rhinologic complaints during the previous 3 months (Table I). They showed a negative SPT for the 18 most frequent aeroallergens in Belgium. All controls were nonsmokers.

The study was registered at www.ClinicalTrials.gov (NCT 01223820). The study was approved by the Ethical Committee on Clinical Investigations at the University Hospital of Leuven, and informed consent was obtained from all subjects.

Evaluation of Nasal Symptoms

All patients and controls were invited for an outpatient visit to the Department of Otorhinolaryngology of the University Hospitals of Leuven. A first screening visit was scheduled for evaluation of all inclusion and exclusion criteria. Informed consent was obtained, and the standard SPT was performed, involving the most frequent inhalant allergens (as mentioned above). All patients and control subjects were asked to mark their momentary nasal symptoms on a visual analogue scale (VAS) (0–10 cm) before and after CDA nasal provocation. The three major symptoms, that is, nasal obstruction, rhinorrhea, and sneezing, were evaluated before and 15 minutes after CDA provocation. All patients had been asked whether they experienced nasal symptoms when they were exposed to sudden changes in temperature. All rhinitis patients had responded “Yes” to this question.

Nasal endoscopy was performed in all individuals by an otorhinolaryngologist to exclude anatomic deformities, rhinosinusitis, and/or endonasal infection.

Peak Nasal Inspiratory Flow

Nasal obstruction was evaluated using the peak nasal inspiratory flow (PNIF) device (Cement Clarkx International, Essex, UK). PNIF measurements are considered a rapid, useful and validated tool to evaluate nasal patency.¹⁶ Measurements of nasal flow were performed before and immediately after CDA nasal provocation by using a PNIF device. An anesthesia mask was placed over the mouth and nose of the patients after expiration, and patients were instructed to close their mouth and forcefully inspire air through the nose. Three consecutive measurements with an intermeasurement variability of less than 10% were recorded and the median value was noted as reported before.¹⁷

A decrease in PNIF of 20% or more was chosen as the predefined cutoff point to evaluate the presence of NHR. This cutoff point of 20% was based on the forced expiratory volume in 1 second (FEV1) decrease of 20% after exercise challenge test, histamine provocation test, or specific inhalation challenge test, performed for diagnosing BHR in bronchial pathology.^{12,18,19}

CDA Nasal Provocation

The CDA protocol used here and illustrated in Figure 1 is adapted from the studies by Togias et al.¹⁴ and Braat et al.¹⁵ Before exposure to CDA, subjects were asked to acclimatize to room temperature (20°C) for 15 minutes. To avoid diurnal variation and intertest error, all provocations were performed in the morning by a single experienced examiner (L.v.G.). Compressed dry air for medical use (Dräger, Lübeck, Germany) was delivered through a transparent anesthesia mask placed over the nose and mouth of the patient or control. Subjects were instructed to breathe through the nose only.¹⁴ Exposure to CDA lasted for 15 minutes. The flow, measured by a gas flow ana-

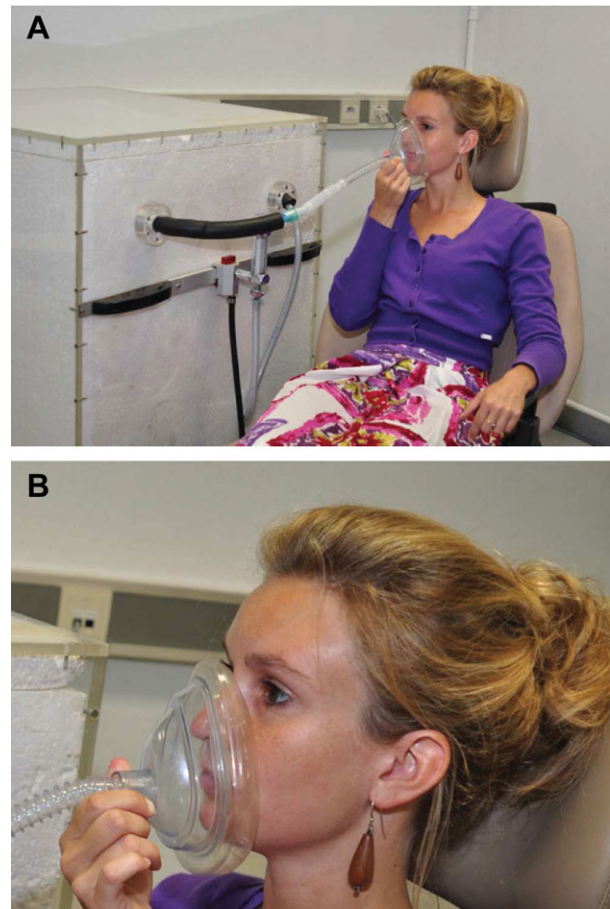


Fig. 1. The cold dry air device. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

lyzer (Dräger), was set at 25 L/min. CDA was obtained by passing the compressed air through a coiled copper tube immersed in a glycol bath. The construction was placed in an industrial freezer, and the entire compartment was isolated. The temperature of the air reaching the nose was at -10°C with a relative humidity of $<10\%$. Before starting each provocation, the temperature and humidity were measured using a Testo 610 device (Lenzkirch, Germany). Variations in temperature reaching the nostrils were allowed between -10°C and -20°C (starting at -10°C , stopping around -18°C).

The CDA nasal provocation of the AR patients was performed during the pollen season of 2011 (May until July 2011), whereas healthy controls and IR patients were exposed between January 2011 and August 2011. To schedule the nasal provocation in AR patients, grass pollen counts in the air were monitored by the Belgian Scientific Institute of Public Health (www.airallergy.be). Patients were called to the clinic at the time the grass pollen counts in the air reached a significant level of 50 grains/m^3 on 2 consecutive days.

Statistical Methodology

The measurements before and after CDA nasal provocation were compared using a paired *t* test if the distribution was normal and a Wilcoxon signed rank test if not. A difference was considered to be significant when $P < .05$.

The area under the curve (AUC) is used to quantify how a change in PNIF (ΔPNIF) versus baseline discriminates between healthy controls and patients (IR and/or AR). The AUC can

range from 0.5 (no predictive ability) to 1 (perfect discrimination). A nonparametric bootstrap procedure is used to obtain a 95% confidence interval (CI) for the AUC. The discriminatory ability for the predefined cut point of a decrease of 20% (if the decrease is larger than 20%, the subject is classified as a patient with NHR) was also evaluated. Diagnostic indices (sensitivity, specificity, negative predictive value, and positive predictive value) of this dichotomization and their exact 95% CIs are given. To verify if the data are in accordance with the a priori cut point (20% decrease), the optimal cut point is estimated. The cut point is defined as the (observed) value that maximizes the distance between the empirical distribution function of both groups (i.e., the value at which the Kolmogorov-Smirnov goodness-of-fit statistic is defined). The 95% CI for this cut point is obtained with a nonparametric bootstrap procedure. Because the data are sparse in both groups, the cut point (and the CI) will heavily depend on the specific observed values. Therefore, as an alternative approach, the cut point is estimated using univariate discriminant analysis, assuming a normal distribution in both groups, but allowing unequal variances. The 95% CI for this cut point is obtained using a parametric bootstrap procedure. There are two observations with a measurement below detection limit (PNIF <30 L/min). Both occurred in the patient (one allergic, one idiopathic) group after 15 minutes. A PNIF of 25 L/min was assumed in both cases.

Analyses were performed using the Graph Pad Prism program (Prism 4, version 4.03, 1992–2005 Graph-Pad Software Inc., San Diego, CA) and SAS software (version 9.2; SAS, Cary, NC).

RESULTS

Induction of Nasal Obstruction by CDA Exposure

The clinical response to CDA nasal provocation was primarily characterized by induction of nasal obstruction (Fig. 2A). The changes in VAS for nasal obstruction were significantly greater in the patient groups (IR, $P = .004$; AR, $P = .001$) compared to the healthy controls ($P = 1.000$) (Fig. 2A). The VAS for nasal obstruction increased from 5.5 cm (range from 5.0 to 8.9) to 9.1 cm (range from 6.9 to 9.7) in IR patients and from 0.8 cm (range from 0.0 to 1.7) to 5.0 cm (range from 1.3 to 6.6) in AR patients. In contrast to nasal obstruction, the changes in VAS for rhinorrhea were not significant in the patient groups, with a nonsignificant trend in the IR group (Fig. 2B). VAS scores for sneezing showed a decrease in both patient groups and was significant in the IR group ($P = .016$) (Fig. 2C). Itchy nose was not a frequent finding in the IR group and was therefore not used as a measurable clinical parameter (data not shown).

Induction of Decrease in PNIF by CDA Exposure

The objective measurements of PNIF before and after nasal CDA provocation showed a significant drop in PNIF values in the AR (post-CDA: 50.0 L/min [37.5, 97.5] vs. pre-CDA: 95.0 L/min [52.5, 127.5], $P = .002$) and IR (post-CDA: 75.0 L/min [47.5, 102.5] vs. pre-CDA: 100.0 L/min [67.5, 130.0], $P = .002$) group compared to healthy controls ($P = 1.000$) (Fig. 3A, 3B).

The AUC for Δ PNIF was 0.96 (95% CI, 0.85–1.00) in discriminating between IR patients and controls. When we set the diagnostic criterion as Δ PNIF larger than 20%, the sensitivity and specificity were 66.7% and

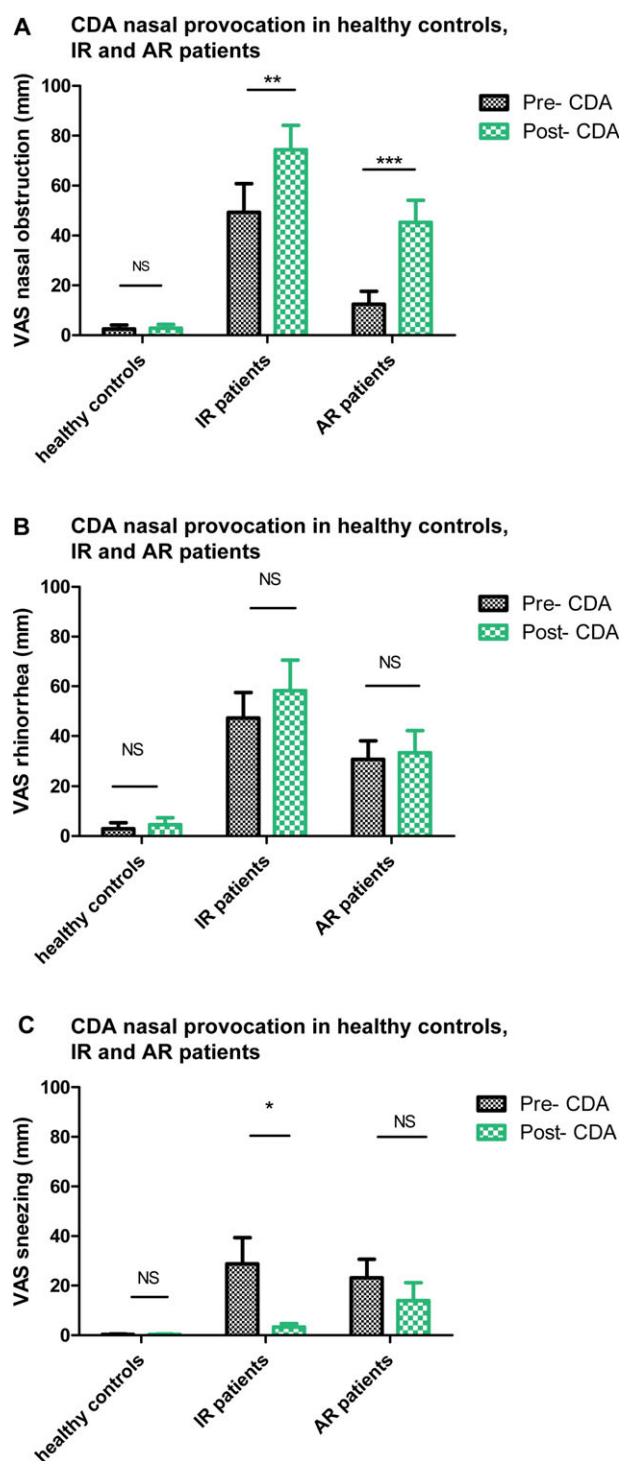


Fig. 2. CDA = cold dry air; IR = idiopathic rhinitis; AR = allergic rhinitis. The subjective outcome parameters (VAS for nasal obstruction (A), for rhinorrhea (B) and sneezing (C)) before and after CDA nasal provocation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

100%, whereas the positive and negative predictive values were 100% and 75%, respectively (Table II). The AUC for the predefined cut point of 20% decrease was 0.83 (95% CI, 0.69–0.96). The optimal cut point with the nonparametric method equals -15.4% (95% CI, -27.3%

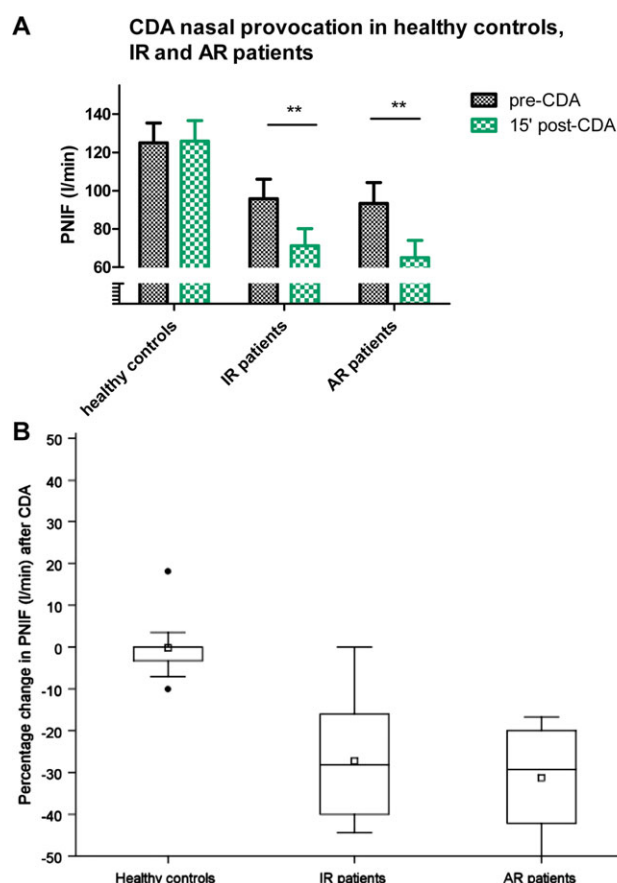


Fig. 3. A. The objective outcome parameter PNIF before and after CDA nasal provocation. B. The percentage change in PNIF after CDA exposure. CDA = cold dry air; PNIF = peak nasal inspiratory flow; IR = idiopathic rhinitis; AR = allergic rhinitis. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

to -15.4%). Based on a normal distribution with unequal variances, the optimal cut point equals -11.6% (95%CI, -19.2% to -4.3%). Hence, there is no strong reason to reject the a priori cut point of 20%.

Comparable results were found for the discrimination between healthy subjects and AR patients (Table II).

DISCUSSION

This study confirms that intranasal CDA provocation is a reliable method for measuring NHR in rhinitis patients. Furthermore we present a shortened and therefore more attractive protocol of CDA exposure with a high sensitivity and specificity for demonstration of NHR in rhinitis of allergic and idiopathic nature.

CDA is a natural, safe, and tolerable stimulus for induction of nasal obstruction, despite of the fact that exposure conditions remain artificial. The shortened protocol of 15 minutes of exposure to CDA used in this study is effective in discriminating between AR and IR patients and controls, with a high sensitivity and specificity. Other CDA protocols exist but are more time-consuming and therefore less attractive for routine use in the daily outdoor otorhinolaryngology clinic.¹⁵ Recently, Kim and Jang²⁰ published an even shorter CDA-provocation protocol of only 6 minutes in patients with self-reported hypersensitivity to CDA. The ill-defined patient population does not allow us to compare their data to ours in AR and IR patients. The protocol by Kim and Jang²⁰ involved a CDA flow of 400 L per 6 minutes, which is almost three times higher than in our protocol and may be perceived as uncomfortable by rhinitis patients.

PNIF as an objective clinical outcome parameter for nasal obstruction has not previously been used to measure nasal patency in relation to CDA provocation. Although our results are comparable with those measured by acoustic rhinometry, multiple advantages prompted us to use PNIF measurements as a technical tool for evaluation of nasal flow. PNIF measurements are easy to perform with a cheap device, fast methodology, and readily available tool for determining the extent of nasal airway patency.¹⁶ The pitfalls include investigator dependency and device dependency. Therefore, we had the same investigator perform all the measurements using the same device. Changes in PNIF appeared to be, according to our results (Fig. 3A, 3B), very reliable as objective outcome parameters to diagnose the presence of NHR. The predefined cut point of a 20% decrease was based on the FEV1 decrease of 20% in provocation tests of the lower airways.^{12,18,19} Using the Δ PNIF measurements with the predefined cut point of 20%, our sensitivity was 66.7% and specificity was 100% for determining IR patients versus controls, which is comparable with the results of Braat et al.¹⁵ (sensitivity of 87% and specificity of 71%) and Kim and Jang²⁰ (sensitivity of 84.4% and specificity of 77.4%). The last two groups used Δ flow at 150 Pa (anterior rhinomanometry) and Δ total nasal volume (acoustic rhinometry), respectively, instead of Δ PNIF as the objective outcome parameter.

A review of the literature on CDA challenges showed that changes in VAS for nasal obstruction was a good subjective clinical outcome parameter to assess the effect of CDA.^{14,15,17} Surprisingly, in our study, we could not find a significant increase in VAS scores for rhinorrhea

TABLE II.
Performance of the Predefined Cut Point of -20% .

	Healthy vs. IR	95% CI	Healthy vs. AR	95% CI
Sensitivity, %	83.33 (10/12)	51.59-97.91	66.67 (8/12)	34.89-90.08
Specificity, %	100.00 (12/12)	73.54-100.00	100.00 (12/12)	73.54-100.00
PPV, %	100.00 (10/10)	69.15-100.00	100.00 (8/8)	63.06-100.00
NPV, %	85.71 (12/14)	57.19-98.22	75.00 (12/16)	47.62-92.73

IR = idiopathic rhinitis; CI = confidence interval; AR = allergic rhinitis; PPV = positive predictive value; NPV = negative predictive value.

after CDA challenge, unlike other investigators.^{14,15,20} This discrepancy may be linked to the time point of VAS scoring for rhinorrhea. We asked the patients and controls to score their nasal symptoms immediately after the provocation, whereas other groups had scoring performed after 5 minutes. The evaluation after 5 minutes may reflect changes induced by heating of the nasal mucosa after CDA exposure, rather than the direct effect of cooling down. Another explanation might be that the sensation of rhinorrhea is diminished by cooling down the sensory nerves in the nasal mucosa.

Evaluation of sneezing and itching after CDA provocation has not been performed in most previous studies on the effects of CDA challenge. Togias et al.,¹⁴ Braat et al.,¹⁵ and Kim and Jang²⁰ reported a very low incidence of sneezing, and other researchers used only VAS for nasal congestion and rhinorrhea as the main outcome parameters. Nasal itching was investigated in only one paper, and no differences were found between patients and healthy controls.²⁰ The cooling of the mucosa and thus of the surface nerve endings during CDA challenge could be a reason for this and might explain the significant decrease in VAS for sneezing we found in the IR group after 15 minutes of CDA challenge.

CONCLUSION

We present a short protocol of exposure to CDA with high sensitivity and specificity for the demonstration of NHR in AR and IR. The feasibility of this clinical tool in daily practice may help to elaborate protocols of novel studies unraveling mechanisms involved in NHR in rhinitis.

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