

REVIEW

# COLD AIR-PROVOKED RESPIRATORY SYMPTOMS: THE MECHANISMS AND MANAGEMENT

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## ABSTRACT

**Objectives.** To describe the mechanisms and management of cold air-provoked respiratory symptoms.

**Study design.** A literature review.

**Methods.** The review includes human epidemiological studies, human and animal experimental studies, as well as human studies about management of the cold air-provoked respiratory symptoms.

**Results.** Cold air is unlikely to be a causal factor initiating respiratory diseases but a symptom trigger. In the present review, the airway responses beyond these symptoms were divided into three types. The short-term responses are those that develop within minutes in response to sudden cooling of the airways. Subjects with asthma or rhinitis are especially prone to these responses. The long-term responses are those that develop in response to repeated and long-standing cooling and drying of the airways, usually in endurance athletes. Finally, there are the physiological, reflex-mediated lower-airway responses to cooling of the skin or upper airways.

**Conclusions.** The mechanisms beyond cold air-provoked respiratory symptoms vary considerably and mainly depend on the individual's susceptibility and the ventilation level during the cold exposure. An understanding of these mechanisms is essential for successful management of the symptoms. (*Int J Circumpolar Health* 2007; 66(2) 91-100 )

**Keywords:** cold climate, signs and symptoms, respiratory, rhinitis, asthma, chronic obstructive pulmonary disease

### INTRODUCTION

Cold air-provoked respiratory symptoms are frequent in countries with a cold climate. Approximately 50% of healthy and allergic subjects report cold air-induced rhinorrhea (“the skier’s nose”) (1,2). In Lapland, the northernmost province of Finland, 10-19% of healthy subjects experience shortness of breath (SOB) during exercise in cold weather, with smoking being an important risk factor (3). The prevalence of such symptoms is markedly higher among subjects with respiratory disorders. In Lapland, 78-82% of asthmatic subjects experience SOB during exercise in cold weather and similar prevalence rates have been reported in Sweden (4). Among subjects with chronic bronchitis living in Lapland, 27-59% experience SOB during exercise in cold weather (3). At present, there are no epidemiological studies about the prevalence of cold air-provoked SOB in subjects with moderately to severe chronic obstructive lung disease (COPD).

Given the high prevalence of breathing difficulties in cold weather, one might assume that obstructive lung diseases might be more common in areas with cold climates compared with areas with more temperate climates. However, this seems not to be the case. Physician-diagnosed asthma is as common in the southernmost part of Finland compared to Lapland (5). Neither do international comparisons support the assumption that asthma would be extraordinarily prevalent in countries with a cold climate (6,7). A study in Canadian Arctic region suggested that cold climate might cause a condition similar to COPD (8), but later studies have shown that differences in COPD prevalence rates mainly reflect smoking habits of the populations investigated (5,9).

Taken together, it seems that cold climate may not be a causal factor initiating lung diseases but a symptom trigger. Therefore, the present review focuses on the various ways that cold ambient air under normobaric conditions may provoke respiratory symptoms. Several physiologic responses to cold air (effects on respiratory rate and mucociliary function, etc.) are not discussed. In this review, adequate clothing and normothermia of the body is assumed. Hypothermia-induced changes in respiratory function have been reviewed elsewhere (10).

### EFFECTS OF COLD AIR ON THE SKIN AND THE AIRWAYS

Cooling of the skin can be enhanced not only by cooling of the ambient air but also by increasing the movement of air across the skin (11). In the airways, the equivalent for wind is hyperpnea; the cooling of the airways is enhanced by increasing the airflow within the airways. Breathing of +20°C air at a minute-ventilation level of 15 l/min decreases the tracheal temperature to 34°C whereas breathing similar air at 100 l/min decreases this temperature to 31°C (12). Therefore, hyperpnea of temperate air shares similar effects to the inhalation of cold air.

The special feature of an airway is that it is lined by a thin layer of liquid, the airway surface fluid (ASL). Hyperpnea of cold air may cause the ASL to evaporate more rapidly than it can be replaced (13,14). This would lead to drying and hypertonicity of the ASL. Of note, the absolute water content of subfreezing air is always near zero regardless of the level of saturation (15). Therefore, while the effect of cold air on the skin is mainly cooling, the effect on the airways is cooling and drying. It

is often impossible to define which one of the two phenomena is the final trigger for various airway responses.

### THE POSSIBLE TRIGGER SITES FOR COLD AIR-PROVOKED AIRWAY RESPONSES

For an adequately clothed person, only the skin on the face is exposed to subfreezing temperatures. Cooling of the facial skin down to 10°C takes place at -5°C ambient temperature with 5 m/s wind (16). At rest and during light exercise, humans preferentially breathe through the nose (17). Even subfreezing air is almost completely saturated and warmed to near body temperature when it has passed the nasal cavity (15,18,19). Therefore, at rest and during light exercise the possible trigger sites for cold air-provoked respiratory symptoms include the facial skin and the nasal mucosa but not the lower airways (20).

Exercise is associated with hyperpnea. A shift from nose to combined nose-and-mouth breathing takes place when the ventilation level exceeds approximately 30 l/min (21). When the ventilation level further increases, incompletely conditioned air can reach the pharynx,

larynx and lower airways (12). Therefore, during heavy exercise the possible trigger sites for cold air-provoked respiratory symptoms include facial skin, nasal mucosa, oral mucosa, pharynx, larynx and the lower airways.

### CLASSIFICATION OF COLD AIR-PROVOKED AIRWAY RESPONSES

In this review, the potentially harmful cold air-provoked airway responses are divided into three types (Table I). The magnitude and nature of the responses depend on the level of ventilation during the exposure, the frequency of the exposure and the susceptibility of the subject.

### COLD AIR-PROVOKED SHORT-TERM RESPONSES

Nasal breathing of cold air induces an engorgement of the venous sinuses in the submucosa (22,23), which leads to congestion, sneezing and, especially, rhinorrhea both in healthy and rhinitic subjects (1,24). However, these responses are greater in subjects with rhinitis than in healthy subjects (25) and greater in subjects with asthma and rhinitis than in subjects with rhinitis alone (26). The cold

**Table I.** Classification of the potentially harmful cold air-provoked airway responses.

Type	Trigger	Response
1. Cold air-provoked short term responses	Nasal breathing of cold air	Rhinorrhea, congestion, sneezing
	Cold air hyperpnea	Bronchoconstriction in asthmatic subjects, cough
2. Cold-air-provoked long term responses	Repeated cold air hyperpnea	Damage of the airway epithelium and changes in airway wall structure and function
3. Cold air-provoked reflex lower airway responses	Cooling of the facial skin	Slight bronchoconstriction
	Cooling of the upper airways	Slight bronchoconstriction (?)

air-provoked nasal congestion is reversed by exercise due to the vasoconstrictor effects of circulating noradrenaline and adrenaline (22). Unfortunately, exercise does not inhibit the cold air-provoked rhinorrhea (1), probably due to the fact that this symptom is partly mediated via a neural reflex which is independent of the state of the venous sinuses (2).

Cold air-provoked nasal symptoms can be effectively treated by nasal decongestants (22), but their long-term use is discouraged. Anticholinergic nasal sprays markedly decrease cold-air-provoked rhinorrhea (1,24,27) but do not affect nasal congestion or sneezing. These drugs are well tolerated even in long-term use and are therefore suitable for cold air-provoked rhinorrhea. The cold air-provoked nasal symptoms are poorly controlled by histamine-1 receptor antagonists (28) and topical corticosteroids (29).

Cold air hyperpnea provokes bronchoconstriction in asthmatic subjects (30), especially in children and young adults (31,32). The pathophysiological mechanism beyond this response has been a matter of considerable debate. Studies about the direct effect of cooling on the airway's smooth muscle have been conflicting (33-37). Certain lower-airway sensory receptors can be sensitive to cold and capable of inducing bronchoconstriction in animals (38,39). Cooling of the lower airways may induce vasoconstriction in the bronchial mucosa, followed by reactive hyperemia and edema, which would narrow the airways after hyperpnea (40,41). Perhaps the most popular hypothesis suggests that cold air hyperpnea leads to hyperosmolarity of the ASL, which induces a mediator release from cells within or along the airway mucosa (42-44). The cells that respond to hyperosmolarity could be the eosinophilic cell or the mast cell and the

mediators may be leukotrienes, prostaglandins and histamine. Importantly, exercise-provoked bronchoconstriction does not induce eosinophilic airway inflammation or non-specific airway hyperresponsiveness in subjects with asthma (45). This finding suggests that regular exercise does not worsen asthma over time.

Cold air hyperpnea-provoked bronchoconstriction can be effectively attenuated by heat- and moisture-retaining masks. These masks may be regarded as the best physiological way to treat this problem: as the user exhales, heat and moisture are trapped within the mask. During the subsequent inhalation, cold air is warmed and humidified as it travels through the mask. These masks are as effective as a pre-treatment with inhaled  $\beta_2$ -adrenergic agonists (46,47), and when combined they virtually abolish the response (46).

Among the various anti-asthma drugs, inhaled  $\beta_2$ -adrenergic agonists (46,48-50), nedocromil sodium (50-52) and leukotriene receptor antagonists (49,53,54) are capable of attenuating cold-air hyperventilation-provoked bronchoconstriction. The histamine-1 receptor antagonists (55,56) and anticholinergic drugs (57) seem to be rather ineffective in this setting. A long-term treatment with inhaled corticosteroids attenuates the response to cold air (58-61), indicating that this response is associated with the degree of asthmatic inflammation in the lower airways.

As inhaled long-acting  $\beta_2$  agonists rapidly lose their protective effect on exercise-provoked asthma when used on a regular basis (62-64), their use may not be advocated in subjects who exercise regularly in cold weather. For those subjects, leukotriene receptor antagonists may be more suitable since they are as effective as long-acting  $\beta_2$  agonists in this setting (49,65)

and do not lose their protective effect when used on a regular basis (63-65). In addition, the response to rescue short-acting  $\beta_2$  agonists after exercise is fully maintained during regular treatment with leukotriene receptor antagonists, which may not be true during treatment with regular  $\beta_2$  agonists (65,66).

Besides bronchoconstriction, cold air hypoventilation also provokes coughing in susceptible persons (48,67). Coughing and bronchoconstriction seem to be independent responses since pre-treatment with salbutamol blocks cold air-provoked bronchoconstriction but has no effect on cold air-provoked coughing (48). One study suggested that inhaled ipratropium bromide might be more effective than salbutamol in relieving cold air-provoked coughing in asthmatic subjects (68).

#### COLD AIR-PROVOKED LONG-TERM RESPONSES

In horses, exercise at cold ambient temperatures induces an increase in epithelial cells in bronchoalveolar lavage fluid (69). Accordingly, in humans, nasal cold air breathing increases the number of epithelial cells in nasal lavage fluid (70). Furthermore, cold exposure induces an increase in bronchoalveolar lavage fluid granulocytes in healthy humans (71). Animal studies have shown that repeated cooling and desiccation of peripheral airways leads to a loss of ciliated epithelium, thickening of the lamina propria with increased concentrations of inflammatory cells, hyperresponsiveness and airway obstruction (72,73). Thus, experimental studies suggest that cooling and drying can damage the airway epithelium and, if repeated, can lead to changes in the airway's wall structure and function. These phenomena

may represent a physiological adaptive response to an abnormal stress on airways (74).

Repeated cooling and drying of the airways are likely to take place in endurance athletes who frequently exercise at elevated ventilation levels. Indeed, a high prevalence of respiratory symptoms and airway hyperresponsiveness has been found in skiers, swimmers and long-distance runners (75). Endobronchial biopsies of elite, competitive skiers demonstrate elevated numbers of clustered lymphocytes, neutrophils and macrophages (76,77). The increased expression of tenascin possibly reflects ongoing healing and repair processes and remodeling of the airways (77). The mucosal cellular infiltrate in the skiers' airways differs from that in asthma, with a greater number of neutrophils and a lesser number of eosinophils, mast cells and macrophages (77). Therefore, the term "ski asthma" (78) should probably be avoided. In this review, the term "athletes' airway disorder" is used.

Recreational skiing was not associated with asthma or respiratory symptoms in a large epidemiological study (3), probably reflecting the lesser intensity of the cold exposures. Also, outdoor work in cold weather seems not to increase the risk of asthma (3). However, there are studies reporting a high prevalence of non-specific respiratory symptoms and airflow limitation among subjects with daily exposure to a cold occupational environment (3,79).

A randomized, double-blind, placebo-controlled study failed to show any benefit from inhaled budesonide on elite skiers' respiratory symptoms and airway hyperresponsiveness (80). In another high quality study, a leukotriene receptor antagonist, montelukast, failed to affect ice hockey players' respiratory symptoms, airway hyperresponsiveness,

sputum inflammatory cell counts and exhaled nitric oxide concentration (81). As these drugs are effective in asthma, these negative studies again highlight the differences in the pathophysiology between athletes' airway disorder and asthma.

A study with competitive swimmers suggested that stopping high-level training decreases airway hyperresponsiveness (82). An experimental study with dogs showed that virtually all structural airway changes induced by repeated dry air challenges vanished after cessation of the challenges (73). Furthermore, a large questionnaire study showed that the prevalence of asthma and other airway disorders in former elite endurance athletes is less than that in controls (83). These findings consistently suggest that stopping the high-level training can reverse the structural and functional abnormalities associated with the athletes' airway disorder.

### COLD AIR-PROVOKED LOWER-AIRWAY REFLEX RESPONSES

It has been known for decades that cooling of the facial skin by ice packs triggers slight bronchoconstriction in humans (84,85). Facial cooling caused by  $-5$  to  $-20^{\circ}\text{C}$  ambient air combined with wind provokes an immediate 3-10 % fall in  $\text{FEV}_1$ , in healthy subjects as well as in subjects with asthma and COPD (16,20,86). Thus, this response can be considered a physiological response to a physiological stimulus. The facial cooling-provoked bronchoconstriction seems to increase with age (87), possibly due to age-related loss of function of the inhibitory muscarinic  $\text{M}_2$  receptors, which has been reported in the human heart (88).

The studies on the effect of nasal cooling

on the lower airways are contradictory. Some investigators have found cooling of the nose to provoke a slight bronchoconstriction (89-91). The magnitude of the increase in airway resistance in response to nasal breathing of cold air was found to be equal between healthy subjects, asthmatic subjects and subjects with COPD (89,92,93). This again highlights the physiological nature of the reflex responses to cold air. However, other investigators have not detected any changes in  $\text{FEV}_1$  in response to nasal breathing of subfreezing air (20,23). This discrepancy may reflect different methods to cool the nose and to measure the bronchoconstriction. The fact that nasal breathing instead of oral breathing strongly diminishes cold air hyperventilation-provoked bronchoconstriction in asthmatic subjects (23,94) suggests that the possible nasal cooling-provoked lower-airway reflex bronchoconstriction is of minor clinical importance.

Cooling of the oral cavity seems not to be capable of provoking bronchoconstriction (89) but cooling of the pharynx and larynx provokes bronchoconstriction in cats (38). The larynx is a densely innervated organ and cold-sensitive receptors have been identified there (95). However, the fact that upper-airway local anesthesia does not attenuate cold air hyperpnea-provoked bronchoconstriction in asthmatic subjects (96) suggests that the possible laryngeal cooling-provoked lower-airway reflex bronchoconstriction is of minor clinical importance.

It seems that the reflex bronchoconstriction provoked by facial or upper-airway cooling is too mild to cause breathing difficulties in a person with near-normal lung function. However, for a subject with severely impaired lung function these responses may be of clin-

ical significance (86). In subjects with moderate to severe COPD, an exercise challenge at  $-20^{\circ}\text{C}$  has been shown to provoke more dyspnea than that at  $24^{\circ}\text{C}$ . This was accompanied by facial cooling-provoked reflex bronchoconstriction and significantly lower exercise capacity at a cold ambient temperature (97).

Animal studies have shown that facial cooling-provoked bronchoconstriction can be prevented by atropine and bilateral vagotomy (98). Human studies have shown that nasal cooling-provoked bronchoconstriction can be prevented by inhalation of ipratropium bromide (93). Thus, these responses are probably mediated through the vagus nerve and the muscarinic receptors (98). Therefore, symptoms secondary to cold air-provoked reflex bronchoconstriction may respond to covering the face and to treatment with inhaled anticholinergic drugs. More studies are needed to confirm these suggestions.

## Conclusions

Cold ambient air is unlikely to be a causal factor initiating lung diseases but a symptom trigger. The mechanisms beyond cold air-provoked respiratory symptoms vary considerably and mainly depend on the individual susceptibility and the ventilation level during the cold exposure. Understanding of these mechanisms is essential for successful management of the symptoms. In future, the role of the cold air-provoked reflex lower-airway responses should be studied in more detail. The mechanisms of cold air-provoked coughing merit investigation. Also, more studies are needed on the prevalence, mechanisms and management of cold air-provoked excessive exercise dyspnea among subjects with COPD.

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