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Role of cooling and drying in hyperventilation induced asthma

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ABSTRACT Respiratory heat loss has been proposed as a mechanism of exercise induced asthma. Whether the predominant stimulus is airway drying or cooling remains unclear. We have measured changes in FEV_1 after isocapnic cold air hyperventilation (CAH) (−23·4° (SD 0·43°) C) and dry ambient air hyperventilation (AAH) (18·7° (0·52°)C) in seven asthmatic patients (mean age 31 (SD 9) years and baseline FEV_1 3·2 (0·9) l) and in seven normal subjects (age 28 (6) years and FEV_1 3·6 (0·7) l). The inspired water content in both cases was 0·3 mg/l air. The rate of respiratory heat exchange per breath was calculated in watts (W) with microcomputer based equipment. Cold air hyperventilation caused a fall in FEV_1 almost twice that of ambient air hyperventilation at each level of ventilation: CAH *v* AAH (% fall) 8·0 (5·1) *v* 3·9 (4·0) at 15 l/min, 11·6 (7·8) *v* 7·0 (4·4) at 30 l/min, and 20·7 (10·9) *v* 12·4 (6·3) at 60 l/min. Identical latent heat loss (evaporative drying) was imposed on the airway during the two challenges. Sensible heat loss (convective cooling) in cold air hyperventilation was 41 W at 15 l/min, 63 W at 30 l/min, and 114 W at 60 l/min; whereas in ambient air hyperventilation the loss was 6, 13, and 23 W respectively. It is concluded that the rate of cooling of the upper airway is the predominant stimulus in hyperventilation induced asthma.

Studies on exercise induced asthma have led to interest in the role of airway drying and airway cooling as mechanisms of bronchoconstriction. Millar and coworkers[1] demonstrated a fall in FEV_1 of 20% from baseline in asthmatic subjects exposed to a −20°C environment for seven minutes. Strauss *et al*[2] increased exercise induced asthma by cold air inhalation and Deal *et al*[3] proposed cooling of the airway mucosa as the predominant stimulus in exercise induced asthma. McFadden *et al*[4] measured air temperatures of 25°C in the large airways during cold air hyperventilation in normal subjects and restated the role of airway cooling in exercise induced asthma. Gilbert *et al*[5] observed similar temperatures in the asthmatic airway during cold air hyperventilation and proposed that rapid airway rewarming after cold air hyperventilation may be important in the onset of bronchoconstriction.

In contrast, Anderson[6] has suggested that airway drying is the predominant stimulus in exercise induced asthma and that this causes a transient increase in the osmolarity of the airway epithelium. It was calculated that ambient air hyperventilation required a greater mass of water to humidify the inspirate than was available from a stationary boundary of water lining the airway down to the seventh generation bronchi. Hahn *et al*[7] exercised subjects breathing air at different temperatures and matched water vapour content. No significant variation in the airway response that followed was reported despite differences in the imposed airway cooling stress.

To examine the contribution of airway drying and cooling in hyperventilation induced bronchoconstriction we have studied the effect of cold air hyperventilation and ambient air hyperventilation using air with the same water content.

Methods

Airway drying and cooling has been measured as a single variable—the rate of respiratory heat exchange (RHE). This is a power index (expressed in watts) and relates to the net work done by the airway in conditioning the inspirate to expiration temperature and water vapour content, at a rate determined by the level of ventilation. The respiratory heat exchange comprises sensible (cooling based) and latent (drying based)

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heat transfers. It is defined in SI units in the equation:

$$RHE = \dot{m}\,[c_p\,(T-T_i) + h_{fg}\,(w_2-w_i)],$$

where $\dot{m}$ = air mass flow rate (kg/s); c_p = specific heat of air (kJ/kg K); T = air temperature; h_{fg} = latent heat of water (kJ/kg); w = water vapour mass (kg_{water}/kg_{air}); i = inspiration; e = expiration. (As defined the respiratory heat exchange will take the unit kilowatts, kW.) Expired air is assumed to be fully saturated with water vapour. It can therefore be computed by knowing only the expired air temperature.

EQUIPMENT

Cold air was produced by pumping room air at 150 l/min through a single stage refrigerent R502 based heat exchanger (Kooltech, ACU-1, Glasgow), which conditioned the inspirate to −23·4° (SD 0·43°) C and 0·3 mg H_2O/l air. Ambient air was produced by redirecting the heat exchanger outlet through a 2·5 m bank of thin walled copper tube mounted on a heated radiator, which yielded air at 18·5° (0·52°) C and 0·3 mg H_2O/l. Throughout the test 5% carbon dioxide was added to the inspirate and subjects remained seated. Air was delivered from the heat exchanger through a vacuum insulated boom 1 m long designed to preserve the low air temperature.

Subjects breathed orally from the conditioned air stream via a T piece connected to a perspex two way non-breathing valve. A heated pneumotachograph (F300L and amplifier CS5, Mercury Instruments, East Kilbride) was sited downstream of the expiratory port. The flow rate signal was integrated to yield a measure of tidal volume. Expired air temperature was measured by a T type thermocouple (RS Ltd, Corby) located immediately downstream of the expiratory port. The location was chosen because cooling by the inspiratory airflow would have led to the formation of expiratory condensate on the thermocouple. This would have depressed the measured expiratory temperature, a phenomenon termed the wet bulb effect. Moreover, a single thermocouple probe is unlikely to respond over the 60°C range of temperature during cold air breathing within a respiratory cycle. A thermocouple upstream of the inspiratory port samples inspired air temperature. A requirement of the cold air facility was to generate real time values of respiratory heat exchange per breath. In software terms it is more efficient to switch between the two thermocouples for expiration and inspiration than to try to process a continuously varying signal from one probe.

An Apricot Xi 1200 microcomputer and analogue to digital converter (Biodata Ltd, Birmingham) recorded expiration air temperature, tidal volume, air flow rate, and inspiration air temperature every 40 milliseconds. Exhaled air temperature and air flow rate were each characterised by about 25 values, which varied throughout the expiratory phase. During inspiration these values were reduced to their root mean square value. The respiratory heat exchange rate per breath was then computed and stored before the next expiratory phase, when data aquisition would continue. The data collection software was written in MSBASIC.

PROTOCOL

Seven patients with mild allergic asthma and a baseline FEV_1 greater than 70% of predicted normal values were enrolled. We also studied seven non-smoking control subjects. Patients taking oral corticosteroids, antihistamines, and anticholinergic drugs were excluded. Inhaled β_2 agonists were discontinued for at least 12 hours before the tests. The study was approved by the hospital ethics committee and informed consent was obtained from each subject.

Throughout the challenges each subject observed the pneumotachograph electromanometer display of tidal volume. On to this display a "target" needle was positioned to correspond to a 0·5, 1, and 2 litre tidal volume. Respiratory frequency was controlled by synchronising breathing with a metronome (60 breaths/min), which when combined with the preset target tidal volume produced ventilation rates of 15, 30, and 60 l/min. Cold air and dry air challenges were carried out randomly during two visits, when subjects hyperventilated the conditioned air for three minutes at increasing levels of ventilation separated by a 20 minute interval. Normal subjects omitted the 15 l/min challenge. After each hyperventilation challenge FEV_1 was recorded at 0·5, 1·5, 3, 5, 7, 10, 12, and 15 minutes on a dry wedge spirometer (Vitalograph, Buckingham) at ambient temperature and humidity. The best result in three attempts was recorded and results were expressed as the maximum percentage fall from the baseline value. Data were analysed by an F test with a Minitab statistics package.

Results

Anthropometric and lung function data on the trial participants are given in table 1. Figure 1 illustrates the maximum percent fall in FEV_1 for different ventilation rates with cold air and ambient air hyperventilation in normal and asthmatic subjects. There was a significantly larger fall in FEV_1 after cold air than ambient air hyperventilation in both groups. The percentage reductions in FEV_1 after cold air and ambient air hyperventilation in the asthmatic group were: 8 (SD 4) *v* 3·8 (4) at 15 l/min ($F = 8·2$, $p < 0·05$); 11·6 (8) *v* 7 (4·4) at 30 l/min ($F = 3·6$, NS); and 20·7 (11) *v* 12·3 (6·3) at 60 l/min ($F = 11·4$, $p < 0·05$). In the normal group smaller percentage falls in FEV_1 were recorded: 4·7 (1·4) *v* 1·2 (1·2) at 30 l/min ($F = 24$, $p < 0·05$); and

Table 1 *Anthropometric and lung function data on the subjects*

Subject No	*Sex*	*Age (y)*	*Height (cm)*	*Baseline FEV_1 (l)*	*(% pred)*
Asthmatic:					
1	F	35	162	2·62	91
2	F	50	159	2·57	112
3	M	30	188	4·77	106
4	F	28	160	3·13	106
5	F	19	158	2·12	71
6	M	22	163	3·04	98
7	F	36	174	4·31	117
Mean		31·5	166·3	3·22	100·1
(SD)		(9·5)	(10·2)	(0·9)	(15·4)
Normal					
8	F	39	155	2·16	72
9	M	27	173	3·43	89
10	F	24	163	3·11	100
11	M	24	168	4·25	110
12	M	28	175	4·20	104
13	M	34	180	4·37	107
14	F	20	165	3·87	121
Mean		28	168	3·63	100·4
(SD)		(6·02)	(7·7)	(0·74)	(15·9)

7·1 (3·1) *v* 3·3 (3·0) at 60 l/min ($F = 11·4$, $p < 0·05$).

In the asthmatic patients increasing ventilatory challenge with cold air yielded significantly ($p < 0·05$) larger falls in FEV_1, whereas in ambient dry air the trend was smaller. The maximum fall in FEV_1 was observed about two minutes after the cold air and ambient air hyperventilation challenges, FEV_1 then recovered and was within 5% of the baseline value by 20 minutes. During cold air hyperventilation the mean expired air temperature was lower than during ambient air hyperventilation for both asthmatic and normal subjects (table 2).

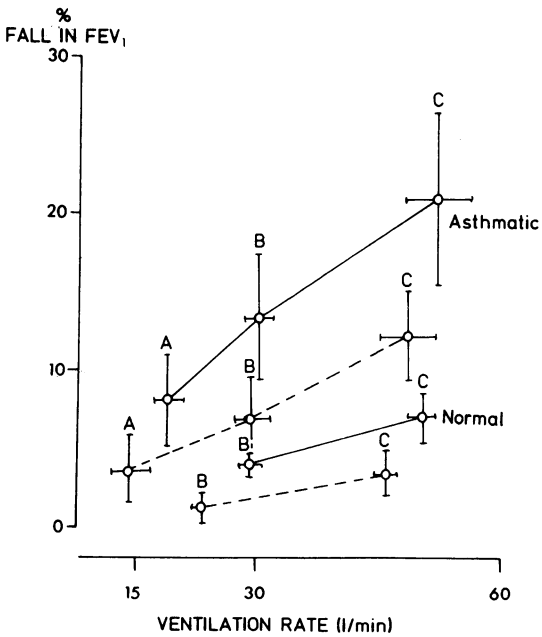

Fig 1 *Percentage fall in FEV_1 versus ventilation rate in seven asthmatic and seven normal subjects during cold air and dry ambient air hyperventilation. ———— cold air; - - - - dry air; A—15 l/min; B—30 l/min; C—60 l/min ventilation target; bars represent 1 SD.*

The respiratory heat exchange per breath for both groups was calculated on the basis of these temperatures and plotted against FEV_1 response (fig 2). In the asthmatic subjects there was a linear ($r = 0·98$) relation between heat loss and maximum fall in FEV_1, regardless of the type of thermal burden (appearing to conform to some kind of superposition rule). The contribution of latent and sensible heat losses was examined by separating the net respiratory heat exchange into component form on the basis of the above equation (table 3). The lower expired air temperatures in cold air hyperventilation imply greater airway water retention and less latent heat loss than in ambient air hyperventilation. For the same latent heat loss, however, the associated airway response is greater with cold air than ambient air hyperventilation. Higher rates of sensible heat loss in cold air hyperventilation (caused by the larger in-

Table 2 *Expired air temperatures in ambient air hyperventilation (AAH) and cold air hyperventilation (CAH)*

Target ventilation (l/min)	*Mean (SD) temperature (°C)*	
	CAH	*AAH*
Asthmatic (n = 7)		
15	27·1 (0·46)	28·8 (0·73)
30	26·5 (0·71)	29·7 (0·49)
60	26·8 (0·85)	30·3 (0·53)
Normal (n = 7)		
30	27·2 (0·66)	29·4 (0·35)
60	27·1 (0·66)	30·0 (0·9)

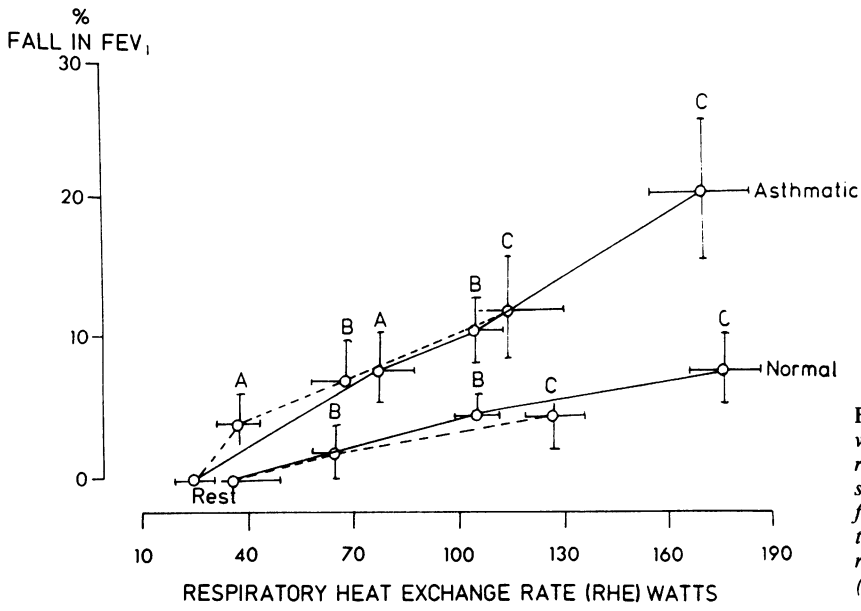

Fig 2 *Percentage fall in FEV_1 versus respiratory heat exchange rate in seven asthmatic and seven normal subjects. (See fig for key.) The total heat loss for the asthmatic group is linearly related to the fall in FEV_1 ($r = 0{\cdot}98$).*

spiratory-expiratory gradient temperature) are followed by a greater fall in FEV_1. For a given sensible heat loss the associated airway responses in cold air and ambient air hyperventilation are similar. Additional airway cooling appears to provoke airway response additional to that already due to airway drying.

Discussion

The accuracy of the expired air temperature measurements is limited by the technical factors already mentioned under "Methods." These will lead to underestimation of expired water vapour content and consequently the calculated respiratory heat exchange. No condensate was noted on the inside surface of the non-rebreathing valve, although water droplets on the disc leaflet valve of the expiratory port were observed. By implication the recorded expired air temperature would have been lower than that at the mouth. Our own laboratory tests, performed manually by plunging a thermocouple into the expiratory airstream, suggest an error of 0·5–0·75° C during tidal breathing of ambient air.

Increasing ventilation during cold and ambient air hyperventilation was followed by larger falls in FEV_1. Moderate airway drying was encountered in both forms of hyperventilation. Water loss rates have been calculated for the asthmatic group on the basis of a fully saturated expirate of known temperature and the actual ventilation rate (table 3). During maximal ventilation (60 l/min target) water loss rates of 1·05

Table 3 *Latent and sensible heat loss in the asthmatic group*

Ventilation (l/min)		*RHE (watts)*				
Target	*Actual (mean (SD))*	*Sens*	*Lat*	*Tot*	*Max % fall FEV_1 (mean (SD))*	*H_2O loss (g/min)*
Rest	9·9 (3·8)	8	28	36	—	0·25
Cold air hyperventilation:						
15	17·2 (0·5)	41	46	87	8 (5·1)	0·44
30	25·5 (0·6)	63	54	117	11·6 (8)	0·61
60	43·8 (1·2)	114	64	178	20·7 (11)	1·05
Ambient air hyperventilation:						
15	13·1 (0·4)	6	41	47	3·8 (4)	0·40
30	24·7 (0·2)	13	65	78	7 (4·4)	0·72
60	41·3 (1·1)	23	100	123	12·3 (6·3)	1·24

RHE—respiratory heat exchange; Sens—sensible heat, via convective cooling; Lat—latent heat, via evaporative drying; Tot—total heat exchange rate; H_2O loss—water loss/min based on a fully saturated expirate.

g/min (cold air hyperventilation) and 1·24 g/min (ambient air hyperventilation) were predicted, in contrast to the estimated ambient rest value of 0·25 g/min. Net water loss in cold air hyperventilation was reduced, despite the same inspiratory drying stress as in ambient air hyperventilation, owing to greater condensation of water vapour back on to the cool upper airway. The maximum fall in FEV_1 in the asthmatic group occurred about two minutes after the challenges, and was followed by recovery to the baseline value. A similar transient response in asthmatic patients is evident after treadmill exercise, peaking at about 10 minutes.[8 9] Hyperventilation induced asthma is used as a model of the effect of respiratory heat and water loss arising in exercise induced asthma, although the mechanisms remain unclear. Airway receptors anaesthetised by lignocaine do not confer protection from exercise induced asthma[10] and therefore direct sensory stimulation of the airway by cooling and drying is thought to be unlikely. There may be differences in the release of mediators between exercise induced and hyperventilation induced asthma. Barnes and Brown[11] reported a rise in histamine concentrations in asthmatic subjects after exercise, whereas in normal subjects no change occurred. Hyperventilation produced no increases in plasma histamine in either group, although both exercise induced and hyperventilation induced asthma caused similar reductions in peak flow (PEF). Nagakura[12] and Lee[8] reported neutrophil chemotactic factor release during exercise induced asthma but found none during hyperventilation induced asthma. The two types of challenge elicited the same fall in FEV_1. Similar observations have been made by Deal *et al*[9] during a study of antigen provocation versus hyperventilation induced asthma.

Hahn and coworkers[7] exercised subjects in a temperature of 10–75°C with a fixed water vapour content of 9–10 mg/l. Large reductions in PEF were reported during the 35°C challenge, although a similar challenge with humidified air (29 mg/l) appeared to confer protection against exercise induced asthma. Epithelial water loss was proposed as the predominant stimulus for exercise induced asthma. Expired air temperature was not recorded. On the assumption that this was about 34°C the maximum range of temperature imposed on the airway would have been 25°C. In the present study the range was up to 60°C and airway cooling was more severe. Heating air depresses its relative dryness. The transport rate of water from a particular region of the airway depends on the water vapour concentration gradient between the epithelium and the air and on the temperature of the inspired air. For example, wet epithelial tissue exposed to air at 40°C and 0·3 mg/l of water will have twice the water loss rate of that produced by air at −25°C and 0·3 mg/l water. We may reasonably expect that the upper respiratory tract, the zone in initial contact with the inspirate, will have greater rates of drying during an arid burden.

McFadden *et al*[14] showed that the rate of airway rewarming after a thermal burden influences the severity of exercise induced asthma. If the *rate* of heat loss is crucial the airway may accommodate heat loss due to steady state hyperventilation of cold air but be unable to do so when exposed to the step change increase in inspiratory temperature during the period after exertion. During the present study subjects resumed inhalation of room air immediately after the challenges. Because the present subjects were hyperventilating rather than exercising, ventilation returned to resting values almost immediately after the challenges ended, giving rise to a lower rewarming burden than would have arisen had postexertional increased ventilation been present.

In our own study[13] we observed pharyngeal temperatures of 34°C during the tidal inspiration of 22°C ambient air, giving an oropharyngeal temperature gradient of 12°C. During a cold air hyperventilation (−18°C) study by McFadden[4] an oropharyngeal gradient of 40°C was implied. Throughout the ambient air hyperventilation challenge all patients and normal subjects reported pharyngeal dryness and four patients also described discomfort at the level of the sternal notch. In all cases the sensation of dryness was distinct during ambient air hyperventilation, whereas only four patients reported dryness with the cold air hyperventilation challenge. This may have been due either to differences between patients in ability to maintain the ventilation target described earlier or to additional water vapour retention inherent in cold air hyperventilation. Six subjects also described discomfort in the upper airway and all developed a distinct wheeze after cold air hyperventilation.

Both drying and cooling appear to influence airway responses. In the ambient air hyperventilation challenge low rates of sensible heat loss arose (about 20% of the total respiratory heat exchange), the burden being primarily the action of drying, which was followed by a fall in FEV_1 of 12% with a ventilation rate of 60 l/min. In the cold air hyperventilation challenge a fivefold increase in the level of sensible heat loss and latent heat loss similar to that encountered in ambient air hyperventilation produced a fall in FEV_1 of 20% (60 l/min) (table 3). Direct stimulation by cooling or drying of the airways receptors beyond the third generation would appear to be unlikely. In vivo, air temperatures of 25°C recorded at the third generation airway during cold air hyperventilation[4] would demand severe heat loss in the upper airway. In the present study the burden of conditioning inspired air was placed on the upper airway, particularly the

oropharynx, in keeping with the sensations experienced by the subjects.

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