

Original article

Quality of life and capsaicin sensitivity in patients with sensory airway hyperreactivity

Background: A group of patients with asthma-like symptoms and sensitivity to chemical irritants has shown an increased cough sensitivity to inhaled capsaicin compared to patients with asthma and to healthy controls. The condition is called sensory hyperreactivity (SHR), and the patients often feel that they are socially handicapped because of the risk of exposure to chemical irritants in daily life.

Methods: Twenty-six patients with asthma-like symptoms after exposure to nonspecific irritating stimuli, but without IgE-mediated allergy or demonstrable bronchial obstruction, were selected for a study of the response to a capsaicin test and measurement of quality of life by a general health profile (the Nottingham Health Profile [NHP]). We also investigated whether there was a correlation between quality of life and sensitivity to capsaicin.

Results: The patients demonstrated a dose-dependent response to the capsaicin provocation, with coughing and respiratory and other symptoms, that significantly differed from 12 healthy controls. The health profile showed that patients with SHR had a significantly reduced quality of life compared to reference values, and there was a significant correlation between the health profile and sensitivity to capsaicin.

Conclusions: Patients with asthma-like symptoms verified by the capsaicin inhalation test for sensory hyperreactivity have a poor quality of life. The correlation between quality of life and sensitivity to capsaicin objectively demonstrates the validity of this general health profile study.

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A group of patients with asthma/allergy-like symptoms triggered by strong odors and other chemical irritants has previously been described (1–5). The customary diagnostic asthma and allergy work-up – including reversibility test, PEF curve, methacholine test, and skin testing – is negative in these patients, and they experience little or no improvement with common asthma and allergy medications. Many patients are on sick leave or early disability retirement as a result of their airway problems. The patients describe a social handicap that entails consequences for various situations in daily life. One major problem in these patients has been the difficulty of establishing an objective diagnosis. Inhalation of capsaicin and recording the number of coughs appears to be one method of diagnosis because it has been shown that these patients have a significantly increased number of coughs after the capsaicin inhalation test compared to healthy controls and to patients with asthma (4). Capsaicin – the ingredient that produces the heat in hot peppers (capsicum) – is well known as a cough-inducing agent

when inhaled (6–8). Capsaicin stimulates demyelinated, afferent, sensory C-fibers. The capsaicin receptor was recently identified (9). However, coughing may not be the only symptom induced by capsaicin inhalation; other symptoms were also reported (4). The results indicate a mechanism of sensitivity of the afferent nerves that mediate coughing; therefore, the term “sensory hyperreactivity” (SHR) is suggested.

The Nottingham Health Profile (NHP) is a well-known and well-tested instrument that has been used in a number of different conditions to measure the “impact on well-being”: how disease and symptoms affect the patient’s health, well-being, and ability to function in daily life (10–15). Even if objective measurements used to evaluate state of health indicate that there are important changes in the patient’s clinical situation, they do not always reflect how patients personally describe how they feel and function in daily life (16). The NHP, which focuses on questions concerning patients suffering from various chronic illnesses, has been shown to have both high validity and

reliability (17–19). Bilingual health-care personnel have translated the NHP from English into Swedish, with the aim of expressing how patients experience the effects of illness, as stated in their own words.

Quality of life in patients with SHR has not previously been measured, but the NHP could be of value here because the diagnosis has been difficult to establish, and the patients often feel that they have not been taken seriously by health-care workers. To chart the patient group, we have chosen both to evaluate quality of life by using a general health profile, and to compare the results with the response to capsaicin provocation.

Material and methods

Patients

The study included 26 consecutively selected non-smoking patients with a history of sensitivity to strong odors and chemicals: 20 women and six men aged 31–60 years (average age 48 years). The patients had been referred to our outpatient clinic for asthma-like problems, but asthma could not be verified during the work-up. All participants had normal lung radiographs and lung function ($FEV_1 > 80\%$ predicted), negative methacholine tests, and negative skin prick tests (standard panel with 11 allergens). None had demonstrated spirometric reversibility or variability in pulmonary function. Eighteen patients used β_2 -agonists and/or inhalation steroids regularly, but with no tangible effect. All of the patients had tried β_2 -agonists and inhaled steroids, but eight of them had completely stopped taking medication because of its lack of effect. None had a history of gastroesophageal reflux or heart disease. Exclusion criteria included ongoing infection or other illness during the past month, chronic respiratory or systemic disease, smoking, or pregnancy. Prior to capsaicin provocation, all medications were withheld for at least 4 h; long-acting β_2 -agonists and antihistamines for at least 5 days.

Control group for capsaicin provocation

The control group consisted of 12 healthy, nonsmoking subjects aged 25–56 years (average age 43 years), including 10 women and two men. None had a history of respiratory difficulties, asthma, or allergy, and none took medications regularly. The same exclusion criteria were used for the control group.

Capsaicin provocation

One milliliter of saline was nebulized (Pariboy 36, Paulritzau Pari-werk KG, Starnberg-am-See, Germany) and inhaled to completion for 6 min to induce coughing, followed by a 4-min rest. The number of coughs was counted for 10 min from the onset of

provocation, and recorded on tape. Thereafter, provocations were carried out in the same way by using increasing concentrations of capsaicin: 0.4, 2, and 10 μM in a 1-ml solution. With over 70 coughs from one dose of capsaicin, provocation was terminated out of consideration for the patient. FEV_1 was measured with a spirometer (Vitalograph, Buckingham, UK) before and after each provocation, and the best of three trials was recorded. Symptoms were registered by a score following each provocation on a scale of 0–3 (0=no symptoms, 1=mild, 2=moderate, and 3=severe symptoms). Eleven main symptoms were analyzed: breathing problems, nasal irritation, throat irritation, hoarseness, chest pain/pressure, mucus production, eye irritation, dizziness, headache, fatigue, and sweating. The selection of symptoms was based on previous experience.

Nottingham Health Profile (NHP)

The NHP, which was developed at Nottingham University (UK), measures “the subjective impact of disease” (10–15). This questionnaire consists of two parts, part I containing 38 statements in six categories: physical mobility, pain, sleep disturbance, lack of energy, emotional reaction, and social isolation. Each question is answered with a “yes” or “no”, depending on whether it fits the individual’s current situation. Reference values for part I have been developed by weighting each question, which means that positive responses to all questions within an area equal 100, and negative responses to all questions equal 0. The weighting procedure is based on Thurstone’s “paired comparison” method (20). For the total score of part I, or the NHP total (the sum of questions 1–38 multiplied by their weights), the sum is divided by 6 to reach a value between 0 and 100. NHP part II contains seven questions (“yes” or “no”) concerning the impact of health problems on the individual’s social function respecting paid employment, housework, social life, family life, sex life, hobbies, and holidays. For part II, the proportion of positive responses to each of the seven questions is calculated separately and compared with the reference values. The questionnaire was handed out to the patients in connection with their visits to the Asthma and Allergy Center, together with a patient information sheet. The patients were encouraged to answer the questions according to how they felt during the previous week. They were permitted to take the questionnaire home with them and mail it back after completion. One basic rule for the NHP is that it must be self-administered.

Reference values for the NHP

Norm and reference values distributed by age and sex

for parts I and II of the NHP were used. These values are based on data from larger populations, which are currently in use in family practice (21).

Statistical methods

For part I of the NHP, the Mann–Whitney U test was used to compare two independent groups, and the chi-square test was used for part II. The analyses of the results with different doses of capsaicin and comparison between the different groups were done with ANOVA and the Mann–Whitney U test. The relationship between the NHP and the results of capsaicin provocations was tested with linear regression analysis.

The local ethics committee approved the study.

Results

Capsaicin provocation

Seven of the patients with SHR interrupted the provocation because of over 70 coughs after the third dose of capsaicin (10 μ M), and one patient discontinued after the second dose (2 μ M). Even after withdrawing, they continued to cough, a fact which was recorded. In the control group, all subjects inhaled all three doses of capsaicin.

The patients with SHR reacted dose-dependently with coughing during capsaicin provocation. Even saline caused coughing. The healthy controls reacted similarly, but with less coughing. The mean number of coughs after inhalation of the highest dose of capsaicin was 76 in the SHR group and 28 in the controls (Fig. 1). Patients with asthma-like disorders differed significantly ($P<0.001$) from the control group of healthy subjects for the number of coughs as an effect of each concentration of capsaicin and as an effect of saline ($P<0.01$).

The SHR group registered significantly higher scores (Fig. 2) for nasal irritation, throat irritation, hoarseness, dyspnea, mucus production, eye irritation, sweating ($P<0.01$), chest pressure/pain, and fatigue ($P<0.05$). Regarding dizziness and headaches, there were no statistically certain differences between patients and controls (Fig. 2). The investigators also noted hoarseness, mucus production, red eyes, and sweating, but no further classification was made. Mucus production seemed to stem mainly from the upper airways.

The values for FEV₁ were entirely normal throughout, and no significant differences were found after capsaicin provocation in any of the groups. There was little variation in these values during provocation.

NHP

All patients answered all questions in both parts I and II of the NHP. In part I, there was a significant deviation ($P<0.05$) from the reference group for pain, mobility,

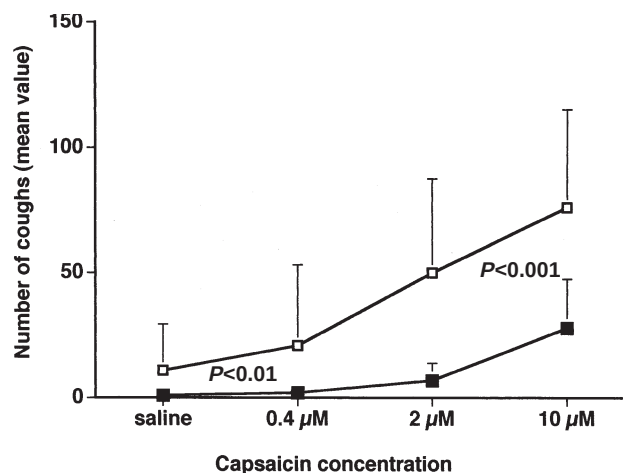


Figure 1. Inhalation of capsaicin in increasing concentrations induced increasing number of coughs in 26 patients with SHR (open squares) and 12 controls (closed squares). Groups differed significantly from each other. Bars represent SEM.

energy, and total score (Fig. 3). Even in the three other areas (sleep, emotional reaction, and social isolation), the patients had higher values but without significant difference compared to the reference group. Part II demonstrated a significant difference between the patient group ($P<0.01$) and the reference values for five of the seven questions: paid employment, housework, social life, hobbies, and holidays (Fig. 4). There was no deviation between the patient and reference values for family life and sex life.

Relationship between the NHP and capsaicin-induced coughing in patients with SHR

There was a statistically significant correlation ($P<0.001$, $r=0.63$) between the number of coughs after the highest inhaled capsaicin concentration and the number of positive answers (of seven possible) in part II of the NHP (Fig. 5).

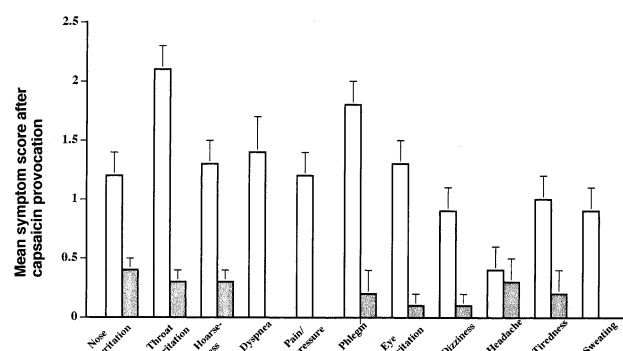


Figure 2. Mean scores of 11 symptoms after inhalation of highest tolerated dose of capsaicin in 26 patients with SHR (open columns) and 12 controls (closed columns). Bars represent SEM.

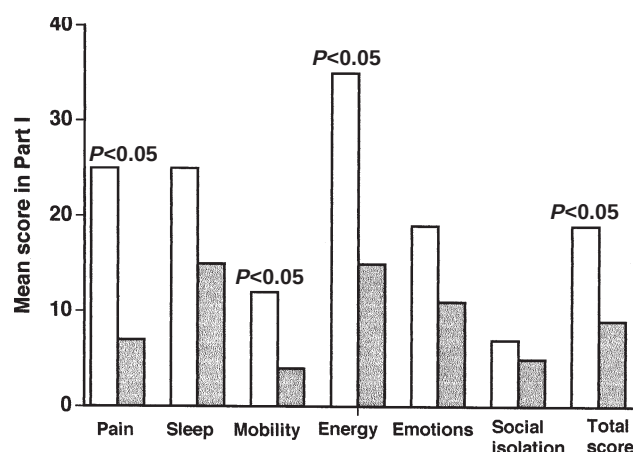


Figure 3. Mean scores in part I of NHP for 26 patients with SHR (open columns) and reference values (closed columns). There were significant differences in areas of pain, mobility, energy, and total score.

Discussion

Sensitivity to strong odors and other chemical agents is found in many patients and is particularly reported in asthma, but only a few studies verify bronchial obstruction after exposure to strong odors (22, 23). Methacholine sensitivity with associated bronchial obstruction is a cardinal sign of asthma (24), but a recent study found that asthmatic patients with pronounced sensitivity to methacholine did not react with bronchial obstruction after perfume provocation (25). Asthma-like symptoms that developed after a single high exposure to a chemical irritant have been described as reactive airways dysfunction syndrome (RADS) (26, 27). Those patients all had positive methacholine tests, and, in contrast to patients with SHR, had a history of an acute specific injury incident. Vocal cord dysfunction

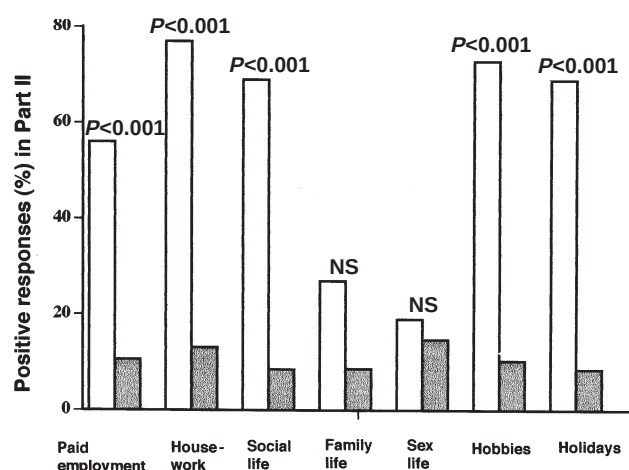


Figure 4. Mean scores in Part II of NHP for 26 patients with SHR (open columns) and reference values (closed columns). Positive response indicates problem. There were significant differences in five of seven questions.

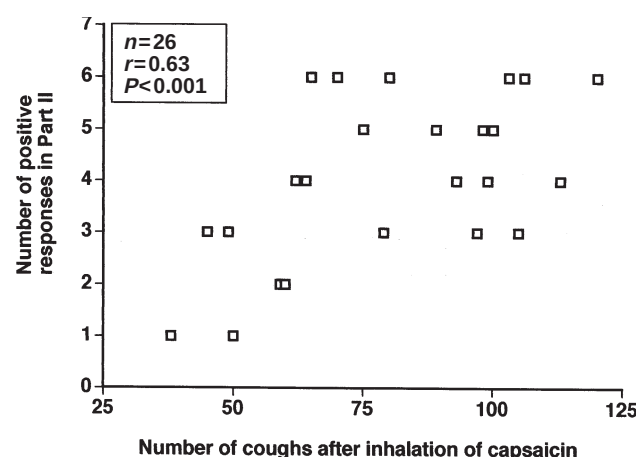


Figure 5. Correlation between number of positive responses in part II of NHP concerning activities of daily life and number of coughs after inhalation of highest tolerated dose of capsaicin in 26 patients with SHR. There was a significant correlation between these values, ($P<0.001$, $r=0.63$).

is another asthma-like condition, but it is associated with exercise-induced problems rather than chemical irritants (28, 29). The basic cause of multiple chemical sensitivity (MCS), also known as idiopathic environmental intolerance (IEC), is sometimes considered to be previous major exposure to some form of chemical irritants, leading to a general sensitivity to chemical irritants with multiple symptoms from different organs (30–34). With MSC, it is difficult to find any clear mechanism or terminology, because both the symptomatology and diagnostic methods vary. MCS has mostly been classified as a psychological disorder and is not regarded as an established organic disease (35). Even with the sick building syndrome (SBS), there is sensitivity to odors, but in connection with a certain environment (36). However, in these different conditions, there are airway symptoms similar to those described in our patient group, and a sensory mechanism may be involved.

We have described a well-defined group of patients with uniform, asthma/allergy-like symptoms characterized by pronounced sensitivity to common environmental chemicals. Brief exposure to substances such as perfume, after-shave, or smoke could evoke asthma-like symptoms and other symptoms. Exposure to odors is an inevitable part of everyday life and has a negative impact on patients with SHR, as well illustrated in part II of the NHP, where this effect was expressed as a significantly elevated number of positive responses to five of seven questions. Compared with other chronic conditions studied, the quality of life of patients with SHR is strongly affected according to part II of the NHP, and also to the total score in part I (13–15). The validity of the NHP's results in our patients is strongly supported by the fact that there was a significant correlation between the number of positive replies in part II and cough sensitivity to capsaicin (Fig. 3).

The response to capsaicin was not restricted to airway symptoms. Eye irritation was common, as well as nasal/throat irritation. According to the patients, mucus production appeared to originate mainly from the upper airways. This agrees with previous studies in which patients experienced similar difficulties after provocation with perfume (2, 5). There are probably a number of patients with SHR who visit ophthalmologists and otorhinolaryngologists, as well as allergists and pulmonologists; where the patient seeks care may depend on the predominant symptom. Interestingly, a large portion of the patients experience chest pressure and pain after capsaicin inhalation. Chest pain without cardiac disease is a well-known problem (37, 38) and may actually be linked to SHR. According to part I of the NHP, the patients also reported a significant increase in pain, but its nature was not clear. The patients suffered from an impairment of social life (part I), but not from social isolation (part II). The patients probably regarded social isolation as something other than problems with various aspects of social life. The influence of paid employment, housework, hobbies, and holidays does not necessarily lead to social isolation. Furthermore, family life and sex life were not influenced.

In conclusion, this study showed that patients with asthma-like symptoms demonstrated an increased cough-sensitivity and other symptoms after provocations with capsaicin. The patients also had a significantly reduced quality of life according to a general health profile, and there was a good correlation with capsaicin sensitivity. In the future, provocation with capsaicin inhalation may be of importance for identifying patients with sensory hyperreactivity. Further research is indicated to develop new diagnostic methods. For the patients' well-being, it is important to have their symptoms verified by an objective test. Also from the socioeconomic viewpoint, considering health-care investment and medication, diagnostics must be improved. The importance of taking this patient group seriously is illustrated by the major effect on quality of life found according to the NHP.

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