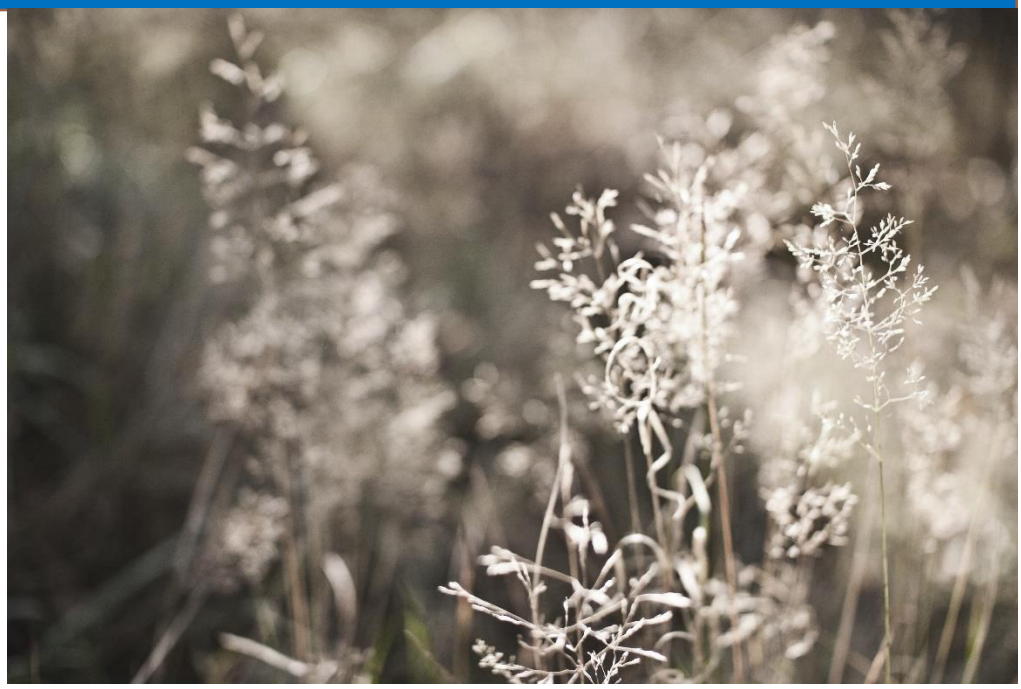
ECARF European Centre for Allergy Research Foundation

Final Report



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Efficacy of an air purifier on the concentration of airborne pollen

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Date: 14 December 2015

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Part 1

Study Findings

1. Introduction

Asthma is an enormous public health issue with about 8.0 % in Germany and 8.5% of people in the US diagnosed with asthma.

Asthma leads to missed school days for children and work days for adults, demands on families to manage asthma care for their children, and increased health care costs.

Airborne allergen exposures and viral infections are indicated as the two major environmental contributors to the development and/or exacerbation of asthma. Reducing exposures to allergy and asthma triggers in residential settings is an important goal in treating asthma patients, since Europeans spend ~70% of their time indoors at home. Asthma guidance for health care providers includes recommendations for controlling airborne triggers at home. Airborne triggers are allergens, e.g. pollen, dust mite or animal allergens, passive smoke, chemicals and others. Therefore, most interventions focus on housekeeping activities, such as using high-efficiency particulate air (HEPA) vacuum cleaners, improved bedding covers and laundering and use of high-efficiency portable air purifiers.

The goal of the current work is to assess whether readily available air purifiers can have a measurable impact on reducing asthma and rhinitis/conjunctivitis symptoms on patients suffering from a grass pollen allergy. Grass pollen were chosen due to the fact that they have a globally broad geographical extension and a very high prevalence of sensitization (cf. Haftenberger et al. (2013): Prevalence of sensitisation to aeroallergens and food allergens, Department of Epidemiology and Health Monitoring, Robert Koch Institute, Berlin. cf. Maloney et al. (2014).: Safety of sublingual immunotherapy Timothy grass tablet in subjects with allergic rhinitis with or without conjunctivitis and history of asthma, in: Allergy (2014) 70:302-309.).

1.1. Test product

Philips AC4012 Air Purifier

1.2. Study design

Individual observation, in-use observation, controlled, prospective, single arm

1.3. Test parameters

Before the subjects were exposed to grass pollen in the mobile exposure chamber (www.mcxperts.com), the following parameters were recorded:

- Basic information on the test subjects including documentation of smoking behaviour and allergological/respiratory history
- Symptoms of the eyes, nose and bronchia on a scale of 0 – 3 (none, mild, moderate, severe symptoms)
- Peak nasal inspiratory flow (PNIF)
- Spirometry (FEV1) and peak expiratory flow (PEF) for documentation of airway obstruction and as a control for possible bronchial side effects

During exposure to the grass pollen in the mobile exposure chamber, the following parameters were recorded:

- Symptoms of the eyes, nose and bronchia on a scale of 0 – 3 (none, mild, moderate, severe symptoms) every 10 min
- Peak nasal inspiratory flow (PNIF) every 30 min
- Peak expiratory flow (PEF) for documentation of airway obstruction every 30 min

1.4. Objective of the study

To determine the efficacy of the tested air purifier in removing airborne grass pollen with the aim of preventing of nasal allergy symptoms in persons with allergic rhino-conjunctivitis (hay fever).

2. Material and methods

2.1. Mobile exposure chamber

Exposure to the grass pollen was conducted in a mobile exposure chamber with testing areas for up to 9 persons, which is technically designed to ensure standardized allergen exposure of each individual test subject (Sehlinger et al., 2015). It has undergone a comprehensive clinical evaluation for exposures to grass and birch pollen (Bergmann et al., 2015).
For this study, subjects were exposed to a concentration of 4,000 pollen per 90-minute observation period. Comparative measurements prove that the selected concentration triggers a score of 6 points on the symptom severity scale. For comparison: This level of symptom severity occurs in nature on high pollen count days in the summer. For grass pollen, the average daily pollen count in the air is between 30 and 250 pollen per cubic meter of air (German Pollen Information Service website; Sofiev, Bergmann, 2013: p. 101).

2.2. Technical study setup

With the objective of measuring the impact of an air purifier alone on allergy symptoms triggered by grass pollen, patients with a grass pollen allergy needed to be exposed to filtered and unfiltered air contaminated with grass pollen.

Identical test conditions can be created inside the pollen chamber in terms of temperature, oxygen level, airflow and other relevant factors. Furthermore, a specific type and number of pollen can be released through outlets in the ceiling of the chamber. For the purposes of this study, 4,000 grass pollen were released through the air purifier device with or without the filter cartridge in place to evaluate the performance of the air purifier.

The test setup is shown in Figure 4, Attachment 1. To connect the pollen outlet in the chamber's ceiling to the inlet of the Philips air purifier, the air purifier was placed under the pollen outlet with the air inlet facing the pollen outlet. Due to the suction of the machine, no other connection was needed to direct the full amount of the pollen through the air purifier. The proper functioning of the setup was measured with a laser particle counter. The air outlet was directed in a horizontal position towards the test room in which the test persons were placed. The air quality of the room was constantly measured, in particular for the presence of pollen. During test exposure, 2 test persons were situated in the pollen chamber at a time, and each experienced an exposure as described above.

2.3. Devices/Methods

- Nasal obstruction: peak nasal inspiratory flow meter, Clement Clarke International Ltd., Essex, UK
- Pulmonary function measurements using EasyOne, ndd, Switzerland
- Peak flow metering using a peak flow meter

2.4. Determining the symptom severity

The used scores, Total Symptom Score and Total Nasal Symptom Score, are the main indicators in clinical studies for measuring symptoms of hay fever (cf. Pfaar/ Klimek). The measuring of the symptoms of hay fever has been described comprehensively by *Karatzas et al* (2014): Materials and methods (p. 2 et seqq.); and the used scores in this article TSS and

TNSS correspond to the "symptom severity" measurement in the article by Karatzas et al. (2014). The Total Symptom Score (TSS) is compiled by evaluating the following symptoms:

Eyes

- Itching
- Irritation
- Redness
- Tearing

Nose

- Nasal itching
- Sneezing
- Runny nose
- Stuffy nose

Bronchia

- Wheezing
- Coughing
- Shortness of breath
- Asthma

Other

- Itching of the palate
- Itching of the skin

All symptoms are scored on the following scale:

Symptom severity	**TSS score**
No symptoms	0
Mild symptoms	1
Moderate symptoms	2
Severe symptoms	3

Tab. 1: Symptom description on the Total Symptom Score (TSS) scale

The TSS scale allows a symptom score of 12 points (eyes, nose, bronchia) per category and 6 (other) points. The higher the total score, the greater the acute suffering experienced by the

test subject. In Europe, evaluation of electronic patient diary on allergy symptoms have shown that the peak of symptoms from hay fever are at 5 to 6 points on the total Symptom Scale (cf. Karatzas et al. (2014): 30:1-11.). The mean value of total nasal symptoms from hay fever is in Europe about 80% of all symptoms, i.e. at 4 to 5 points on the scale (TNSS). This value is not yet published but is the experience of the author and researchers at ECARF Foundation.[1] Comparative studies have shown, that the same values can be reached in exposures to aeroallergens in the Mobile Pollen Chamber as in medical practice and in provocation studies.

Since nasal symptoms account for over 80% of total symptoms, the Total Nasal Symptom Score (TNSS) is a critical parameter for determining the results of interventions.

3. Test subjects

Four persons participated as subjects in the study. The subjects were asked for their written and oral consent in an in-depth discussion with the study doctor who provided information on their participation in the study and the storage of their data. The discussion began with an explanation of the background, method and objectives of the study. The participants had the opportunity to ask a study doctor any questions they may have had. All of the subjects provided written consent to participate in the study.

[1] See also for comparable research by: Karatzas et al. (2014): The patient's hay-fever diary: three years of results from Germany; in: Aerobiologia (2014) 30:1-11.): Fig. 6a (with the Y-axis in Figure 6a of this article corresponding with TSS and TNSS respectively) shows average values of all users in Germany for eye, nose and lung as well as overall symptoms. In the chamber nasal symptoms correspond for about 80% of all symptoms.

3.1. Inclusion criteria:

- Age: > 18 years
- Sex: M/F
- Patients of the allergology-pulmonology clinic at the Allergie-Centrum-Charité (ACC)
- Diagnosis: allergic rhinitis and/or conjunctivitis for at least 2 years during the months of the respective pollen season
- Detection of specific IgE antibodies against one or more pollen types in a skin test (prick test) with a wheal measuring at least 3mm in diameter

3.2. Exclusion criteria:

- Persons having completed or currently undergoing subcutaneous or sublingual immunotherapy within the last 5 years
- Treatment with an antihistamine during the past week
- Pregnancy/suspected pregnancy

The profile of the subjects is shown in Table 2.

Subject	Sex	Age	Height	Weight	Smoking behaviour	Allergy
058-ACG	m	29	186	83	Non-smoker	Grasses
081-ADD	m	27	175	79	Quit smoking 2 years ago	Grasses
068-ACQ	w	25	170	68	Non-smoker	Grasses
082-ADE	m	25	176	62	Non-smoker	Grasses + birch

Tab. 2: Profile of the patients

3.3. Decision of the ethics commission:

A positive vote for the study was obtained from the ethics commission of Charité, Ethics Committee, 1 at Campus Charité Mitte.

4. Results:

4.1. Preliminary tests

Tests were carried out to determine the potential influence of the active (and its airflow at the outlet) on the triggering of symptoms in subjects with allergic rhinitis (sensitized to grass pollen).

The four subjects sat in the pollen chamber at a distance of 150 cm from the outlet of the air purifier, which was equipped with a filter. No pollen were released. The subjects were only exposed to the inside air and the airflow from the air purifier at a relatively short distance from the air outlet. This distance was selected to maintain the same distance at which they would be exposed in further tests with pollen and the outlet of the air purifier with and without the filter.

Rationale

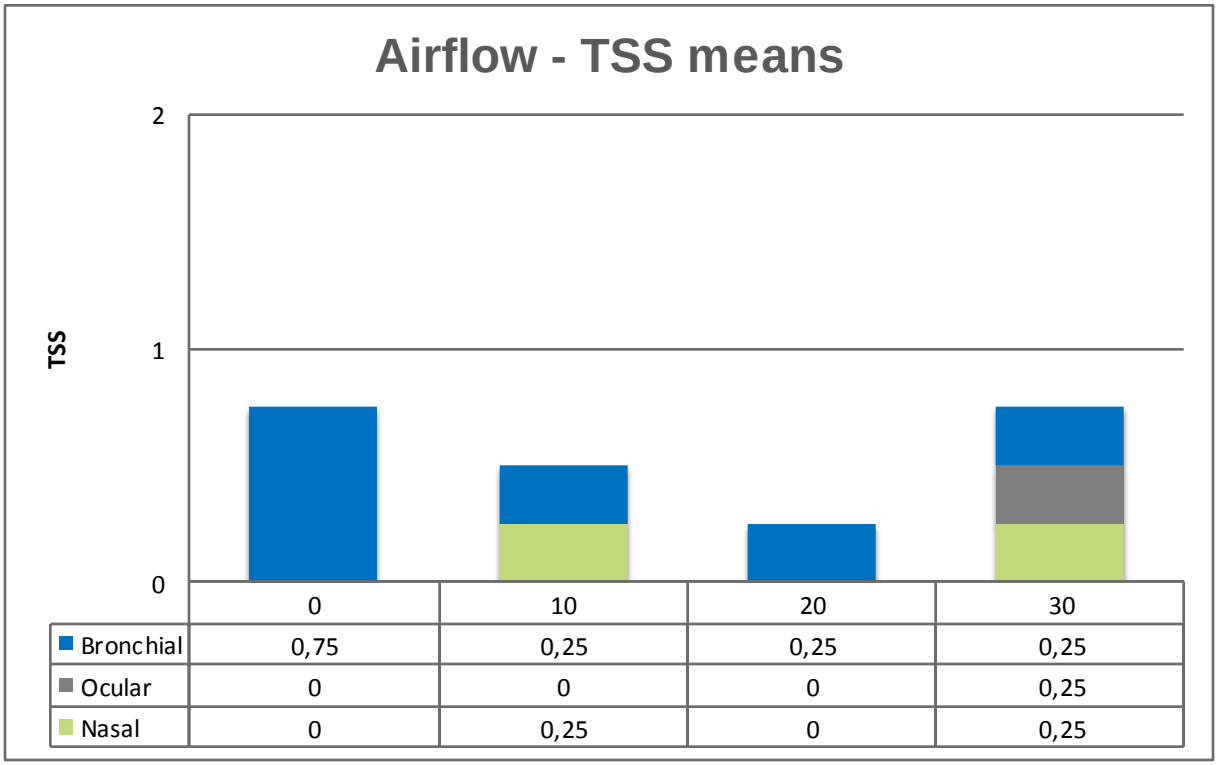
Patients with allergic rhinitis demonstrate an allergy-specific and a non-allergy-specific nasal – and usually concurrent conjunctival – hyperresponsiveness. This causes them to react to both the allergens relevant in their case, e.g. pollen or house dust mites (allergen-specific hyperresponsiveness) and to non-specific triggers such as temperature changes or increased airflow to the nose or eyes. This potential effect of the air purifier needs to be determined in

order to document any symptoms that may be caused solely by operating the air purifier and take these into account when triggering symptoms through pollen exposure.

Results of preliminary tests

During the 30-minute exposure period with the air purifier in the chamber, the symptoms occurred as shown in Fig. 1.

They show the baseline values (mean) and the symptoms after 10, 20 and 30 minutes. There was mild bronchial irritation (0.75 points) at the baseline value, which lessened after 10 to 30 min. and minimal data after 30 minutes in the eyes and after 10 and 30 min. in the nose.



	0	10	20	30
Bronchial	0,75	0,25	0,25	0,25
Ocular	0	0	0	0,25
Nasal	0	0,25	0	0,25

Fig. 1: Overview of the Total Symptom Score before and after 10, 20 and 30 min. in four subjects with allergic rhinitis without medication who were exposed to the airflow from the outlet of the tested air purifier at a distance of 1.5 m.

Evaluation

Very mild nasal symptoms that were still registered by the subjects were triggered by the airflow at the outlet of the air purifier at the tested distance. All of the symptoms scored under 1 point, i.e. the symptoms were so mild that, although they could be sensed by the person evaluating the symptoms, they did not have an impact on how he or she felt. Symptoms with a score of less than 1 are therefore not clinically significant.

Comment

In practical use, the outlet of the air purifier is generally not placed at a distance of 150 cm from the user with the airflow directed at the face. It is therefore correct to note that the air purifier itself does not trigger any clinically relevant symptoms when used by patients with allergic rhinitis.

4.2. Exposure test with and without filter

The four test subjects profiled above were exposed in the pollen chamber to 4,000 grass pollen over a period of 90 minutes. They were exposed to, first, the pollen directly and, second, to the same amount of pollen, however, with the intermediate air purifier in place, twice with and twice without the filter. The results show that the pollen concentration was effectively influenced by the filter.

The practical pollen concentration, the length of exposure time and the environmental conditions (such as temperature, humidity, prevention from exposure with protective clothing) were established in accordance with the evaluated study design for provocation with grass pollen (Abstract Barcelona 2015; see attachment).

Results of exposure tests without filter

In the presence of the air purifier without filter, the subjects developed 'normal' nasal, conjunctival and bronchial symptoms as observed from the evaluation tests. The totality of the symptoms of this organ is given as Total Symptom Score (TSS).

In the first and second run, the mean TSS reached a score of 4.2 to 4.5 points after 50 min., and 3.2 and 6 points after 90 min.

Since the nasal symptoms account for over 80% of the total symptoms, the Total Nasal Symptom Score (TNSS) is the critical parameter for determining the intervention results. In the first and second run, the mean TNSS reached a score of 3 and 5.5 points after 90 min.

Results of exposure tests with filter

After an identical exposure to 4,000 grass pollen and the presence of the air purifier with filter, the subjects developed virtually no nasal, conjunctival or bronchial symptoms.

Both the TSS and the TNSS remained under a score of 1 during the entire 90-minute exposure period, i.e. they had no clinically detectable symptoms that are different than the symptoms occurring from being in the exposure chamber with no pollen exposure whatsoever and in the presence of the running air purifier.

The progression of the symptoms in the four subjects is represented in mean values in Figures 2 – 4.

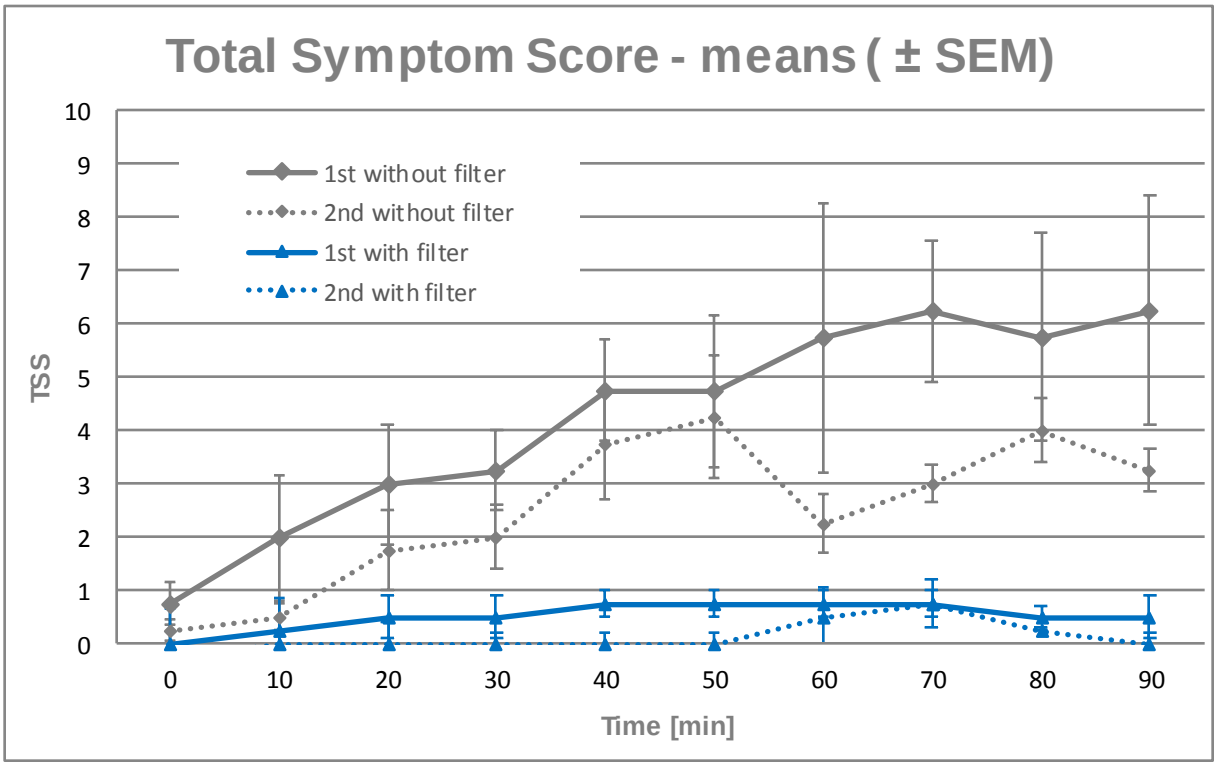


Fig. 2: Representation of the progression of the Total Symptom Score in four subjects during exposure to 4,000 grass pollen over a 90-minute period with and without the effect of the filter of an air purifier.

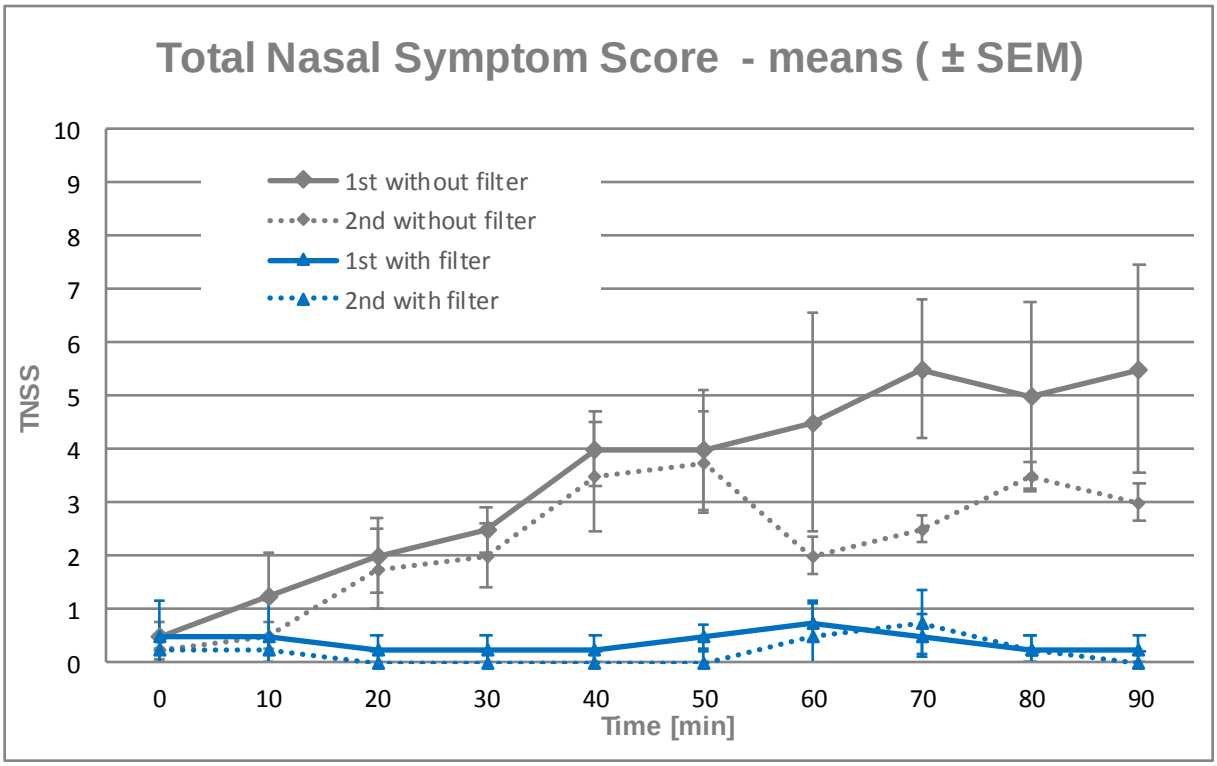


Fig. 3: Representation of the progression of the Total Nasal Symptom Score in four subjects during exposure to 4,000 grass pollen over a 90-minute period with and without the effect of the filter of an air purifier.

5. Safety

No side effects occurred during any of the exposure periods.

Within the scope of the spirometry, no clinically relevant changes in respiratory function (FEV1, vital capacity) were documented.

6. Summary

The procedure for the examinations was carried out as planned.

The evaluation can be summarized as follows:

1. The presence of the air purifier in active use (i.e. used as intended) did not result in any irritations in the nose, eyes or bronchia in 4 persons with allergic rhinitis triggered by grass pollen, i.e. hay fever patients not on medication.
2. Exposure to 4,000 grass pollen over a 90-minute period under standardized conditions in an exposure chamber led to the development of nasal symptoms on a scale of up to 6 points. This Total Nasal Symptom score (TNSS) level is specifically corresponding to the evaluation of the exposure chamber with this type of pollen and pollen concentration, and corresponds to standard conditions. The TNSS level of 6 points is congruent with the TNSS levels that many pollen allergy sufferers experience in real life on a day with high concentration of airborne pollen.
3. The presence of the tested air purifier, used as intended, resulted in the complete prevention of symptoms in the nose, eyes and bronchia in the tested grass pollen allergy sufferers. The level of symptom severity was under 1 point in both the Total Symptom Score and the Total Nasal Symptom Score. Grass pollen allergy sufferers using Philips Air purifier AC 4012 experienced significantly less symptoms of grass pollen allergy suffering like: Sneezing, tears, eye redness, nose itching, skin itching, rhinorrhea. Similar beneficial effects are also expected for sufferers of allergic asthma that are sensitized to grass pollen. The study has proven a grass pollen allergy symptom reduction by using Philips Air Purifier AC 4012. The same results are expected for other Philips air purifiers with identical construction and higher Clean Air Delivery Rate performance.

7. Final evaluation of performance

In a clinical test, the AC4012 air purifier, when used as intended, prevented clinical symptoms from occurring in the nose, eyes and bronchia in allergy patients with allergic rhinitis (hay fever) not on medication when exposed to a high concentration of grass pollen.

Berlin, 14 December 2015

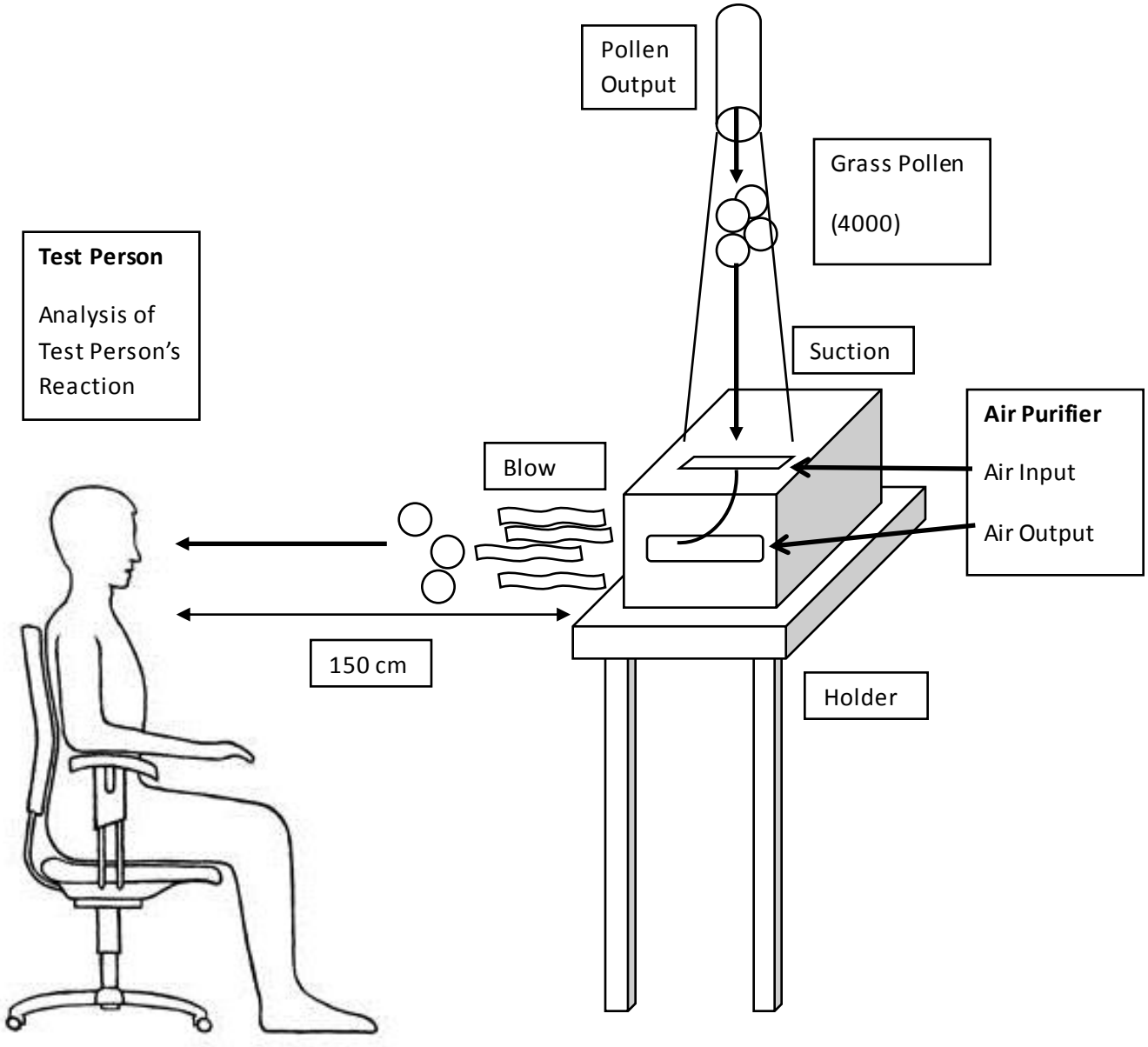
_____	_____
Prof. Dr. Torsten Zuberbier	Prof. Dr. Karl-Christian Bergmann

Part 2

Attachments

Attachment 1:

Fig. 4: Study Design in Mobile Pollen Chamber



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Attachment 2:

A novel Mobile Chamber for Allergen Exposure Tests

Abstract EAACI, Barcelona 2015,

T. Sehlinger[1], K.C. Bergmann[2], T. Zuberbier[2], F. Goergen[1]

1 Bluestone Technology GmbH, Woerrstadt, Germany

2 Allergy-Centre-Charité, Universitätsmedizin Berlin, Germany

Rationale: Incorporating exposure chamber tests in clinical studies presents a feasible possibility to lower trial costs. Nevertheless, using exposure chambers in multi-center, and possibly multi-national trials requires comparable exposure systems at all trial sites in order to gain the maximum benefit for the trial. Bringing all patients to only one stationary chamber would eliminate the cost benefit and would also raise other issues such as introducing test subjects to different environmental conditions before the test.

Methods: A flexible deployable test chamber, able to generate a standardized, controllable and reproducible airborne particle concentration (e.g. pollen), with minimum requirements to the onsite situation and able to be operated in a wide range of outside temperature, should allow data comparability in multinational multi-center trials. Therefore, an inter-connectable container compound was developed, consisting of two standard sized 24" containers, one hosting the test chamber and the technical installations, and the other hosting a control room and a changing room. The test chamber can host up to 9 subjects with temperature and humidity levels being adjustable in a wide range. Each subject can be exposed to an individually adjustable particle concentration, controlled by dedicated disperse units. These units are loaded with traceable particle blisters, contain a particle counting unit allowing for each particle to be counted before dispersal, and a disperse nozzle which ensures an

even particle distribution in a very dedicated and confined area. The test chamber can be operated at an outside temperature ranging from -10°C up to 35°C.

Results: The system developed showed comprehensive characteristics not only in terms of particle concentration, test environment stability and reproducibility compared to fixed chambers but also whilst operating in various outside conditions, namely temperature and humidity. The system also proved fast and flexible in its deployment with a set up time of less than half a day. Furthermore, the system allowed for an individual exposure while no particles where found within the breathable air of another test subject.

Conclusions: Mobile allergen exposure chambers fulfill the need for using exposure chambers in multi-center trials.

Attachment 3:

Clinical validation of a mobile allergen exposure chamber

Abstract EAACI, Barcelona 2015

K.C. Bergmann[1] , T. Sehlinger[2], G. Böhlke[1], T. Zuberbier[1],

1 Allergy-Centre-Charité, Universitätsmedizin Berlin, Germany

2 Bluestone Technology GmbH, Woerrstadt, Germany

Rationale: As required by the European Medicines Agency and the US Food and Drug Administration for pivotal trials involving allergen immunotherapy (AIT) products, clinical efficacy assessment is currently based on double-blind, placebo-controlled field studies with natural allergen exposure during the allergen season. Problems with the field studies include the variability of allergen exposure in different trial sites, the uncertainty of time exposure and confounding environmental factors (temperature, humidity etc.).
A novel mobile Allergen exposure chamber (AEC/GA2LEN chamber) was designed to operate with stable and reproducible allergen exposure under standardized environmental conditions. Technical validation parameters for the mobile AEC have been described. To be accepted as an appropriate alternative to natural allergen exposure for clinical trials the clinical validation of the AEC must document a high reliability of provoked symptoms in repeated provocations and the possible impact of seasonal priming on the test results has to be evaluated systematically.

Methods: The mobile chamber monitoring temperature, relative humidity, oxygen and CO2 levels was used for exposure with grass and birch pollen in adult non-smoking subjects with or without allergic symptoms due to birch and grass pollen during the last two seasons. Each subject was exposed to an individually adjustable pollen concentration, controlled by dedicated dispersion units. Exposure for a period of time of at least 90 minutes has been done in

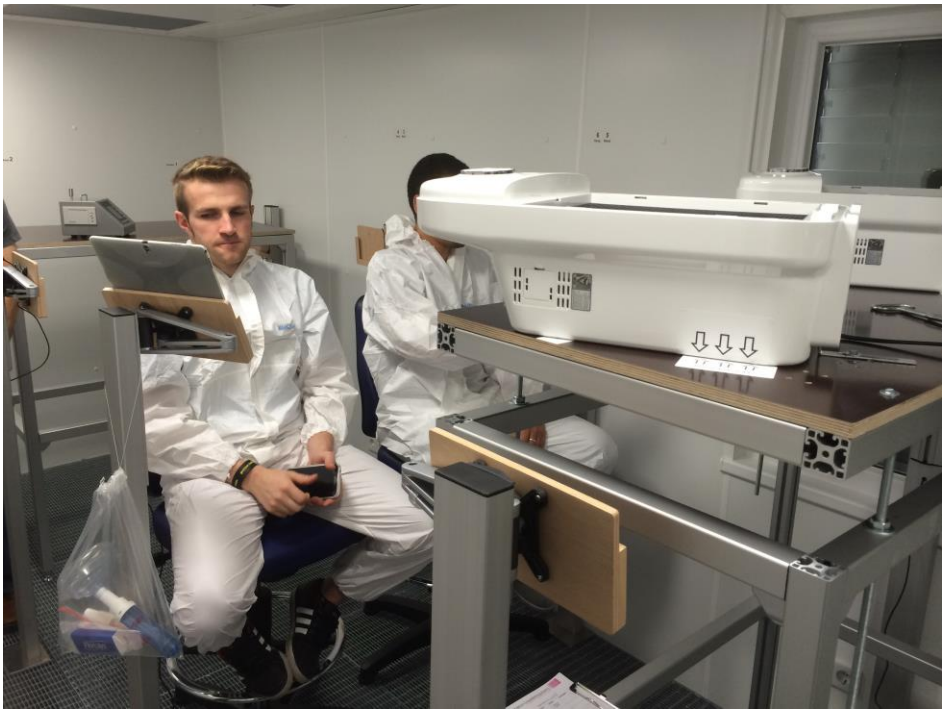
and outside the birch and grass pollen seasons to evaluate the impact of seasonal priming. Before, during and at the end of provocation spirometry, peak-flow, exhaled nitrogen oxide (FeNO), peak nasal inspiratory flow, and the classical symptoms on eye, nose and bronchi have been documented. Possible late-reactions after 24 hrs. were recorded.

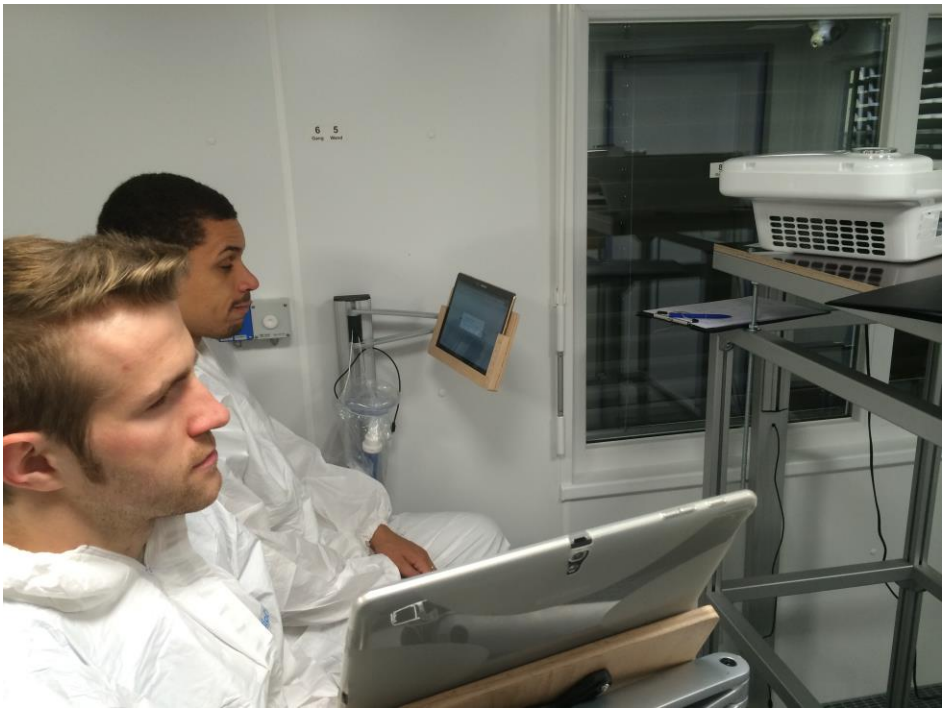
Results: The repeated exposures (up to four times) with birch and grass pollen in different concentrations elicited reproducible clinical symptoms on all the three organs. Generally, the symptoms started to occur after 10 min. and reached a plateau following 30 – 50 min of continuous exposure to pollen.
The influence of possible priming due to a preceding exposure of another pollen species (e.g. birch exposure before grass pollen exposure) in mono- or multisensitized persons has to be clarified in the next step of investigation.

Conclusions: The novel Mobile Allergen Exposure Chamber fulfills the need for a reproducible and very well controlled pollen exposure and seems to be appropriate for allergen immunotherapy studies phase one and two.

Attachment 4:

Study in Mobile Pollen Chamber Berlin, 31 July 2015





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Part 3

About ECARF

ECARF European Centre for Allergy Research Foundation

For a better life with allergies

The non-profit European Centre for Allergy Research Foundation (ECARF) was founded in 2003. It is headquartered at Europe's biggest university clinic, Charité – Universitätsmedizin Berlin, and is managed by Stifterverband, the business community's innovation initiative for the German science system. ECARF is the only internationally active foundation for allergies. ECARF is dedicated to making the lives of allergy sufferers easier and reducing their symptoms. The Foundation is committed to the ongoing promotion of research and increasing awareness in order to be able to provide a wide range of excellent treatment options to allergy sufferers in the future and gain sufficient knowledge on how to deal with allergies.