

Airway reactions and breathing movements in sensory hyperreactivity

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Ineko AB

*"Även om man hela tiden får mer av livet
bakom sig måste det finnas en rörelse framåt"*

Med personlig tillåtelse, Sven – Eric Liedman 2013

*To Zoe, my eagle sister in heaven
I can sense your presence, I can hear your wings
To Per my brother in heart and soul
So far away yet always amongst us
I miss you constantly*

*With all my Love and sincere gratefulness to
Mine, through thick and thin,
Always supportive and
Constantly growing family,
All my dear friends,
Respected colleagues
And the cat*

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8T

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ABSTRACT

Patients diagnosed with sensory hyperreactivity (SHR), suffer from airway symptoms such as cough, breathing difficulties and chest pain, induced by a variety of environmental irritants, as well as by cold air and physical effort. Their lung function tests show normal values and specific asthma tests are usually negative. Capsaicin, the hot ingredient in hot peppers (capsicum), is known to stimulate the cough reflex in humans and is used to distinguish and diagnose this condition. SHR affects more than 6% of the adult Swedish population, mainly women and there is no pharmacotherapy to offer. The **overall aim** of this thesis was to elucidate different aspects of symptoms and reactions, from the airways and the chest for which these patients seek medical attention for. A further aim was to evaluate the effect of a physiotherapeutic intervention. **Study I** evaluated the induced symptoms; physiological parameters and capsaicin cough sensitivity in patients suffering from exercise induced dyspnea (EID) and SHR, after exercise in cold air. **Study II** evaluated capsaicin cough sensitivity in patients with SHR and chronic idiopathic cough after a eucapnic voluntary hyperventilation (EVH) test. **Study III** evaluated chest mobility, respiratory movement and pain sensitivity in patients with SHR compared with patients with asthma, chronic obstructive pulmonary disease (COPD) and allegedly healthy control subjects. **Study IV** evaluated the effect of a 12-week physiotherapeutic home based training program in patients diagnosed with SHR. **Main findings:** Exercise provocation in cold air increased capsaicin cough sensitivity and decreased end-tidal CO₂ without affecting lung

function. When provoked with the EVH test, cough sensitivity was down-regulated. The patients with SHR had increased breathing frequency, reduced chest mobility and lower respiratory movement compared to both healthy control subjects and to patients with asthma. Except for lung function, the significantly younger group of patients with SHR was comparable, in several aspects with the group of older patients suffering from severe or very severe COPD. Further, patients with asthma, COPD and SHR had significantly lower pain thresholds compared to the healthy controls. A physiotherapeutic home based training program increased chest mobility and decreased the subjective feeling of chest pressure after the training period. The capsaicin cough threshold for two coughs (C2) increased (improved) after the intervention period.

Conclusions: Patients suffering from SHR have in many ways reactions differing from healthy control subjects and from patients with other airway diseases. However, in some aspects, like breathing symptoms, pain sensitivity and chest mobility, the findings in the various airway diseases overlapped each other. The airway symptoms and the increased cough sensitivity reported by the patients with SHR are reproducible by exercise in cold air. On the other hand an EVH test, in line with animal studies and results in healthy volunteers, had the opposite effect and down-regulated the cough sensitivity following the EVH test. That a physiotherapeutic treatment program turned out to be effective in enhancing chest mobility, decreasing chest symptoms and improving capsaicin cough sensitivity indicates a possibility to provide a treatment for these patients. We hypothesize that cold air, exercise and dry air via the recently identified receptor system of transient receptor potential (TRP) ion channels influenced cough and other airway symptoms among the patients. The findings may provide an explanation for some of the airway and chest symptoms reported by patients suffering from SHR.

Keywords: Airway Sensory Hyperreactivity-SHR, Breathing Movements, Chest Mobility, Pain Thresholds, Physical Therapy, Chemical Sensitivity, Cough, Capsaicin, Asthma, COPD.

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SAMMANFATTNING PÅ SVENSKA

Bakgrund. Patienter med diagnosen sensorisk hyperreaktivitet (SHR) beskriver symtom från luftvägarna, bland annat hosta, svårigheter att andas och smärtor i bröstet. Symtomen kan utlösas av doftande och irriterande ämnen men även av kall luft och fysisk ansträngning. Vid test av lungfunktionen påvisas normala värden och specifika astmatester är vanligtvis negativa. Capsaicin, den heta ingrediensen i chili (capsicum), som är känt för att stimulera hostreflexen, används för att undersöka retbarheten i luftvägarna hos dessa patienter. SHR drabbar mer än 6 % av den vuxna svenska befolkningen, främst kvinnor och det finns ingen farmakologisk terapi att erbjuda.

Syfte. Det övergripande syftet med denna avhandling var att belysa olika aspekter av symtom och reaktioner från luftvägarna och bröstkorgen hos patienter med väldefinierad SHR men även i relation till patienter med astma och kroniskt obstruktiv lungsjukdom, KOL. Vidare, att utvärdera effekten av ett sjukgymnastiskt behandlingsprogram, baserat på tolv veckors hemträning.

Resultat. I. Ansträngningsprovokation i kall luft ökade capsaicin-känsligheten och minskade mängden utandad CO₂ hos patienter med ansträngningsutlöst andnöd (EID) och SHR, utan att det påverkade deras lungfunktion. **II.** När patienter med SHR istället provocerades med inandad torrluft via ett eucapniskt hyperventilationstest, (EVH) nedreglerades hostan och känsligheten för capsaicin. **III.** Patienter med SHR uppvisade förhöjd andningsfrekvens, minskad bröstkorgsrörlighet och andetagrrörlighet jämfört med både friska kontrollpersoner och patienter med astma. Bortsett från lungfunktionsvärden, var den betydligt yngre gruppen av patienter med SHR i flera avseenden jämförbar med den grupp av äldre patienter med svår eller mycket svår KOL som deltog i studien. Liksom patienterna med astma, hade de med KOL och SHR, signifikant lägre smärtrösklar jämfört med de friska kontrollpersonerna. **IV.** Den sjukgymnastiska behandlingen ökade bröstkorgsrörligheten och minskade den subjektiva känslan av tryck över bröstet hos patienterna. Tröskelvärdet för dosen av capsaicin som utlöser två hoststötter (C2) ökade (förbättrades) efter behandlingsperioden. Även i denna studie hade patienter med SHR lägre smärtrösklar jämfört med en grupp kontrollpersoner från en tidigare studie.

Slutsats. Patienter med SHR har symtom och reaktioner som på flera sätt skiljer sig från friska kontrollpersoner och från patienter med andra sjukdomar i luftvägarna. Men i vissa avseenden, såsom andningssymtom, smärtkänslighet och bröstkorgsrörlighet, var resultaten liknande dem hos patienter med KOL och astma. Luftvägssymtom och ökad hostkänslighet som rapporterats av patienter med SHR visade sig vara reproducerbara i förhållande till ansträngningen i kall luft. Å andra sidan, efter EVH test och i linje med tidigare djurstudier samt resultat på friska försökspersoner, hade inandad torrluft en motsatt effekt med nedreglering av hostkänsligheten. Den sjukgymnastiska behandlingen förbättrade bröstkorgsrörligheten samt minskade symtomupplevelsen av tryck över bröstet. Vidare minskade känsligheten för capsaicin, tröskelvärde för C2 ökade. Resultaten kan ge en förklaring till en del de luftvägs- och bröstkorgssymtom som beskrivs av dessa patienter och visar på en behandlingsmöjlighet.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals. The papers have been printed with the kind permission of the publishers.

- I. Ternesten-Hasséus Ewa, Johansson Ewa-Lena, Bende Mats and Millqvist Eva. Dyspnea from exercise in cold air is not always asthma *J Asthma*. 2008 Oct;45(8): 705- 9.

- II. Johansson Ewa-Lena, Ternesten-Hasséus Ewa and Millqvist Eva. Down-regulation of cough sensitivity after eucapnic dry air provocation in chronic idiopathic cough. *Pulm Pharmacol Ther*. 2009 Dec; 22 (6):543-7.

- III. Johansson Ewa-Lena, Ternesten-Hasséus Ewa, Fagevik Olsén Monica and Millqvist Eva. Respiratory movement and pain thresholds in airway environmental sensitivity, asthma and COPD. *Respir Med*. 2012 Jul; 106(7):1006-13.

- IV. Johansson Ewa-Lena, Ternesten-Hasséus Ewa, Fagevik Olsén Monica and Millqvist Eva. Physical therapy treatment of impaired chest mobility and respiratory movements in patients with airway environmental sensitivity. In manuscript.

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ABBREVIATIONS

<i>C10</i>	<i>Ten coughs at given concentration</i>
<i>C2</i>	<i>Two coughs at given concentration</i>
<i>C5</i>	<i>Five coughs at given concentration</i>
<i>CI</i>	<i>Confidence Interval</i>
<i>CIC</i>	<i>Chronic idiopathic cough</i>
<i>CO₂</i>	<i>Carbon dioxide</i>
<i>COPD</i>	<i>Chronic obstructive pulmonary disease</i>
<i>CSS-SHR</i>	<i>Chemical sensitivity scale for sensory hyperreactivity</i>
<i>DBD</i>	<i>Dysfunctional breathing disorder</i>
<i>EIB</i>	<i>Exercised induced bronchobstruction</i>
<i>EID</i>	<i>Exercise induced dyspnea</i>
<i>EVH</i>	<i>Eucapnic voluntary hyperventilation</i>
<i>FEV₁</i>	<i>Forced expiratory volume in one second</i>
<i>FRC</i>	<i>Functional residual capacity</i>
<i>FVC</i>	<i>Forced ventilator capacity</i>
<i>GAD</i>	<i>Generalized anxiety disorder</i>
<i>GERD</i>	<i>Gastro-esophageal reflux disease</i>
<i>GINA</i>	<i>Global initiatives for asthma</i>
<i>HARQ</i>	<i>Hull airway reflux questionnaire</i>
<i>HRQL</i>	<i>Health-related quality of life</i>
<i>IgE</i>	<i>Immunoglobulin E</i>
<i>MCS</i>	<i>Multiple chemical sensitivity</i>
<i>MVV</i>	<i>Maximal voluntary ventilation</i>
<i>PEF</i>	<i>Peak expiratory flow</i>
<i>PPT</i>	<i>Pressured Pain Threshold</i>
<i>PSaO₂</i>	<i>Peripheral Oxygen saturation by pulse oximetry</i>
<i>PVFM</i>	<i>Paradoxical vocal fold movement</i>
<i>RARs</i>	<i>Rapidly adapting stretch receptors</i>
<i>SARs</i>	<i>Slowly adapting stretch receptors</i>

<i>SD</i>	<i>Standard deviation</i>
<i>SF-36</i>	<i>Short-Form 36</i>
<i>SHR</i>	<i>Sensory hyperreactivity</i>
<i>TRP</i>	<i>Transient receptor potential ion channel</i>
<i>TRPM8</i>	<i>Transient receptor potential ion channel, melastin subunit 8</i>
<i>TRPV1</i>	<i>Transient receptor potential ion channel, vanilloid subunit 1</i>
<i>TRPV4</i>	<i>Transient receptor potential subunit 4</i>
<i>VCD</i>	<i>Vocal cord dysfunction</i>
<i>VO_{2max}</i>	<i>Maximum oxygen uptake</i>
<i>WHO</i>	<i>World health organization</i>

1 INTRODUCTION

To breathe is to live; through the function of breathing we support the body with oxygen and transport carbon dioxide (CO₂) out of it. Everyone knows that “if I don’t breathe I will die” The feeling of breathlessness and “not getting air enough” creates anxiety and leads to considerable distress.

Discomfort, pain, or sense of trouble in the body or parts of the body could, through the sensory feedback to the brain, lead to increased tonus of the musculature (Figure 1). Heavy breathing, sense of dyspnea and decreased chest mobility may lead to dysfunctional breathing and follow this vicious circle of pain, increased tonus, and even more pain (1, 2).

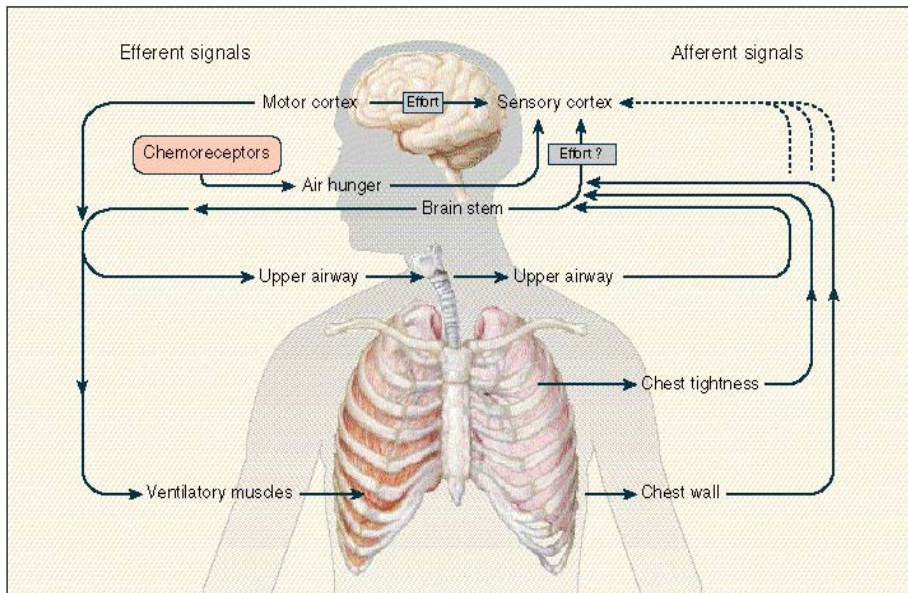


Figure 1. Efferent and Afferent Signals That Contribute to the Sensation of Dyspnea. Reproduced with permission from The New England Journal of Medicine, Massachusetts Medical Society (1).

Sensory hyper reactivity, (SHR) is as a discrete entity of individuals with non-asthmatic, non-allergic airway symptoms induced by environmental irritants such as chemicals and scents (3). Patients with SHR often seek care at pulmonary clinics for respiratory diseases like chronic obstructive pulmonary disease (COPD) and asthma and in some senses they are associated in spite of many differences. Chronic cough is characteristic and common for these conditions and of also several other respiratory diseases. A subgroup of patients with what is often called “idiopathic cough” have coughing triggered by environmental irritants (4) and may be diagnosed with SHR and also with the recently established cough hypersensitivity syndrome (5). Laryngeal dysfunction such as vocal cord dysfunction (VCD) is often characterized not only by dyspnea due to involuntary closing of the vocal cords but also by cough and environmental trigger factors (6). Dysfunctional breathing disorder (DBD) and hyperventilation are related to SHR but the definition of SHR comprises airway environmental sensitivity (7). The sensitivity to nonspecific irritants in SHR indicates the relation to multiple chemical sensitivity (MCS), a syndrome that does not necessarily includes airway symptoms (8). To develop the diagnostics for SHR and the differential diagnostics it seems necessary to avoid misinterpretation, inadequate information and unnecessary medication.

In a historical review article about physical therapy related to breathing exercises, the author, Diana Innocenti, showed that it is over a hundred years since the first scientific article about the effects of physical therapy treatment for breathing problems was published (9), emphasizing towards physical activity and movements. Knowledge about pulmonary physiology and airway diseases and their treatment have increased immensely on all levels during this century. The main purpose of a physiotherapeutic intervention in respiratory and other diseases is however still, to offer exercises and tools for normalization of movement and function of breathing and to do so in relation to the patient’s symptoms, experiences and needs (10).

1.1 The function of breathing

Breathing involves the upper and lower airways for humidification and filtration of inspired air and the lungs for gas exchange via the alveoli. The breathing control system is complex; automatically it adapts to the signals from the respiratory tract including muscles, stretch receptors and central chemo receptors. Coordinated by the pons, these signals reach the interconnecting groups of six neurons located in medulla, generating the respiratory rhythm. The inspiratory/expiratory respiratory cycle is a three-phase action emerging from the first of the dorsal and ventral respiratory groups of the medulla:

1. The onset of motor discharge causing contraction of the pharyngeal dilator and inspiratory muscles
2. Declined motor discharge of the inspiratory muscles followed by a lowered inspiratory muscle tone, start of the passive expiratory phase
3. Silent inspiratory muscles, increased activity in expiratory muscles.

The second respiratory group of the medulla is involved in the voluntary control of breathing such as speech and respiratory gymnastics. The involuntary and non rhythmic control, such as sneezing and hiccupping are involved in the third group of the first of the dorsal and ventral respiratory groups of the medulla (11, 12).

Respiratory muscle activity is an integrated interaction of factors such as respiratory load, posture and minute volume as well as disease and anaesthesia. In inflating the lungs with air, the inspiratory muscles, the diaphragm, external intercostals and scalene, act in parallel and the body posture determines the dominant muscle group (13). Body posture affects the relationship between the breathing movement's impact from the rib cage and abdomen. The movements of the ribcage are dominant in a seated position while in the supine position the abdominal movements are more prominent. In the supine body position the postural muscle activity in the trunk is lowered and the diaphragm is positioned by gravity about 4 cm higher in the trunk. This affects the length and contractile ability of the muscle fibres such that they are more effective, delaying airway closure and therefore compensating for the lowered functional respiratory capacity (FRC) (14).

The minute volume is the tidal volume multiplied by the breathing frequency at rest 12-16 breaths per minute is considered as normal in adult humans. The work of breathing is overcoming the resistance of airflow and elastic tissues of the lungs and chest wall (13). There are several ways to measure lung volume in clinical work, the forced expiration of volume in one second (FEV_1) and the forced ventilator capacity (FVC) being the most common. Expiratory flow rate in term of peak expiratory flow is a convenient way to measure lung function and is used to monitoring airway obstruction; its result correlates well to FEV_1 . All methods used to measure lung function are dependent on technical performance and muscle endurance and can be influenced by pain. Hence, they should be conducted after thorough instructions and training (15).

The respiratory effects of central nervous system, CNS activities, such as cortical control, peripheral sensory information from odour and temperature and visceral cardiovascular inputs are probably coordinated by the central afferent pathway to the pons. Upper respiratory tract reflexes emerge from the nose, the pharynx and the larynx. Water and chemical stimulants such as ammonia and cigarette smoke in the nose can cause stimulation of the diving reflex followed by apnoea (16). In the pharynx mechanoreceptors sensitive to pressure are considered to activate the pharyngeal dilator muscles. Local anaesthetics are known to inhibit this action. In the larynx most reflexes arise from the supra glottis where three groups of receptors are located. Mechanoreceptors, cold receptors and irritant receptors cause increased pharyngeal dilator muscle activity, depression of ventilation and the cough reflex, respectively (16).

The reflex activity is complex in the lungs; receptors sensitive to chemical and mechanical stimulation, to inflation and deflation are communicated primarily through the afferent function of the vagal nerve. The slowly adapting stretch receptors (SARs) are located in the smooth muscles of the trachea-bronchial tree; they function as volume sensors of the lung. The significance of SARs in humans is questioned, partly because bilaterally pulmonary transplanted patients show of a next to normal ventilator pattern even though both lungs are de enervated (17). The rapidly adapting stretch receptors (RARs) located in the mucosal layer, the function of the RARs is connected to changes in tidal volume, respiratory frequency and lung compliance. The RARs are also known to be chemo sensitive, responding to inflammatory mediators, mechanical and chemical stimuli. They are related to the C

fibre receptors located in the bronchial mucosa and in the lungs and are considered to be responsible for the initiation of the cough reflex (18).

1.2 Airway Sensory Hyperreactivity, SHR

1.2.1 Definition and symptomatologi

The expression “airway sensory hyperreactivity” was first suggested in 1998, as an explanation for symptoms in the upper and lower airways induced by chemicals and scents (7). SHR is defined as a combination of expressed airway symptoms induced by environmental irritants, increased cough sensitivity to inhaled capsaicin and a high score on the Chemical Sensitivity Scale for Sensory Hyperreactivity questionnaire (CSS-SHR) (3, 19).

The symptoms described by the patients include cough, phlegm, chest weight and a sense of breathlessness. More general symptoms such as headache, sweating and dizziness are also reported (7). Perfume, cigarette smoke and automobile exhausts the scents of flowers and household detergents, cold air and physical activity can cause the elicitation of these symptoms (20, 21).

Free nerve endings emerging from the trigeminal nerve react to irritating and harmful stimulations such as tickling, burning, cooling and stinging in the upper and lower airways and the eyes. Via the sensory part of the vagal, trigeminal and glossopharyngeal nerve, adverse stimuli transmit to the airways and eyes, inducing pain and irritation (22).

When the sensitivity increases or the thresholds lower the essential warning system from what it is originally meant to be symptoms of irritation and danger are observed even from levels commonly regarded as non-toxic and safe. The consequence is a sensory hyperreactivity that has now has been labelled as a diagnosis for a discrete entity of patients – SHR (23).

1.2.2 Diagnosis

The asthma specific diagnostic routine including lung function test, β_2 reversibility test and methacoline bronchial provocation test, usually show negative results in patients with SHR (24).

Capsaicin inhalation provocation test

Several studies have shown that patients with upper and lower airway symptoms induced by chemicals and scents have increased cough sensitivity to inhaled capsaicin, which is known to reflect the sensory nerve reactivity of the airways (3, 21, 25). This capsaicin inhalation provocation test with stepwise increasing concentrations was found to reproduce and distinguish the subjective symptoms reported by patients who were sensitive to chemicals and scents (3, 7, 20). When the airway provocation with inhaled capsaicin was preceded by inhalation of lidocaine, a common local anaesthetic, the symptoms were partly blocked as was the capsaicin induced cough (20).

1.2.3 Prevalence

In a population based study using the CSS-SHR, Johansson et al found a prevalence of 19% airway intolerance for odours in the adult population being twice as common in women (26). Exploring the relationship between the CSS-SHR and the sensitivity to inhaled capsaicin, the prevalence was estimated to be 6.3% with a female to male ratio of approximately 2 to 1 (3).

1.2.4 Quality of life

Being sensitive to airborne chemicals and scents often means having an impaired health related quality of life (HRQL) (27). The experienced risk of being provoked by a trigger factor inducing symptoms is often followed by avoidance and isolation (28). In accordance with the increased capsaicin cough sensitivity, found to be persistent over time, HRQL was reduced at the start and end of a five year follow-up study in patients diagnosed with SHR (21). The CSS-SHR questionnaire was developed to measure behavioural consequences of self reported odour sensitivity and limits are set for a positive score (19). SHR was defined as a combination of a positive standardized capsaicin inhalation test and a value in the CSS-SHR exceeding the limit set for a positive score (3).

In 2010, Johansson et al examined the relationship between asthma and SHR and whether patients with SHR showed signs of psychiatric morbidity. They found no significant connection between SHR, depression and anxiety and the prevalence of SHR in patients with asthma was 6% in agreement with the prevalence in of a general population (29).

1.2.5 Treatment

There is today no medicinal treatment for patients suffering from SHR. The healthcare service can mainly offer an exclusion of other and more treatable airway diseases and information and knowledge about the condition. Though lack of evaluated methods concerning this group of patients, the physiotherapist is often involved in helping the patients with their breathing symptoms.

1.3 Cough

Cough is the most common reason for seeking medical help in the Western world (30) and is the most important protective reaction to clear the airways from foreign particles and mucus. The cough that develops after a common cold typically lasts one to three weeks but a persistent cough can be a warning signal that indicates serious diagnoses. The danger of suppressing cough is known from the complications that may arise after anaesthesia, such as secretion retention followed by infections. The cough reaction starts in the sensory nerves of the epithelium in the throat, upper and lower airways. Via the vagal nerves afferent signals to the brain stem activate the efferent neural pathway to the laryngeal, thoracic and abdominal muscles involved in the cough reaction (Figure 2). The cerebral cortex can be expected to be involved by afferent input, whenever voluntary cough is expressed (31).

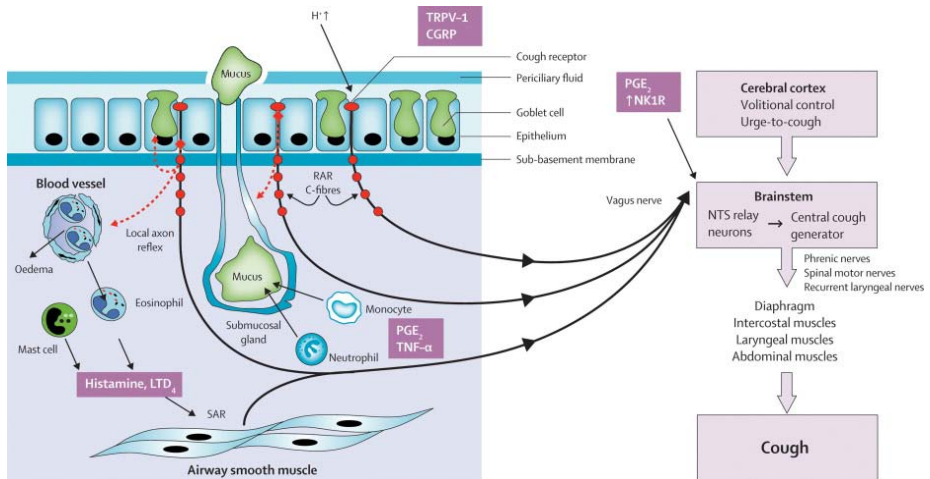


Figure 2. Representative scheme of afferent and efferent pathways that regulate cough, and of the pathophysiology of the enhanced cough reflex. Laryngeal and pulmonary receptors, such as rapidly adapting receptors (RARs), C-fibres, and slowly adapting fibres (SAR), and cough receptors provide input to the brainstem medullary central cough generator through the intermediary relay neurons in the nucleus tractus solitarius (NTS). The central cough generator then establishes and coordinates the output to the muscles that cause cough. An output to airway smooth muscle and mucosal glands (not shown) is also present. The cerebral cortex can control the motor output of cough voluntarily, or influence the urge-to-cough sensation. Factors that act in the upper airways or brainstem, to enhance the cough reflex, are illustrated. CGRP=calcitonin gene-related peptide. LTD₄=leukotriene D₄. PGE₂=prostaglandin E. NK1=neulokinin-1. TRPV=transient receptor potential vanilloid. TNF=tumour necrosis factor. Reproduced from Chung and Pavord 2008, (30)

Cough is defined as the characteristic sound following the forced expiratory effort against a closed glottis. The motor component of cough consists of three phases including deep breathing inspiration, built-up pressure with expiratory muscles against a closed glottis and finally a forced expulsion resulting in an explosive outflow of air and irritant material (32, 33)

1.3.1 Chronic cough

Chronic cough is defined as coughing daily and weekly for more than eight weeks (34, 35). Diseases causing chronic cough include asthma, eosinophilic bronchitis, gastro-esophageal reflux disease (GERD), postnasal drip syndrome or rhinosinusitis, COPD, pulmonary fibrosis, and bronchiectasis. Idiopathic cough is a term used when no cause of the coughing can be found even after thorough and systematic

investigation (36). The term “chronic refractory cough” aims to describe long lasting, persistent and hard to treat cough (37, 38).

1.3.2 Cough hypersensitivity syndrome

The diagnosis describes patients suffering from chronic cough also including the association with a hypersensitive cough response to inhaled protussive stimuli such as citric acid or capsaicin (5, 39). This syndrome focuses on and emanates from the coughing patient and provides an “umbrella” for different conditions with cough as a major component. The symptoms in the syndrome include persistent tickling or an irritating sensation in the chest or throat, hoarse voice, dysphonia or VCD that together with cough may be induced by environmental irritants such as tobacco smoke and scenting products. The pathophysiology behind the hypersensitivity is suggested as an up-regulation of transient receptor potential vanilloid subtype (TRPV-1) receptors (40).

1.3.3 Transient Receptor Potential, TRP ion channels

There are several TRP ion channels in six subfamilies and with a wide spread of expressions, interacting between the organ systems and the environment (41). These TRP channels sense, among others, temperature, noxious stimuli, pain, stretch and osmolarity (42). The TRPV1 is also known as the “cough-receptor” (43). It is assumed to be up-regulated in SHR, since these patients have an augmented cough response to inhaled capsaicin (7). Capsaicin, the hot ingredient in Spanish pepper, simulates TRPV1 on non myelinated sensory C fibres nerve endings in releasing neuropeptides (44). The TRPV1 receptors are located on primary sensory neurons where pain is generated (45) and have in recent years attracted great interest in pain research (46). The TRPV receptors 3 and 4 are involved in mechano sensitive and osmotic cell swelling and the TRP family of melastin involves the cold sensing receptor TRPM8 (41).

1.4 Diagnoses associated with SHR

1.4.1 Chronic Obstructive Pulmonary Disease, COPD

COPD is predicted to be the third largest cause of death worldwide in 2030. In 2004 the World Health Organization, WHO estimated 64 million people to suffer from COPD.

The definition of COPD according to Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, GOLD. “Chronic Obstructive Pulmonary Disease (COPD) is a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients” (47).

It is the combination of obstructive bronchiolitis and emphysema that leads to airflow limitation and the loss of elasticity of the lung parenchyma. Cigarette smoking is considered to be one of the greatest risk factors for COPD. In developing countries, there may be other risk factors such as passive smoking, occupational exposures and indoor pollutions caused by of house holding (48). The COPD diagnosis is determined from the symptoms of chronic cough, dyspnea, increased sputum production and exposure to risk factors. Lung function tests showing FEV₁/FVC less than 70% after bronchodilator inhalation confirm the diagnosis. The COPD grading of severity includes four stages, mild, moderate, severe and very severe and is based on post bronchi dilator FEV₁ measurements (47).

Smoking cessation, with or without pharmacy therapy is thought to be of great importance in preventing the progress of COPD (49). The pharmacological treatment is aimed to ease the symptoms and reduce the frequency of exacerbations in COPD. It is usually administrated as inhalations of aerosols and dry powder or as nebulized drugs. The recommendations contain short and long acting β_2 agonists and short- and long acting anti cholinergic drugs and cortisone, either as single use or in combination with long acting β_2 agonists (50). The most common comorbidities of COPD are heart disease, osteoporosis and depression (51).

Non-pharmacological treatment as in physical therapy is addressed in subchapter 1.5.

1.4.2 Asthma

According to the WHO, 235 million people suffer from asthma. It is considered under-diagnosed and under-treated and it is the most common chronic disease among children.

The Global Initiative for Asthma, GINA defines asthma “Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction within the lungs that is often reversible either spontaneously or with treatment” (52).

The asthma diagnosis is set in a combination of the clinical symptoms, measurement of lung function including reversibility to β_2 agonists and variability over time (53). In cases of normal or close to normal lung function values, in spite of the clinical symptoms, test and measurements of airway responsiveness are required (52).

The pharmacological treatment in asthma is a stepwise approach aimed to gain and maintain control of the airway reactions and symptoms in asthma (54). It is mainly administrated as inhalations of aerosols, dry powder and as nebulised drugs. Most common are inhaled cortisone, short and long acting β_2 agonists and cortisone, Leukotriene modifier and allergen specific immunotherapy treatment as tablets or injections (54).

Asthma and COPD are chronic diseases and requires a lifetime of expensive medication on a daily basis and affect everyday life both physically and mentally (55, 56). In this perspective it is most important to be able to distinguish between different airway symptoms and the more medically treatable airway diagnoses.

1.4.3 Dysfunctional Breathing Disorder, DBD

Breathing disorders or DBD can be considered as conditions where different breathing and airway related symptoms such as heavy breathing, breathlessness or cough are described by the patient,

sometimes without detectable physiological causes or established diagnoses (57, 58). The mechanism in breathing disorders is suggested to be physiological, psychological and biochemical and the assumption is that these components interact (59, 60).

In the investigation of symptoms, lung function tests are often within normal levels and specific asthma tests are negative. The patients have none or very little relief with asthma medication in terms of β_2 agonists (61, 62).

Löwhagen et al and Ringsberg et al early described a group of patients with asthma-like symptoms where asthma tests were negative and asthma medication did not help (63, 64). This group of patients has a close connection to DBD.

In studies where the outcome of the hyperventilation screening Nijmegen questionnaire, has been positive, symptoms of hyperventilation has been interpreted as, or part of DBD (57). In other studies, patients with breathing related symptoms did not show any correlation between symptoms and hypocapnea (60, 65).

However, dysfunctional breathing is also described to be a part of diagnosed asthma (66), where shallow and frequency increased breathing remains even after successful medical treatment of the asthmatic obstruction. Independent of severity, patients with persistent asthma were found to suffer from chronic pain and muscular dysfunction in terms of mobility and flexibility of the chest wall, spine and shoulders (67). Changes in breathing pattern in patients with severe COPD seemed to be determined by a decrease in inspiratory muscle loading in relation to the strength of these muscles (68). Using inductive pletysmography to measure breathing patterns, Tobin et al found that patients suffering from COPD showed ribcage/abdominal movement asynchronies, besides higher breathing frequency and shortness of inspiratory time (69). DBD in terms of respiratory movement dysfunction or altered thoracic mobility is described as a consequence of ankylosing spondylitis and as a consequence of thoracic surgical procedures (70-72) but as also being seen in patients without any pathological explanation for their breathing symptom (57, 65).

1.4.4 Hyperventilation

Hyperventilation is the result of increased ventilation above normal depth and/or rate, causing lowered CO₂ in exhaled air (end-tidal CO₂) or if invasively measured as pressure of CO₂ in arterial blood (PCO₂). Hypocapnea is considered when PCO₂ is below 4.5 kPa and blood Ph rises above 7.45kPa (73). Acute hyperventilation, respiratory alkalosis causes a variety of somatic symptoms such as feeling of breathlessness, peripheral tingling and numbness, dizziness and tiredness (59). Schleifer et al used a theoretical frame work to show how the sympathetic dominance increased by respiratory alkalosis, and how it lead to a increased muscle tone, parasthesia and reactions in breathing in depth and rate (74). Hyperventilation can be assessed with the Nijmegen questionnaire were 16 symptoms associated with disordered breathing are assessed on a five point scale (75). The Nijmegen questionnaire has however not yet been validated in Swedish.

1.4.5 Vocal Cord Dysfunction, VCD

Paradoxical vocal fold movement (PVFM) usually referred to as VCD is a laryngeal disorder that affects respiratory functions ranging from mild breathlessness to severe respiratory distress (76). It is a condition in which the vocal cords involuntary close during the phase of inspiration instead of opening at the same time making the characteristic sound of stridor or laryngeal wheeze (6). VCD is induced by a variety of reported triggers including cough, eating, laughing and singing but also strong scents, air pollution and physical exertion and emotional stressors are also reported (6). Young, physically active and ambitious women are over represented in reporting this problem and are often mistaken for having asthma (77). The diagnosis is set by fiber optic laryngoscopy that enables visualization in real-time, before, during and after exercise. During symptom, the flow volume curve may show an inspiratory flow limitation. Treatment is usually a combination of information, speech therapy and breathing exercises; in some cases anti cholinergic drugs for inhalation or hypnosis have been successful (78, 79).

1.4.6 Multiple Chemical Sensitivity, MCS

MCS is an acquired condition in which symptoms emerge from a multiple organ system after exposure to household and environmental chemicals. In 1987, Dr. Mark Cullen defined the condition in seven points according to its major features: MCS is an acquired disorder characterized by recurrent symptoms referable to multiple organ systems. These symptoms occur in response to demonstrable exposure to chemically unrelated compounds at doses far below those known to cause harmful effects in the general population. No single widely accepted test of physiological function has been shown to correlate with MCS symptoms (8). This general definition of MCS may cover a number of conditions in patients with various symptoms and undiagnosed disorders. When the prevalence of MCS was investigated by telephone, Caress and Steinemann found that MCS affects 13-15% of the population in the west eastern part of the US (80). Some patients with SHR could also be diagnosed with MCS although the MCS syndrome does not necessarily includes airway symptoms (81). Holst et al also showed that patients with MCS and lower airway symptoms had increased capsaicin cough sensitivity (82). These patients were furthermore shown to have higher capsaicin evoked pain intensity compared with controls (83), suggesting facilitated central sensitization in MCS (84). Immunological deficit may be an explanation for the condition, but others name a neurogenic inflammation as a plausible explanation (85, 86). Other authors suggest MCS to be caused by psychiatric disorders or being a consequence of psychological factors (87). The many numbers of theories indicate that as yet, no clear mechanism is recognized to cause MCS.

1.5 Physical therapy treatment

In the definition of physical therapy given by the World Confederation of Physical Therapy (WCPT), functional movement is considered central to what it means to be healthy. Physical therapy includes developing, maintaining and restoring maximum movement and functional ability throughout the lifespan. This includes providing services in circumstances where movement and function are threatened by ageing, injury, diseases, disorders, conditions or environmental factors (10).

There are evidence base for physical therapy treatment in relation to a variety of airway diseases and conditions associated with breathing difficulties (88). Physical therapy treatment may include education, body posture and physical fitness. Also restoration of appropriate lung volumes after surgery, different airway clearance techniques, but also muscular flexibility, relaxation and breathing re-training may be included in the physical therapy approach (58, 89-92).

In international guidelines, physical therapy is considered to be one of the most important parts of the multidisciplinary treatment for patients suffering from COPD (47, 93, 94). When investigating the effectiveness of pulmonary rehabilitation without the limitations due to prior selection of participants, Hogg et al found “in real life results” that confirmed those of clinical trials (95). Individualized physical activity programs aim to increase tolerance for exercise and decrease the symptoms of dyspnea in COPD and may include a variety of interventions depending on the individual needs, conditions and the severity of COPD (93, 96). Yoshimi et al evaluated a comprehensive multidisciplinary rehabilitation program including patients with mainly severe or very severe COPD. The results showed an improvement in HRQL, walking distance and several lung function parameters including pressure maximum of inspiration and expiration (97).

In asthma treatment today, the physical therapy is primarily considered when individually needed and asked for. The modern pharmacotherapy treatment of asthma, including regularly inhaled corticoids and long acting β_2 agonists, has made patients with mild to moderate asthma more independent and self regulating in daily life. In their latest treatment recommendations, GINA guidelines put emphasis on the patient and doctor relationship (54). With regard to severe asthma or difficult to treat asthma where there is a persistently decreased physical

activity and lung function values, physical therapy is considered beneficial in terms of individually devised breathing exercises, physical training program and, when required, airway clearance techniques (89, 98-100). When comparing physical therapy in asthma in terms of breathing retraining and education, Tomas et al showed a long term positive effect in terms of anxiety, depression and hyperventilation (98). In 2008 Stanton et al could not reproduce the data on hyperventilation in their study comprising 102 patients with asthma (101).

Hagman et al found improvement regarding hyperventilation symptoms, HRQL and a decrease in emergency room visit in a five year follow up in patients with DBD, after information, advising and breathing re-training (58). Patel et al evaluated a cough suppression physical therapy treatment effect in a group of patients with chronic refractory cough. The physical therapy consisted of education, counselling, cough control, breathing retraining and vocal hygiene. The patients improved with respect to a reduction in cough frequency, sleep disturbance and cough specific HRQL (102). There is no ready formula to apply in breathing re-training, it has to be created in relation to diagnose and disability of the patients involved, as well as the patients experience and the purpose of the treatment.

The flexibility and relaxation treatment is aimed to ease the consequences of the biomechanical changes in the chest that occurs during disordered breathing (67). The objectives in a flexibility program are to increase range of motion in the major muscle tendons and various types of exercises focusing on flexibility can improve range of movement. Slow paced movements, repeated at least two to four times during three to twelve weeks are recommended (103).

The physiological reaction to relaxation treatment is believed to be reduced sympathetic arousal, general tension and anxiety (104). In 2003 Arntsz found the effect of relaxation therapy to be equivalent to cognitive therapy in generalized anxiety disorder (GAD) (105) and in 2007 authors Siev and Chambless confirmed these results (106).

Increased breathing frequency, lowered chest mobility and respiratory movements can be interpreted as a result of the vicious circle of dyspnea described by Manning and the physiological reactions that follow (1). This circle can be started by a disease with an established

diagnose or by a disordered breathing by a variety of physiological and psychological causes (59, 91).

2 AIM OF THESIS

The overall aim of this thesis was to elucidate different aspects of the subjective symptoms and reactions, from the airways and the chest, for which SHR patients seek medical attention. The aim was to examine and analyze airway reactions to exercise in cold air and dry air and the impact of these provocations on capsaicin cough sensitivity. A further aim was to study the influence on reported airway and chest symptoms in terms of chest mobility, respiratory motion and muscle pain and to evaluate a physiotherapeutic training program in patients with SHR.

1. To study induced symptoms, physiological parameters and capsaicin cough sensitivity after exercise in cold air in patients diagnosed with SHR (I).
2. To study induced symptoms, physiological parameters and capsaicin cough sensitivity after EVH test in patients with chronic cough and SHR (II).
3. To study chest mobility, respiratory movement and pain sensitivity in patients diagnosed with SHR compared to patients with asthma, COPD and a group of allegedly healthy control subjects (III).
4. To study the effect of a 12 week physiotherapeutic home based training program in patients diagnosed with SHR (IV).

3 PATIENTS AND METHODS

This thesis is based on four studies using different methodologies, aimed at addressing aspects that would broaden the understanding and knowledge of airway SHR and its consequences for the affected patients. The studies are listed in table 1.

Table 1. Research design overview

Study	I	II	III	IV
Aim To study	Induced symptoms, physiological parameters and cough sensitivity in patients with SHR, after exercise in cold air	Induced symptoms, physiological parameters and cough sensitivity in patients with chronic cough and SHR, after EVH test	Chest mobility, respiratory movement and pain sensitivity in patients with SHR, compared to patients with asthma, COPD and healthy control subjects	The effect of a 12 week home based RPT training program in patients with SHR
Design	Controlled clinical trial	Randomized controlled trial	Cross sectional study	Cross over randomized clinical trial
Setting	Sahlgrenska University Hospital	Sahlgrenska University Hospital	Sahlgrenska University Hospital	Sahlgrenska University Hospital
Data collection	Exercise provocation, inhaled capsaicin provocation test, lung function tests	EVH- test, inhaled capsaicin provocation test, lung function tests	RMMI, measuring tape, PPT, lung function tests	SF-36 v2 HARQ, symptom score, RMMI, measuring tape, PPT, inhaled capsaicin provocation test, lung function tests
Participants	11 patients suffering from EID and SHR and 11 matched healthy control subjects	14 patients with chronic cough and SHR and 10 matched healthy control subjects	35 patients with SHR, 19 with COPD, 32 with asthma and 28 healthy control subjects	41 patients with SHR randomized into two groups
Analysis	Mann-Whitney <i>U</i> -test, Wilcoxon signed rank test	Mann-Whitney <i>U</i> -test, Wilcoxon signed rank test	Chi -Square test, Kruskal Wallis test, Fisher's Exact test, Mann Whitney <i>U</i> -test	Chi -Square test, Kruskal Wallis test, Fisher's Exact test, Mann Whitney <i>U</i> -test

3.1 Ethics considerations

Informed written consent was obtained from all the participants prior to participation in the studies. They were informed about the possibility to withdraw at any point without giving reason. The Regional Ethical Review Board of Gothenburg approved the research protocols.

3.2 Settings and participants

All studies were carried out at Sahlgrenska University Hospital, Gothenburg, Sweden.

The patients participating in the four studies were diagnosed and treated at the outpatient clinic for asthma and allergology, pulmonary medicine and physiotherapy at Sahlgrenska University Hospital, Gothenburg Sweden.

In studies I, II and III, the control subjects were recruited among hospital workers in healthcare and administration, friends and relatives. They considered themselves healthy, reported no airway symptoms and used no airway related medication. No further medical examination was conducted.

3.2.1 Inclusion criteria Studies I- IV

- Airway symptoms induced by chemicals and scents
- Positive capsaicin inhalation test
- Negative asthma tests
- Negative skin prick test
- Spirometry within normal values
- No bronchial variability or reversibility to β_2 agonists

Study III

- Asthma diagnosis according to international guidelines, medicating as instructed and in habitual status
- COPD diagnosis according to international guidelines, medicating as instructed and in habitual status

3.2.2 Exclusion criteria Studies I- IV

- Cardiac disease
- Gastro esophageal reflux
- Other severe somatic or psychiatric diseases
- Medication with angiotensin– converting enzyme inhibitor
- Smoking
- Inadequate ability to read, write or understand the Swedish language
- Pregnancy
- Scars or injuries on the torso (**III, IV**)

3.3 Study population

Study I: Eleven consecutively included patients, nine females and two men, who experienced exercise induced dyspnea (EID) and previously diagnosed with SHR. Eleven alleged healthy controls, matched by gender and age.

Study II: Fourteen female patients included consecutively and ten alleged healthy controls participated in the study. The patients were previously diagnosed with SHR and fulfilled the criteria for chronic cough.

Study III: Thirty-five patients previously diagnosed with SHR, 32 patients diagnosed with asthma, 19 patients diagnosed with COPD and 28 allegedly healthy control subjects participated in this study.

Study IV: Twenty-six patients with SHR completed this randomized controlled cross over study. The patients were screened from the hospital visiting list of patients that had previously undergone a capsaicin inhalation provocation test. Three-hundred and eighty four were assessed for eligibility. Sixty-one were contacted for information about the study. Forty-one were randomized into the A group to start with 12 weeks of active training or the B group to start with 12 weeks of symptom registration. Intervention flow chart is shown in figure 3.

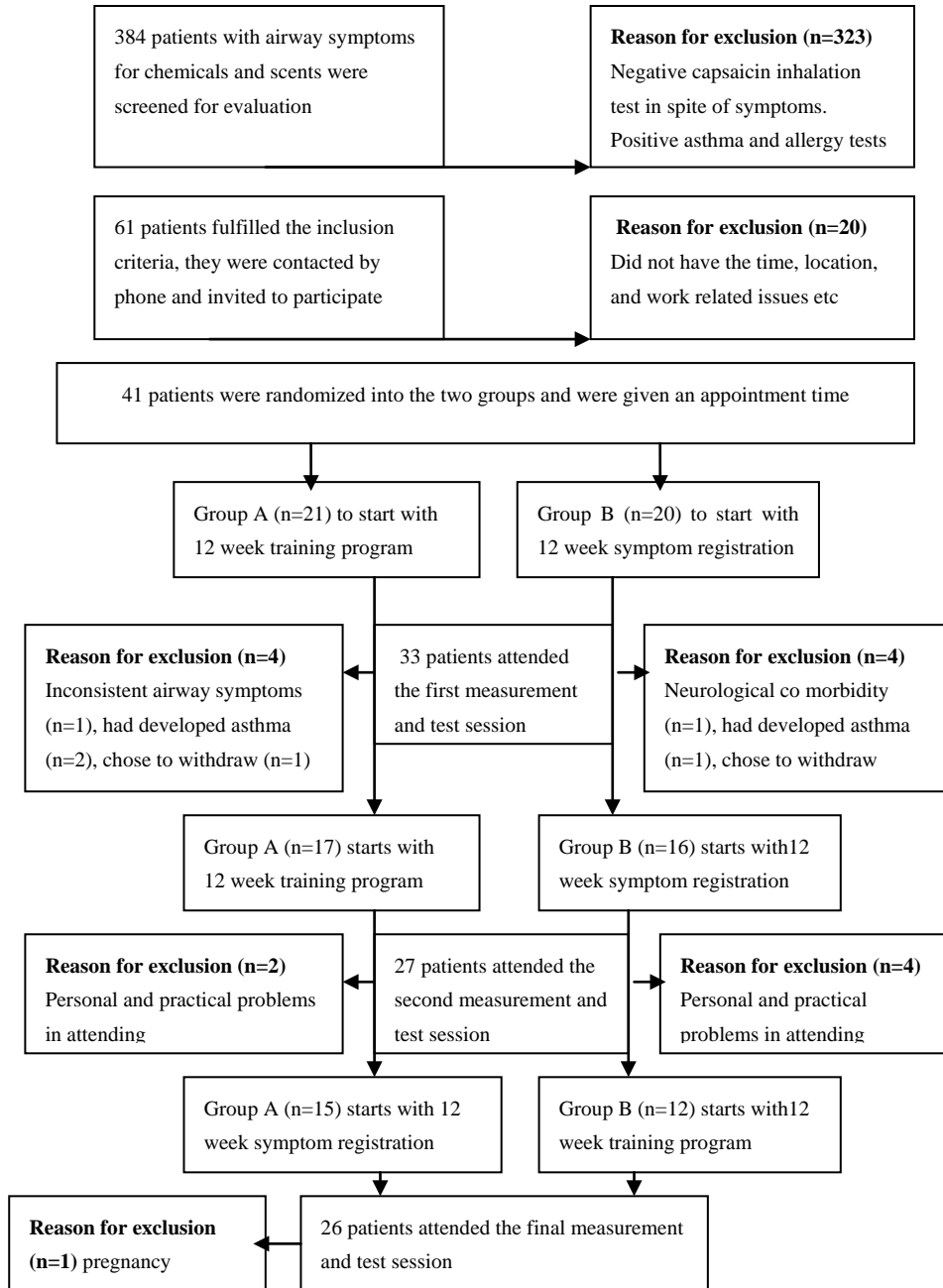


Figure 3. Intervention flow chart of study IV

3.4 Procedure

A study nurse contacted all patients and control subjects in the four studies. They were interviewed by telephone about their present health status, given the information concerning the study and asked to participate.

The provocations and tests were postponed if any participant experienced respiratory infection during the last month.

Study I. The participants, patients and control subjects, visited the hospital twice. An inhaled capsaicin provocation test was performed at each visit, using the tidal breathing method. One of the occasions was preceded by an ergometric bicycle exercise provocation in a cold chamber. A lung function test and airway symptom registration was carried out on each occasion.

Study II. In a randomized order, each patient and control subject visited the clinic on two occasions. On one of the occasions the inhaled capsaicin provocation test was preceded by an EVH test. A lung function test and airway symptom registration was carried out on each occasion.

Study III. One hundred and fourteen participants visited the clinic for physiotherapy on one occasion for measurements of respiratory movements, chest mobility, pressured pain thresholds and lung function.

Study IV. Each patient visited the clinic at three times during the study period of 24 weeks. Measurements of respiratory movements, chest mobility and pressure pain thresholds were carried out each time. They were tested for cough sensitivity using the single breath method for the inhaled capsaicin provocation test. In connection with each visit, the patients filled out two specific questionnaires, CSS-SHR and HARQ and one generic, the SF-36 version 2 questionnaire. The results from the PPT examinations were also compared to healthy controls from a previous study (107). The patients' results from the SF-36version2 were compared to Swedish healthy norm values.

3.4.1 Intervention program (Study IV)

The program consisted of four movement exercises designed to increase the flexibility of the muscles in the chest, one breathing exercise and one relaxation session.

Movement exercise instructions

“These movements are to be performed in a standing position, with knees slightly bent and feet shoulder-width apart. Repeat each movement slowly, preferably in front of a mirror, four to six times a day, once a day” (103).

1. Stretch one arm slightly bent, over the head; let the other hang relaxed by the side of the body. After three seconds, switch arms.
2. Stretch out both arms in front of you, so that the upper back is rounded. Clench both hands and draw your arms backwards with elbows bent, as if rowing a boat.
3. Hug yourself with both arms around the body and crouch. Take a deep breath and hold it for some seconds. Breathe out as you stand up, moving the arms softly backwards.
4. Do swimming strokes with your arms, upwards, to the sides and to the front of you.

Breathing exercise instructions

“Sit leaning forward with your elbows on your knees and with your shoulders and chest relaxed. Take a long breath through your nose; hold it a short time, and exhale normally and not forcefully, through the nose or mouth. Repeat this procedure four to six times, once a day.” This exercise can also be used when acute breathing problems occur in response to contact with environmental irritants.

Relaxation instructions

“At least once a day, take ten minutes to lie down. Loosen your clothes. Think of your body as heavy, and sink into the bed. Picture yourself as warm and soft, calmly accepting the present just as it is (89). “

3.5 Measurements

Table 2. Description of outcome variables used in studies I-IV

Variable	Measures	I	II	III	IV
Affective and behavioral consequences of SHR	CSS-SHR				*
Body Mass Index	Body weight/ body length ²	*		*	*
Capsaicin sensitivity	Cough reaction to capsaicin	*	*		*
Chest mobility	Range of mobility of the chest in cm			*	*
Cold air sensitivity	Airway reaction to cold air	*			
Duration of airway symptoms	Self reported years of airway symptoms from chemicals and scents	*	*		*
End -tidal CO ₂	Carbon dioxide level in expired air	*	*		
EVH	Respiratory consequences of osmotic stimulation of the airways		*		
Exercise challenge	Work load achievement, airway response	*			
Health related quality of life	SF-36 version 2				*
Lung function test, % predicted	Lung function according to gender, age, and body length	*	*	*	*
Pressured Pain Threshold, kPa/s	Measuring and quantifying deep tenderness in muscles			*	*
Pulse rate/min	Heart rate recording per minute	*	*		
Reported evaluation of symptoms related to the chest and oesophagus	HARQ				*
Respiratory movement	Real time bilateral changes in anterior/posterior diameter of the torso			*	*
Respiratory rate/min	Frequency of breathing per minute	*	*	*	*
Symptom score	Self reported upper and lower airway symptoms	*	*		*

3.5.1 Measurement and tests according to body functions

Body Mass Index (Studies I- III- IV)

The BMI (kg/m^2) was calculated as body weight in kilograms divided by body length in square meters.

Chest mobility (Studies III- IV)

Chest mobility was measured, using a measuring tape, as the circumference difference in cm of the chest, after maximal inhalation and maximal exhalation, at the fourth costae (upper chest) (108) and at the process of xiphoideus (lower chest). Thoracic flexion and extension were measured 30cm distally from the seventh cervical vertebrae (109-112).

End- tidal CO₂ (Studies I- II)

End-tidal CO₂ is the amount of CO₂ in expired air. In these studies, this was measured through a mouthpiece with a nose clip, to ensure mouth breathing, using the OSCARoxy Multigas Monitorand Pulse oximeter SCO 123.05.EN, Datex-Ohmeda Division Instrumentatum Corporation, Helsinki Finland.

Lung function tests (Studies I- IV)

Lung function tests such as FEV₁ and FVC were conducted according to guidelines and considered in relation to gender, age and body length, as percent of predicted values (15). In studies **I**, **II** and **III** the Easy One™ nnd Medizintechnik AG, (CH- Zurich, Switzerland) was used. In studies **I** and **II** the Vitalograph, (Buckingham, UK) was also used and in study **IV** the Masterscope spirometer (Masterscope, APS version 5.02 software) was used.

Pulse rate and peripheral oxygen saturation, PSaO₂ (Studies I- II)

Pulse rate was measured at the same time as peripheral oxygen saturation. Using a probe on a finger, the saturation of oxygen as a percent of arterial hemoglobin was measured percutaneously and digitally displayed. The OSCARoxy Multigas Monitorand Pulse oximeter SCO 123.05.EN, Datex-Ohmeda Division Instrumentatum Corporation, Helsinki Finland, was used.

Respiratory movements (Studies III- IV)

The RMMI (ReMo Inc. Keldnaholt, Reykjavik, Iceland) register real-time bilateral changes in the anterior posterior diameter during the upper and lower thoracic and abdominal movements in tidal and deep breathing, as well as the respiratory rate (113, 114). The instrument consists of a mobile rack with six laser diodes (accuracy 0.0003 mm, light precision of 0.2 mm, measuring frequency of 21 Hz. Senix Ultra-U revision B; Senix, Bristol, VT, USA) in three pairs, adjustable to the length of each participant's torso. The diodes were arranged at the level lateral to each individual's armpit folds, xiphoid process and umbilicus. The participants were investigated during tidal breathing for 60 sec and deep breathing for 30 sec in a supine position on a treatment bench, with a small pillow under the head and knees (71, 72, 115). They were instructed to relax and close their eyes during the measurements and during the deep breathing maneuver, to inhale through the nose and exhale through the mouth without breath-holding. The participants were not aware of when during their breathing process the data were collected. The data acquisition system (a NI UCB AD converting unit) converted from analogue to digital signals and transmitted the signals to a PC program. For analysis, all data were manually transferred to an Excel file.

Respiratory rate (Studies I- IV)

In Studies **I** and **II**, respiratory rate per minute was measured with a mouth piece, together with the measurements of end-tidal CO₂, using the OSCARoxy Multigas Monitor and Pulse oximeter SCO 123.05.EN, Datex-Ohmeda Division Instrumentation Corporation, Helsinki Finland. In Studies **III** and **IV** respiratory rate was measured in relation to the registration of the respiratory movements using the RMMI (ReMo Inc., Keldnaholt, Reykjavik, Iceland).

Airway symptom registration (Studies I, II and IV)

Before and after the inhaled capsaicin airway provocation test the participants were asked to register their present subjective upper and lower airway symptoms on a scale of 0 to 3. In accordance with previous studies (7, 20, 21, 116, 117) 11 symptoms were registered: heavy breathing, difficulty getting air, chest weight, phlegm, throat irritation, hoarseness, rhinorrhea, eye irritation, sweating, headache and dizziness. No symptoms = 0, mild symptoms = 1, moderate symptoms = 2 and severe symptoms = 3. In Study **IV** the participants also, once a week, registered their upper and lower airway and chest symptoms in a diary and in addition, if they felt dizzy, were tired or

had a headache. The participants were asked to retrieve the duration of airway symptoms induced by chemicals and scents.

3.5.2 Airway provocations

Inhaled capsaicin airway provocation test; tidal breathing method (Studies I and II)

The inhaled capsaicin airway provocation test was performed in three (I, II, IV) of the four studies. The tidal breathing method was used in the first two studies. This provocation method was developed and is well known and practiced on a daily basis at the outdoor clinic for allergology at Sahlgrenska University Hospital (20, 25). A nebulizer, the Pariboy 36, type 73.0130; Paulritzau Pary-Werk GmbH, Starnberg, Germany was used. The patients were asked to postpone taking any medication at least four hours before the test. Before and after the test the patients were asked to fill in their subjective symptoms in the upper and lower airways on a scale from 0-3 and to perform a lung function test according to guidelines. The provocation started with the inhalation of 1 ml saline to give instruction about and train the inhalation technique. After six minutes of inhalation and four minutes of rest the first concentration, 0.4 μ mol/L capsaicin was introduced followed by 2.0 μ mol/L and 10.0 μ mol/L. The number of coughs induced by a concentration of capsaicin was manually counted. If the patient coughed more than 50 times the provocation was stopped (7, 21, 25).

Inhaled capsaicin airway provocation test, single breath method (Study IV)

The single breath provocation method was used in the fourth study. (82). The Airway Aerosol Provocation System (APS) version 5.02 software, Jaeger (Würzburg, Germany) was used for this test. This method is now recommended by European Respiratory Society, ERS to be used for cough sensitivity provocation in the airways (33). The method evaluates which concentration of capsaicin provokes two (C2), five (C5) or ten (C10) coughs. Doubled concentrations of capsaicin from 0.49 μ mol/L to 500 μ mol/L were given every minute. Pre and post evaluation concerning subjective symptoms and lung function was conducted in the same manner as in the tidal breathing method.

Cold air provocation (Study I)

Cold air exercise provocation was conducted in accordance with international guidelines for exercise challenge testing (118). Each participant was evaluated before and after the test by spirometry, using a ultrasonic spirometer according to guidelines (53). Further, $PSaO_2$, pulse rate, end-tidal CO_2 and respiratory rate were evaluated. Subjective symptoms in the upper and lower airways were evaluated using the 0-3 scale as previously described. The provocation was set up at the Department for Clinical Physiology in a cold chamber controlled for room temperature. An electrified ergometric bicycle (RE 820, Rodby, Södertälje, Sweden) was used inside the chamber the stress loads increased depending on lung function according to MVV. The MVV was calculated as $35 \times FEV_1$ in litres. One investigator was inside the chamber together with the participant, checking status and lung function. The outside investigator increased the stress loads, after instructions from inside the chamber. When the target value of each individual's 50% of MVV was reached, the participants continued to bicycle for another four minutes in order to reach a ventilator steady state (118, 119). In order to ensure breathing through the mouth, the participants wore a nose clip during the test.

Eucapnic Voluntary Hyperventilation (EVH) test (Study II)

The EVH test was developed to identify exercised induced broncho constriction (EIB). The patients are to voluntarily hyperventilate a mix of dry air and 5% compressed carbon dioxide at room temperature for six minutes at a target ventilation of 30 times their individual FEV_1 . The Aiolos Asthma Test for EVH (Aiolos Medicinsk Teknik, Karlstad, Sweden) was used for the test and administered in accordance with international guidelines (120).

3.5.3 Pain provocation (Studies III and IV)

Pain sensitivity was evaluated by pressure pain thresholds (PPT) in order to measure and quantify deep tenderness in muscles. The Somedic algometer (Somedic AB, BOX 194, SE 24222 Hörby, Sweden) was used (121-123). The gun-shaped handle of the algometer creates pressure through a pressure sensitive strain gauge at the tip, connected to a power supply, an amplifier and a display unit. The display shows the actual pressure given (kPa/s), and a scale indicates the rate of pressure to help the examiner to keep the pressure constant. The participants are to alert the examiner when pressure starts to change towards pain, and the pressure immediately ceases.

The mean value of the two tests was registered. The participants were in a seated position and thorough information and instructions preceded the test. Pressure was applied at five bilateral points of the body at two alternately times, two distal points: the distal thumb phalangeal and the gracilis muscle tendon at the inside of the knee and three points at the chest: the costae II, distal of the midst part of the clavicle, the supraspinous muscle and the trapezius muscle's second portion, between the angulus superior at scapulae and the vertebral column.

3.5.4 Questionnaires (Study IV)

CSS- SHR

The CSS-SHR questionnaire was used to quantify the emotional and behavioural consequences of SHR. It is self administrated and consists of 11 statements; their unweighted sum gives a score of 0-54 points where ≥ 43 is set as a diagnostic cut -off value. The CSS-SHR questionnaire is validated and has been shown to have good reproducibility (19, 124).

HARQ

The Hull Airway Reflux Questionnaire, HARQ, was originally developed from the "Reflux Symptom Index" and redesigned to allow analysis of chronic cough (125). Each respondent was asked to evaluate how different symptoms affected their chest and oesophagus during the latest month. The questionnaire is self administrated and consists of 14 items; each item can produce 0-5 points, giving a total score varying from 0-70 points. The upper normal score is set to 13 points. HARQ has been translated into Swedish and is in the process of validation (4).

SF- 36 version 2

The Medical Outcomes Study Short Form 36 questionnaire (SF-36, version 2) is a psychometric and generic instrument. It is self administrated and measures general HRQL. The SF-36 consists of eight domains: physical function (PF), role limitations due to physical problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social function (SF), role limitations due to emotional problems (RE) and mental health (MH). Each domain can generate a score of 0-100, where a higher score is indicates better health. The four physical components (PF, RP, BP and GH) generate the high order category of the physical factor, and PCS and the mental components

(VT, SF, RE and MH) generate the high order category of the mental factor, MCS (126-130).

3.5.1 Statistical analysis

Data were analyzed on a personal computer using StatView5.0.1.0 (SAS Institute, Inc., Cary, NC, USA) and SPSS 13.0 (SPSS, Inc., Chicago, IL, USA); Studies **I-II**. For Studies **III-IV** version 17 of the SPSS software package (SPSS, Inc., Chicago, IL, USA) was used. Results were considered significant at a p value of < 0.05 .

For comparison between continuous and non paired data, the **Mann-Whitney U test** was used. This test is useful when the sample of data is small and the observations are independent and not expected to be normally distributed. The **Wilcoxon signed rank test** was used for continuous and paired data; it is the corresponding test for dependent observations. For pair wise comparison between groups, the **Fisher's exact test** was used for dichotomous variables. For comparison of continuous data between more than two groups, the **Kruskal-Wallis test** was used. This is the non parametric alternative test for one way analysis of variance. The **Chi-Square test** was used for non ordered categorical variables.

Study II

In accordance with dose-response relationships seen in several earlier studies using the same capsaicin provocation model (7, 116, 131, 132), the missing data for those patients whose provocations were halted due to excess coughing were filled in by doubling the number of coughs evoked by 2.0 μ mol/L capsaicin to represent the cough response to 10 μ mol/L capsaicin.

4 RESULTS

The findings from Studies I-IV are presented.

4.1 Study I. Dyspnea from exercise in cold air is not always asthma

The main findings in this study were that exercise provocation in cold air significantly increased capsaicin cough sensitivity ($p < 0.05$) and decreased end-tidal CO₂ ($p < 0.05$), both in comparison to the controls and in comparison to the patients themselves prior to exercise. The patients coughed significantly more than the control group during capsaicin provocation, both without preceding exercise ($p < 0.05$) and with preceding exercise challenge ($p < 0.001$). No significant changes in terms of capsaicin cough sensitivity or end-tidal CO₂ were detected in the healthy control group matched by gender and age (± 7 years).

Exercise Provocation

The 22 participants performed the exercise provocation according to protocol. There were no significant differences in the calculated 50% of the MVV target ventilation between the groups. The mean work load among the patients was lower, 114 ± 25 watts, compared to 165 ± 38 watts among the controls ($p < 0.01$). The mean time of cycling was shorter in the patient group 20 ± 5 minutes as compared to 25 ± 5 minutes in the control group ($p < 0.01$). Directly after the exercise provocation, respiratory and pulse rate were significantly increased in both groups ($p < 0.01$).

The patients coughed more during provocation ($p < 0.05$) and experienced significantly more symptoms in the upper and lower airways than the control group ($p < 0.05$). Heavy breathing, rhinorrhea and throat irritation were the most prominent symptoms. At the subsequent capsaicin provocation, approximately 15 minutes later, these symptoms had ceased.

Inhaled capsaicin airway provocation test

Without the preceding exercise challenge, the patient group and the control group completed the tests with inhaled isotonic saline and the three concentrations of capsaicin 0.4, 2.0 and $10.0 \mu\text{mol/L}$, in

accordance with the original protocol. However, when the test followed the cold air exercise challenge, the concentration of 10.0 μ mol/L capsaicin was discontinued by a considerable part of the patient group due to excessive coughing and the test had to be stopped at the concentration of 2.0 μ mol/L.

Subjective symptoms increased significantly in rhinorrhea ($p < 0.05$), throat irritation ($p < 0.005$), hoarseness ($p < 0.05$) and phlegm ($p < 0.05$) in the patient group after the capsaicin provocation test.

4.2 Study II. Down- regulation of cough sensitivity after eucapnic dry air provocation in chronic idiopathic cough

The findings in this study showed that, after the EVH test, in randomized order and in comparison with healthy control subjects, capsaicin cough sensitivity was decreased in a group of patients with chronic idiopathic cough and SHR ($p < 0.05$). The patients had a general tendency towards a lower end-tidal CO_2 compared to the controls, showing a significant difference before and after the EVH test ($p < 0.05$). The patients also had a higher respiratory rate ($p < 0.01$) after capsaicin provocations.

Eucapnic voluntary hyperventilation test (EVH)

All participants performed the EVH test according to the protocol. There were no differences in the mean target ventilation (85% of MVV) between patients and controls, 66 L/min (95% CI 61–72) and 66 L/min (95% CI 63–70), respectively.

During the six minutes of the EVH test, the patients' mean value of coughs was 18 (95% CI 5–32) which was significantly more ($p < 0.01$) than among the controls, where one subject had three coughs and another had one cough.

In the interim of ten minutes, after the EVH test and before the onset of the capsaicin provocation, the mean number of coughs among the patients was 29 (95% CI 19–39), compared with 12 among the controls (95% CI 0–27) ($p < 0.01$).

Inhaled capsaicin airway provocation test

The results of the two occasions of capsaicin provocation in the patient group are presented in figure 4.

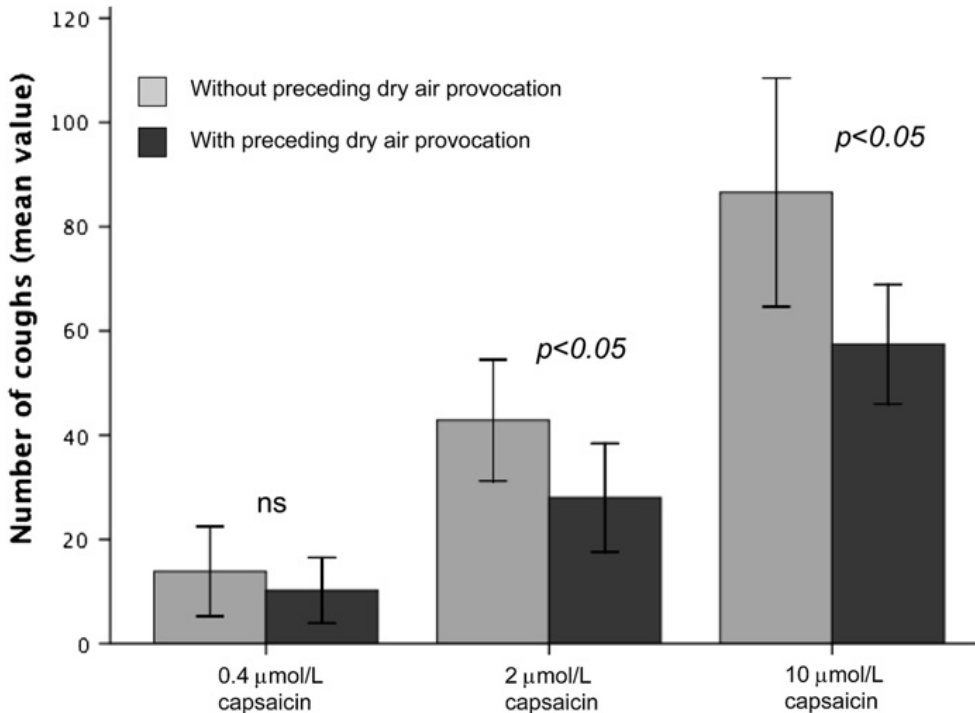


Figure 4. Mean number of coughs ($\pm 95\%$ confidence intervals, CIs) after inhalation of 0.4, 2.0 and 10.0 $\mu\text{mol/L}$ capsaicin in 14 patients with and without a preceding EVH test

At the capsaicin concentration level of 10.0 $\mu\text{mol/L}$, seven of the 14 patients coughed more than 50 times during the tests without a preceding EVH test, and two coughed more than 50 times with a preceding EVH test; the capsaicin provocation was stopped in all these cases.

The mean number of coughs in the control group was 0 without or with a preceding EVH test at the concentration of 0.4 $\mu\text{mol/L}$ capsaicin. The corresponding values for the concentration of 2.0 $\mu\text{mol/L}$ capsaicin were 9 (95% CI 5–14) and 9 (95% CI 4–15) respectively (ns), and those for 10.0 $\mu\text{mol/L}$ capsaicin were 22 (95% CI 12–32) and 27 (95% CI 15–39) respectively (ns).

4.3 Study III. Respiratory movement and pain thresholds in airway environmental sensitivity, asthma and COPD

The main findings of this study were that the respiratory rate was significantly increased and that chest mobility and breathing movement were impaired in patients with SHR and COPD but not in patients with asthma, compared to a group of allegedly healthy control subjects. The patients with SHR appeared, besides lung function, to have the greatest similarities with the group of patients suffering from COPD, comprising mainly patients who were severely or very severely affected by COPD. Furthermore, all three patient groups had increased sensitivity to pain as assessed by pressure algometry.

Chest mobility

The patients with COPD had lower chest expansion ability than the other three groups ($p < 0.0005$), whereas the patients with SHR had reduced values compared with the control subjects ($p < 0.05$). The patients diagnosed with COPD also had lower thoracic flexion values compared with the group of patients with asthma ($p < 0.05$) and the controls ($p < 0.05$) as well as lower thoracic extension ability compared with control subjects ($p < 0.05$). In the group of control subjects, the results of chest mobility regarding expansion, thoracic flexion and extension were within Swedish reference values (112).

Respiratory rate

The patients with SHR and COPD had a higher respiratory rate at rest than those with asthma and the control subjects ($p < 0.001$), whereas the SHR and COPD groups did not differ from each other.

Respiratory movement

During quiet breathing, values of lower thoracic and abdominal respiratory movements were lowered in the group of patients with SHR compared to patients with asthma ($p < 0.05$) and COPD and ($p < 0.005$). Compared to the control subjects, the patients with COPD had elevated values of lower thoracic and abdominal movement during quiet breathing ($p < 0.05$). During deep breathing, the abdominal movement values were lower in the patients with SHR compared to patients with asthma and control subjects ($p < 0.001$) whereas in the group of patients with COPD, the abdominal and lower thoracic movement values were lower than in the control group ($p < 0.05$).

Pain sensitivity

The pain pressure thresholds at central points were lower in all three patient groups compared with the control subjects, Costa II ($p < 0.05$) m. supraspinatus ($p < 0.005$) and m. trapezius ($p < 0.005$), the pain threshold in the SHR group was also lower at m. Gracili's tendon ($p < 0.01$) compared to the controls.

4.4 Study IV. Physical therapy treatment of impaired chest mobility and respiratory movement in patients with airway environmental sensitivity

The main findings of this randomized, controlled cross over study were that in patients with SHR, chest mobility ($p < 0.001$) and upper thoracic respiratory movements ($p < 0.01$) improved after practising a physiotherapeutic home based training program, including breathing instructions for 12 weeks. Capsaicin cough sensitivity with respect to C2 decreased (improved) after the training period ($p < 0.01$). The symptom of chest pressure as reported before and after the capsaicin provocation test decreased after the training period ($p < 0.05$). The pressure pain thresholds, measured with algometry and compared to healthy control subjects, were lowered in four out of five tested pressure points ($p < 0.001$).

From the originally randomized 41 patients, 33 were included in the study. Another eight patients were lost, seven after the first and initial measurement and test session, mainly depending on practical problems the patients had in attending the study. One patient in group A was lost after having completed the training period and begun the symptom registration period because of pregnancy and did not attend her last planned visit (after 24 weeks). This left 27/26 included patients and 14 lost subjects for the analyses (Figure 3, Chapter 3).

Demographics

There were no demographic differences between the two groups according to gender, age or years of airway symptoms caused by chemicals and scents. Neither did the lung function values of FEV₁ or FVC differ.

Questionnaires

Assessed by the CSS-SHR, the HARQ and the SF-36 version 2, there were no significant differences in or between the groups on any measurement occasion throughout the study. Both groups exceeded the score limit for CSS-SHR ≥ 43 points, set for the diagnosis of SHR. In relation to HARQ both groups exceeded the score limit of 13 points. When the patients were matched to the SF-36 version 2 norm values in a healthy Swedish population for gender and age, values were

significantly lower regarding “Role Limitations Due To Physical Health”, RP ($p < 0.05$) and “Role Limitations Due To Emotional Problems” RE ($p < 0.01$).

5 DISCUSSION

The four studies included in this thesis revealed new findings in SHR, never described before. It confirmed the subjective symptoms reported by the patients suffering from SHR.

In the first study **I**, exercise in cold air provoked cough and other airway symptoms and increased the capsaicin cough sensitivity after the exercise provocation, whereas in the second study **II** dry air provocation down-regulated this sensitivity. Further these studies indicated that the patients had an easy evoked hyperventilation followed by lowered end-tidal CO₂. The lung function measured as FEV₁ and FVC was not influenced. In the following two studies **III** and **IV**, the patients showed reduced chest mobility and respiratory movement and also increased pain sensitivity. Even patients with asthma and COPD had lowered pain sensitivity thresholds compared to allegedly healthy controls. After a tailored physiotherapeutic intervention in the SHR patients, there was a pronounced improvement in chest mobility and chest symptoms and the capsaicin cough sensitivity also improved.

5.1.1 General discussion

The findings in the first article of this thesis confirmed the reported symptoms and, after the exercise provocation, also showed increased capsaicin cough sensitivity, known to mirror the activity of the airway sensory nerves. This reaction is quite different from the bronchial constriction in asthma induced by exercise via heat and water loss (133). Since exercise induced airway symptoms are cardinal signs of asthma reports of this kind made by patients with SHR often lead to an incorrect asthma diagnosis, commonly followed by extensive medication (64). The current findings emphasize the importance of correct diagnostic methods in patients with airway symptoms and that the asthma diagnosis should be properly confirmed before any medication is given on a regular basis. It has been shown that the over diagnosing of asthma can be substantial and even dangerous (134, 135).

Most patients diagnosed with asthma experience bronchoconstriction and dyspnea in relation to physical exertion and exercise, especially in a cold climate if the provocation is intensive enough (120). The

asthmatic inflammation is characterized by hyper responsiveness to indirect stimuli such as osmotic changes and direct stimuli such as methacholine (136). Hyperventilation due to an increased respiratory rate and volume during exercise is followed by dehydration and cooling of the airway. This releases inflammatory mediators, airway smooth muscles contract and airways narrow in constriction (133).

It is well established that individuals complaining of airway sensory irritation do not have an allergic IgE mediated reaction towards perfume or other irritating substances, though the symptoms can be misinterpreted as allergy and asthma (137). The relation between asthma and SHR is not always clear; the diseases may overlap each other and some patients may have both conditions (29). Capsaicin cough sensitivity is normal in patients with asthma treated with inhaled steroids, but the sensitivity increased when the asthmatic inflammation was untreated (7, 24, 138). Further, during the pollen season the capsaicin cough sensitivity increased in asthma patients with pollen allergy (139). An active asthmatic inflammation seems to augment the capsaicin cough sensitivity, although not to the same degree as is found in SHR.

Reduced lung function in several pulmonary diseases may cause increased EID compared to healthy subjects. However, there remain many “apparently healthy” patients without asthma or reduced lung function that complain of EID and some of them are likely to have SHR. Löwhagen et al carried out a maximum exercise test among a mixed group of patients with a history of exercise induced respiratory symptoms in order to reveal reasons for discontinuing the test. The authors found that reasons for ceasing physical exercise, besides bronchoconstriction, could be chest pain or discomfort as well as hyperventilation symptoms such as dizziness and palpitations (64). This indicates a breathing dysfunction followed by hyperventilation and lowered CO₂ in line with the findings in this thesis.

The somewhat contradicting findings after exercise in cold air and after the EVH test suggest that hyperreactive cough reflexes from capsaicin are probably also linked to increased reactivity in osmo-sensitive, TRP channels, and there may be an interplay between the different TRP channels and their respective stimuli. The cold air reactions may indicate an up-regulation of the cold-sensing TRPM8, however these results could not be transferable to the more pure osmotic stimulation of an EVH test probably reacting via the osmo-

sensitive TRPV4. In accordance with the present findings others have shown in animals and healthy subjects that cough sensitivity was down-regulated after hyperpnoea (140-143).

In accordance with the present results Ringsberg and Akerlind also showed that when patients with asthma-like symptoms but no verified bronchial constriction were provoked with hyperventilation to reach a certain level of end-tidal CO₂, they recovered more slowly than both patients with asthma and healthy subjects (144). In 1938 Dr AL Banyai described the benefits of inhaled CO₂ in the treatment of pulmonary tuberculosis (145). In a recent published article El Mays et al showed that in rats, bronchial smooth muscles relaxed under the influence of CO₂ (146). Changes in the CO₂ ventilatory drive can modify reflex responses to airway irritation in anesthetized patients, an increase in CO₂ ventilatory drive and hyperpnoea decreased the degree of reflex responses to irritating stimuli (147, 148). In the EVH test used in these thesis, the dry gas includes 20.1% O₂ and 4.98% CO₂ balanced N₂. CO₂ has earlier been shown to reduce the incidence and severity of airway related problems including cough during anaesthesia (149) and this may be part of the explanation for the cough down-regulation after the EVH test. It is a future challenge to test patients suffering from SHR with dry air provocations including different amounts of added CO₂.

Abdominal movement during deep breathing was impaired both in SHR and COPD and this may indicate the need of physiotherapeutic intervention. Although there was a discrepancy in age with the COPD group being older, the younger group of SHR patients was comparable in several ways with the patients who had mainly severe or very severe COPD, illustrating the advanced dysfunction of breathing in SHR. Asynchrony in thoracic and abdominal movements in COPD has earlier been shown using plethysmography (69) and recently by Aliverti et al, using a kinematic optoelectronic plethysmography (150).

All three patient groups had increased pain sensitivity that might seem surprising, at least in patients with well treated and controlled asthma, this is a reminder that airway symptoms often are one expression of a systemic disease. The present finding of augmented pain sensitivity may show a resemblance to fibromyalgia but was in none of the patient groups expressed as a major problem and was also discreet compared to values of pain pressure values in patients with fibromyalgia (151).

Numerous conditions are characterized by breathing problems and symptoms. Some of them have evident organ specific diagnoses with criteria and limits set for the disease and with obvious pathophysiological findings. Others have normal tests with the diagnostic techniques available today, but many patients are seeking medical care for symptoms often being classified, as “functional” without any specific pathological findings (63). A commonly raised question regarding the mechanisms behind SHR is whether they are dependent on increased vulnerability to stress. Several studies have shown that the patients suffering from SHR have impaired HRQL (21, 152) and behavioural and social consequences (19) and a link to psychological vulnerability seems natural to explore. Johansson et al did however not find any significant indication that the condition of SHR was related to either depression or anxiety (29).

Breathing symptoms can have a physiological, mechanical or psychological cause and may be the first sign that all is not well in the body, integration with the respiratory, neurological and musculoskeletal system must be of consideration. Some authors mean that for this reason the patients’ breathing function should be given attention in all physical therapy treatments (90). Physical therapy has a long tradition and thorough experience for use in the treatment of breathing disorders of several different causes. The role of physical therapy is given in conditions such as asthma and COPD and there is a great deal of expert knowledge about the best way to train and treat patients (88). The breathing pattern found in patients with SHR indicated a potential for improvement after training and instructions, which was proved in the last study in this thesis. Improvement in chest mobility after physical therapy intervention has also been shown in other studies where decreased chest mobility was caused by ankylosing spondylitis (153, 154).

However, patients without a well-known diagnosis are also referred to the physiotherapist for breathing re-training and/or respiratory movements and relaxation (58, 90). The amount of patients where the health care establishment does not manage to find a specific diagnosis seems to increase though the epidemiology for this group is uncertain and physical therapy is often the only existent treatment alternative. Breathing disorder is a functional diagnosis, referring to the impairment in the function of the breathing process, this impairment can occur regardless of diagnosis. However, to work without an evident explanation is a challenge in the clinic and the need to study

and to collect basic physiological data about treatment strategies is evident. From a physiotherapeutic point of view the name of the diagnosis often is of minor importance, instead we focus on the patient's functional status in relation to the diagnosis and the patient's individual experiences (90).

5.1.2 Gender perspective

Symptoms of SHR occur mainly in women and research in diseases linked to females has traditionally met with less interest than other conditions. Gender differences in sensitivity to chemicals and scents have been reported in several studies with a predominance of women (3, 155, 156). The reason for this difference is poorly understood, and little is known about differences between men and women in their description of symptoms, HRQL, coping strategies and sense of coherence. The possibility of women having a more developed sensory nervous system must be considered, e.g. women are known to have a superior sense of olfaction compared to men (157).

Hormonal factors may also play a role but epidemiological data on SHR did not show any discrepancies between different age strata neither in women nor in men (3). If levels of oestrogen have an influence on SHR symptoms, older women should be more vulnerable than younger. However, symptoms of SHR occur mainly in women. Surprisingly little, if any, attention has been given to the gender aspects in this condition as is the case for many other conditions mainly afflicting women. The symptoms have often been regarded as diffuse, hard to understand and probably due to some psychological causes. The female patients are well aware of this attitude and describe a difficult situation in the health care system and very little understanding from health care professionals (28). Since no objective test method in the diagnostics of patients with SHR has been available until till the last few years, it has been easy to ignore this group of patients. From the female perspective, it is important that the ongoing research can be developed in further projects.

5.1.3 Treatment

There is a lack of effective pharmacological treatment of SHR, as concerns both the chronic cough and other breathing and airway symptoms. Most patients who have visited an allergy or cough clinic have gotten different kinds of medications such as antihistamines, β_2 -

agonists, anticholinergics nasal steroids, and inhaled corticosteroids, without satisfying outcomes.

Cognitive training may improve the condition in some patients but there is a need of scientific study in this area to evaluate the effects (158). This question has been extensively discussed in MCS (87) but cognitive therapy did not prove to give significant differences in effect measures in a group of patients with MCS (158). In asthma, an optimal treatment of the inflammation appears necessary for several reasons, but there is a neglected risk of overmedication with, for example β_2 -agonists and inhaled steroids, which, while they may not be very harmful, lack a credible effect in SHR and are costly.

Ryan et al showed in 2010 that speech language pathology management could improve cough sensitivity to capsaicin, and cough related quality of life in chronic refractory cough (79) and in a cough suppression physical therapy intervention Patel et al evaluated a group of patients with chronic cough and found significant improvement according to cough frequency and sleep disturbance (102).

Recent findings indicate that specific TRPV1 antagonists can be useful in treating disorders such as pain, chronic cough, and irritable bowel syndrome (159, 160). New compounds, antagonists, and blockers of different receptors are currently under clinical development and may increase the therapeutic possibilities (161).

5.1.4 Patient and healthy subject selection

All patients were recruited from the specialized allergy outpatient clinic at the Sahlgrenska University Hospital in Gothenburg. Patients attending this hospital clinic may represent a more selected group of participants in terms of severity of disease. The healthy controls in Studies **I**, **II** and **III** were hospital staff recruited from health care workers in a variety of professions as well as workers in administration and friends and relatives. The exclusion criteria are off course narrowing the number of participants eligible for participation. Capsaicin sensitivity has been shown to be increased in some groups of asthma and COPD (138, 162, 163) and for that reason it was important to separate the groups in these studies. The majority of patients with SHR in this thesis were women, which is consistent with earlier epidemiological findings.

5.1.5 Methodological considerations

The choice of study design varies in this thesis in order to be able to explore the impact of SHR from different angles. One problem with prospective studies is that strict inclusion- and exclusion criteria often result in small clinical samples; this can be problematic in the sense of drawing generalized conclusions from the results in too small groups. Studies **I**, **II** and **III** therefore included healthy control subjects and they were in study **II** randomized in relation to the test order. This problem became very obvious in study **IV** when we found that a major part of the screened patients (n=323) could not take part in the study and maybe because of the harsh inclusion criteria. The randomized controlled cross over design was an attempt to over-come this problem. However it is important to discriminate the condition of SHR from other airway diagnoses that require pharmacotherapy treatment even if those patients could also be expected to benefit from physical therapy treatment.

The common way to conduct sub maximal exercise provocation tests on a bicycle ergometer is to analyze the cardiac response to the stress load challenge and measure pulse and symptoms using to the BORG scales for rating of perceived exertion (164). Pulse rate, gender and body weight are then used to calculate the individual maximum uptake of oxygen, $\dot{V}O_{2max}$, as well as in relation to ml/kg and minute according to Åstrand (165). In the exercise provocation study, **I**, we wanted to control for provocation of the airways, individually and in both patients and controls. In order to do so we calculated every individual's $FEV_1 \times 35$ to get MVV according to guidelines. Inside the cold chamber, the loads on the bicycle increased stepwise until the participants reached 50% of his or hers MVV. They were then to continue to cycle for four more minutes to reach a load resulting in a ventilator steady state (118, 119). In this first study the controls showed higher mean workload achievement at 50% of MVV. This was expected since the patients had expressed EID and therefore could be expected to be less physically fit. The pulse rate during exercise was not measured since the main focus in this study was the impact on airway reactions resulting from the challenge.

The next study used the EVH test as it was originally developed to provoke and diagnose EIB (120). This test has been found to have good specificity for its purpose and as a surrogate for exercise stress of the airways (166).

Two methods were used in estimating cough sensitivity with capsaicin inhalation provocation, the tidal breathing method and the single-breath, dose-response, threshold method. The diagnosis of SHR was originally assessed using the capsaicin tidal inhalation method to identify patients with SHR and to differentiate this condition from asthma (7, 25, 116). In this test, incremental concentrations of capsaicin are inhaled to induce coughing and limits for the number of coughs in a normal reaction were set (7). This capsaicin inhalation test showed good reproducibility using a simple device for tidal breathing (Pari-Boy or Maxin MA3), and no influence on lung function has been found (7, 25, 116, 167). However, for research purposes, and in clinics with access to more sophisticated nebulizer systems, the single-breath, threshold method may have advantages, giving more specific data on delivered aerosol and being in accordance with ERS guidelines (33). It is today the most commonly used method to measure capsaicin cough sensitivity: Doubled concentrations are given at one-minute intervals to assess the cough thresholds, stating the concentration of capsaicin causing two (C2), five (5) or ten (10) or more coughs during the one-minute period between each dose. Some studies suggest that C5 is the clinically superior value (168), although the tidal breathing method has also proved good long- and short-time repeatability several times (7, 167). Our clinical impression from the new provocation method to assess cough thresholds was that the method was easily managed, could be carried out quickly and caused few symptoms. A disadvantage is, however, that the equipment needed is expensive and requires some expert knowledge.

The RMMI was used to measure movements during tidal and deep breathing manoeuvres in a supine position. This method has been validated and is tested for reliability (113, 114). In our experience this relatively new method of assessing breathing movements was managed without problems and was well tolerated by the patients. Movements of the chest during breathing can also be assessed with a body box or with inductive plethysmography. However, this requires access to a laboratory and it usually measures the patient in a seated position (69).

In study **IV** the mean duration of airway symptoms induced by environmental irritants was 17 years. In this perspective a period of a 12 week physical therapy intervention seems very short especially in relation to any expected effect in daily life and behavioural consequences. Also the size of the study **IV** may be too small to show any differences in the HRQL, HARQ or CSS-SHR questionnaires. It is

important to evaluate these parameters but it probably requires larger samples.

The primary variable in study **IV** was the changes in chest mobility and the power calculation was performed according to that. In this study we also found improvement of cough sensitivity to capsaicin in C2, according to the single-breath, dose-response and threshold method. This could be related to the breathing exercise in the intervention. The C2 represents the first two coughs evoked by a given capsaicin concentration and may be influenced by breathing technique to suppress the initial coughing. This is in accordance with recent findings of speech therapy influencing capsaicin cough sensitivity in patients with chronic cough were reduced laryngeal irritation, resulted in decreased cough sensitivity, decreased urge to cough, and an increased cough threshold (79).

The choice of intervention method was made to reflect the clinical work and corresponds well with the physiotherapeutic approach in airway and breathing associated diseases and disorders (88, 89, 95).

The intervention program was divided into three parts, movement instructions, breathing instruction and relaxation. The program was constructed with the ambition to be easily understood, easy to perform and not to be too time consuming, since we wanted the patients to perform it every day for 12 weeks.

The three parts in the intervention program were not tested for validity and it was not possible to evaluate them separately, this can be considered as a weakness of the study. One can of course discuss if the choice of exercises was the most effective to increase range of motion and decrease the breathing discomfort in relation to other potential movements and exercises. Maybe a program with fewer days of training a week could have shown the same results. This is however the first attempt to create a treatment program for patients with SHR where no other treatment is available and should be viewed from that perspective.

The movements were chosen for to engage the muscles in the torso, the frequency and pace to ensure the major muscular tendon groups to stretch for increased flexibility.

The breathing exercise had the intention to give a feeling of ability to consciously increase inspiratory volume and lower the breathing frequency at the training session but also to be used in any situation of increased airway symptoms. The breath hold part of the exercise was intent to affect the function of the RARs in the airways since they are considered to be responsible for the initiation of the cough reflex.

The relaxation was recommended to 10 minutes a day, the intention was to somewhat decrease any sympathetic arousal, lower pulse rate and breathing frequency but there was of course no way to control that this really happened. During search for literature about relaxation, there were no general recommendations concerning length of sessions to be found, in a review article Öst described treatment with large variations in time, duration and length (169).

The overall impression was that the physical therapy treatment in this study was well tolerated by the patients, they reported performing their training five and six days a week. Several patients also expressed that they wanted to continue with the program after the study had finished.

6 CONCLUSIONS

- Exercise provocation in cold air increased capsaicin cough sensitivity and decreased end-tidal CO₂ without affecting lung function. The induced EID could be associated with an up-regulation of the airway TRPM8 receptors and/or hypocapnea from hyperventilation. The diagnosis of exercise induced asthma should be questioned when there are no signs of bronchoconstriction.
- The EVH test provocations down-regulated the cough sensitivity. This may be due to an up-regulation of the osmo-sensitive TRPV4 receptors in the airway mucosa. It could also be a chemo-sensitive reaction of the ventilator drive to the additional 5% CO₂ in the EVH test.
- Patients diagnosed with SHR had increased breathing frequency, reduced chest mobility and lower respiratory movement compared to both healthy control subjects and to patients with asthma. Except for lung function, the significantly younger group of patients with SHR was comparable in several ways with the group of older patients suffering from severe or very severe COPD. As well patients with asthma, COPD and SHR had significantly lower pain thresholds compared to the healthy controls, indicating a general up-regulation of nociceptors such as TRPV1 and that all three conditions are systemic.
- A physiotherapeutic home based training program increased chest mobility and decreased the subjective feeling of chest pressure after the training period, and the capsaicin cough threshold

for C2 increased (improved) after the intervention period. The results show that regular physical exercise and structural breathing instructions can be used to improve chest mobility and capsaicin cough sensitivity in patients with SHR with indications of dysfunctional breathing.

7 FUTURE PERSPECTIVES

- The impact of hypocapnea in SHR and chronic cough must be further evaluated. It would be interesting to study capsaicin cough sensitivity after inhaled CO₂ without the EVH test, as well as the osmotic reaction without the influence of CO₂. Would warm and humid air in combination with exercise provoke the same reaction as in cold air? Several patients in the clinic describe an improvement in a warm and humid climate. If an up-regulation of the TRPM8 receptors, known to be cold sensitive, is a part of the cold- and exercise induced symptoms in SHR exercise provocations without cold air may not give similar reactions.
- The reaction of down-regulation of capsaicin cough sensitivity after dry air provocation in SHR should be compared to other osmotic stimuli such as Mannitol and hypertonic saline, and preferably compared to both patients with asthma and healthy control subjects. Mannitol is also interesting as a potential sensory stimulus inducing cough, which was shown by Koskela et al. in patients with asthma (170).
- Long term follow-up of the SHR patient-population assessing the effectiveness of physiotherapeutic training and treatment would be of interest. A further interest would be to evaluate any impact on HRQL in such a long-term follow up and to study to what extent the exercised induced symptoms influenced daily activities and HRQL. There is also more work to be done on validating a tailored physiotherapeutic intervention program.
- Designing a study related to exercise for the purpose of increasing VO_{2max} and its impact on capsaicin cough sensitivity is important since patients with SHR showed lower workload achievement compared to healthy controls.

- The home based training program in this thesis was designed to improve chest mobility and respiratory movements. Could this program be developed to more specifically focus on the increased pain sensitivity that was shown in terms of more general muscular training and relaxation? This would be of significance not only for patients with SHR but also for those with asthma and COPD.

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