Effects of skin cooling on airway reactivity in asthma

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INTRODUCTION

Environmental contact with cold air is a common cause of respiratory distress in individuals with obstructive lung disease [1-4]. Both components of this stimulus (i.e. reducing integumental temperatures and inhaling frigid air at increased levels of ventilation) evoke bronchial narrowing, which can result in acute breathlessness and wheezing in sensitive subjects [1-6]. Although each element has a common external origin, they work through different mechanisms and have unique consequences. Chilling the skin induces airway constriction via a somatic afferent-vagal efferent reflex arc [5,7], while breathing cold air directly influences bronchial calibre by its actions on respiratory thermal events [8-12]. Recent data surprisingly indicate that these two components do not produce additive effects when combined, and it has been suggested that the mechanism may be related to an integumental reflex that favourably improves intrapulmonic heat and water exchange [13]. If so, it is possible that the mixture of skin and airway cooling may be physiologically unique and that integumental chilling may amplify the consequences of other airway constrictors. The present study was designed to test this hypothesis by examining whether skin cooling augments the bronchial narrowing produced by methacholine. Our observations form the basis of this report.

METHODS

Ten subjects with asymptomatic asthma, seven women and three men with a mean age of 31.0 ± 2.8 years, served as our subjects. All were non-smokers. None used oral glucocorticoids, cromolyn sodium or long-acting bronchodilators, and each refrained from taking any short-acting agents for 12 h before any study day. No one reported respiratory tract infections for the 6-week period preceding our investigation. The study was approved by the Committee on Research in Human Subjects and informed consent was obtained from each participant.

Maximal forced exhalations were performed in triplicate with a waterless spirometer using the American Thoracic Society standards [14]. The best effort, as defined by the curve with the largest forced expiratory volume in 1.0 s (FEV₁₀), was chosen for analysis.

Skin cooling was achieved by the subjects wearing a thermal suit that covered the chest, back and head (Life Support Systems, Mountain View, CA, U.S.A.). The technical details of the system have been described previously [13]. In brief, the apparel consisted of a

Key words: airway obstruction, airway reactivity, asthma, cold exposure.

Abbreviations: FEV₁₀, forced expiratory volume in 1.0 s; PC₂₀meth, mean provocative concentration of methacholine required to reduce the FEV₁₀ by 20%.

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jacket and cap that contained multiple conduits through which a coolant was circulated from a compressor and pump. The garment was placed next to the skin, and the subjects donned a cotton shift over their trunk to preserve their modesty. Integumental temperatures were monitored by matched shielded thermistors that were attached by tape to the pectoral and infrascapular areas of the right hemithorax and interfaced to a dedicated digital processor (Omega 709 probes and DP81 processor; Omega Engineering, Stamford, CT, U.S.A.) [13]. A third probe measured suit temperatures. Body core temperature was recorded in the auditory canal at 15 min intervals with an IVAC thermometer (IVAC, San Diego, CA, U.S.A.). The accuracy of the thermisters and thermometer was verified to be within 0.1 °C of a U.S.A. Bureau of Standards precision thermometer. The thermal apparel was comfortable to wear and provided a gradual even cooling without producing ‘old burns’ or evoking ventilatory responses such as gasping or hyperpnoea [15]. Spirometry and temperature data were obtained before and serially during the exposures.

Methacholine bronchoprovocations were performed using standard techniques [16]. Aerosols were generated with a De Vilbiss model 646 nebulizer operated by compressed air at 138 kPa (Pulmo-Aide, 561 series, De Vilbiss) and an inhalation triggered dosimeter (Rosenthal–French, Model 2-A, Laboratory for Applied Immunology) set to deliver an aerosol of 0.6 s duration during inspiration. Volume history was standardized by asking each subject to perform five maximal inhalations from functional residual capacity to total lung capacity. Phosphate-buffered normal saline was inhaled first, followed at 5 min intervals by doubling concentrations of methacholine in phosphate-buffered saline diluent. The starting concentration was 0.078 mg/ml (0.4 mmol/l). Dose–response curves were plotted for each subject and the amount of methacholine required to reduce the FEV₁,₀ by 20% (PC₂₀ molar) was calculated by linear interpolation. Complete curves were obtained in all subjects on both occasions so that we could evaluate whether there were changes in slope as well as in the absolute quantity of methacholine.

The experiments were performed on two occasions separated by 4–6 days. During each session the subjects wore the cooling garment and sat quietly in a thermally neutral environment for 30 min. At that point, the methacholine provocation was initiated while the participants remained in the suit. On one visit the coolant was circulated while in the other it was not. The latter served as a control. Air at ambient room temperature and humidity was inhaled during all occasions so that we could evaluate whether there were changes in slope as well as in the absolute quantity of methacholine.

The effects of reducing integumental temperature on pulmonary mechanics are presented in Figure 2. The baseline FEV₁,₀ values for the control and cold trials were statistically similar [FEV₁,₀ control, 2.92 ± 0.23 litres; cold, 2.97 ± 0.26 litres (P = 0.72, paired t-test)]. Without the coolant circulating, the FEV₁,₀ remained constant over the period of observation (ΔFEV₁,₀ 0–30 min control, −0.2 ± 1.7%; P = 0.17, one-factor analysis of variance). Chilling the skin, however, produced mild airway obstruction (ΔFEV₁,₀ 0–30 min cooling, −6.7 ± 2.2%; P < 0.05, paired t-test). The differences between trials was significant at P < 0.05 by factorial analysis.

Table 1 displays the individual PC₂₀ molar data. This information confirms that our subjects had heightened airway reactivity at the time of study. Each responded to methacholine with a ≥ 20% fall in FEV₁,₀ and had pre-challenge values for PC₂₀ molar within the asthmatic range [0.1–1.9 mg/ml (0.51–9.7 mmol/l)]. Reducing skin temperature did not significantly alter either the slopes of the stimulus–response relationships (data not shown) or the PC₂₀ molar [control PC₂₀ molar, 0.47 ± 0.17 mg/ml (2.4 ± 0.87 mmol/l); cold, 0.45 ± 0.13 mg/ml (2.3 ± 0.66 mmol/l); P = 0.85, paired comparisons]. Finally, there were no differences in the absolute quantity of methacholine administered with and without cold [final methacholine dose without cold, 0.61 ± 0.23 mg/ml (3.11 ± 1.19 mmol/l); with cold, 0.58 ± 0.16 mg/ml (2.95 ± 2.32 mmol/l); P = 0.85, paired t-test], nor in the final FEV₁,₀ values with a power of 90% at a P value of 0.05 using a two-tailed technique.

RESULTS

The temperatures of the suit (Tₕ) back (Tₐ) and chest (Tₕ) are shown in Figure 1. In the control experiment the baseline values for these three variables averaged 30.5 ± 0.4, 33.2 ± 0.4 and 33.0 ± 0.5 °C respectively, and each rose slightly during the period of observation. There were no meaningful differences between the pre-exposure values for the active and control trials by paired t-tests. When the compressor was turned on and the coolant circulated, the temperatures at each site fell significantly over time from their respective baselines as well as from control values. By 30 min Tₕ decreased to 17.5 ± 1.1 °C (P < 0.001), Tₐ to 28.7 ± 1.8 °C (P < 0.01) and Tₕ to 30.4 ± 1.7 °C (P < 0.02). Each of the data sets was analysed by one-factor analysis of variance. The differences between the control and experimental arms were significant at the P < 0.001 level for all comparisons (two-factor analysis of variance). There were no significant changes in core temperature within or between experiments [control Tcore; baseline, 36.4 ± 0.3 °C; 30 min, 36.5 ± 0.2 °C (P = 0.79); cold experiment Tcore; baseline, 36.4 ± 0.2 °C; 30 min, 36.5 ± 0.2 °C (P = 0.63)]. The ambient temperature and humidity of the air in the laboratory during these experiments was 22–23 °C and 45–47% respectively.

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Skin cooling and asthma

TEMPERATURES

Figure 1 Temperature measurements during the control and cold exposure experiments

$T_s$, suit temperature; $T_b$, back temperature; $T_c$, chest temperature. Zero time represents the baseline conditions before the start of the experiments. Values are expressed as means (S.E.M.).

Table I Individual $PC_{20\text{meth}}$ data with and without skin cooling

<table>
<thead>
<tr>
<th>Subject</th>
<th>No cooling</th>
<th>Cooling</th>
<th>No cooling</th>
<th>Cooling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mg/ml)</td>
<td>(mmol/l)</td>
<td>(mg/ml)</td>
<td>(mmol/l)</td>
</tr>
<tr>
<td>1</td>
<td>0.130</td>
<td>0.660</td>
<td>0.720</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.265</td>
<td>1.350</td>
<td>1.590</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.420</td>
<td>2.150</td>
<td>4.750</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.100</td>
<td>0.510</td>
<td>0.610</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.370</td>
<td>1.890</td>
<td>2.400</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.875</td>
<td>9.580</td>
<td>6.390</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.235</td>
<td>1.200</td>
<td>0.560</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.156</td>
<td>0.800</td>
<td>1.230</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0.550</td>
<td>2.810</td>
<td>1.020</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.560</td>
<td>2.860</td>
<td>3.590</td>
<td></td>
</tr>
<tr>
<td>Mean ± S.E.M.</td>
<td>0.47 ± 0.17</td>
<td>2.40 ± 0.87</td>
<td>2.30 ± 0.66</td>
<td></td>
</tr>
</tbody>
</table>

reached post methacholine (final $FEV_{1.0}$ without cold, $2.10 ± 0.20$ litres; with cold, $1.98 ± 0.12$ litres; $P = 0.41$, paired $t$-test).

DISCUSSION

We appreciate that our study design is somewhat artificial and that it would be unlikely that an individual would be exposed only to integumental cooling without also breathing cold air. Our protocol
was undertaken to examine in isolation the interactions of somatic reflexes with direct stimulation of the tracheobronchial tree. The results of our experiments demonstrate that lowering the temperature of the integument of the heads and thoraces of subjects with asthma produces mild bronchial narrowing but does not enhance the obstructive effects of an airway agonist like methacholine. The application of cold only changed the PC_{20} meth by an average of 4% from control, and had no influence on either the total dose of methacholine given or the maximum fall in the FEV_{1.0} produced post drug; hence, skin cooling per se does not appear to be a major risk factor for the destabilization of asthma. Contact with cold causes acute decompensation in lung function, but does not carry the risk for further attacks.

The physiological events noted confirm and extend previous observations. The thermal challenge was relatively modest and mimicked the type of temperature swings that would be routinely experienced by individuals living in a temperate climate. Its intensity was not particularly noxious as measured by a lack of shivering and stable core temperature so the airway response would not have been attenuated by the release of adrenergic neurotransmitters. In addition, the garment covered the torso, but not the abdomen, so the expected stimulatory influence would have been excitatory. Finally, although minute ventilation and respiratory frequency were not formally measured, skin chilling was gradual and neither hyperpnoea nor tachypnoea occurred; thus we are confident that these issues did not play a role in our findings. Ventilation values need to double those of resting levels to evoke airway obstruction when asthmatic subjects are breathing air at ambient room temperatures as herein [8,9].

The degree of bronchial narrowing which develops with skin chilling of this magnitude is minor, and the 7% decrement in FEV_{1.0} that we found is statistically identical to the 10% fall noted in our previous investigation although different subjects were employed [13]. It is not yet clear if more severe reductions in temperature would have greater obstructive consequences, but they may not. Chen and Horton [6] recorded alterations in pulmonary mechanics that were roughly twice as large as ours when their subjects took a shower with water at 15 °C and blew air across their bodies with a fan. These results, however, were probably contaminated by significant alterations in breathing pattern that may have amplified the obstruction [13,15]. Stimuli such as those used by Chen and Horton [6] abruptly increase minute ventilation [15], and hyperpnoea is a well-established precipitant of acute airflow limitation in asthmatic subjects [8-10,17]. Koskela and Tukiainen [18], on the other hand, found that isolated facial contact with air at -17 °C only produced a 5–6% fall in FEV_{1.0} in patients with heightened reactivity. These data are particularly interesting since it is known that the face is more sensitive to cold than the trunk [5]. Therefore, it is possible that skin cooling may not operate in a stimulus–response fashion, but rather in a threshold manner like other respiratory reflexes [7].

The reason for the absence of an interaction between integumental chilling and methacholine is not known but since both stimuli activate muscarinic pathways, one would intuitively have expected some sort of amplification. The fact that one did not occur is unlikely to be related to such events as changes in the distribution of methacholine within the lung or to its time of retention. The ventilatory pattern during drug nebulization was held constant between trials and the degree of bronchoconstriction was too small to have had much influence [19]. Any potential ability of skin chilling to constrict the airway vasculature would have increased rather than decreased retention time [20].

Given that reducing the temperature of the torso does not accentuate the response to isocapnic hyperventilation of subfreezing air [13], it may be that this reflex is a unique phenomenon that is designed to assist in the conditioning of inspired air, and does not play any other role in airway physiology. It is also possible that the combination of skin and airway cooling may be necessary to induce a positive interaction, or that constrictors, other than methacholine, would have different effects. Further experimentation is required to exclude these postulates. We are aware of data that suggest that facial cooling purportedly amplifies the obstructive consequences of exercise in asthmatic subjects, but the results of the one available study are problematic [21]. The experimental protocol in this work did not isolate the influences of inhaling frigid air from those of simply cooling the exposed skin. Given that it is well established that the former worsens exercise-induced asthma [4,17,22], this is a serious flaw that renders the findings uninterpretable.

In summary, skin cooling produces bronchoconstriction in asthmatic subjects through a reflex mechanism and does not alter the underlying reponsivity of the airways. Its effects are generally small and self-limited and do not place affected individuals at increased risk of morbidity from other stimuli. A decrease in integumental temperatures therefore contributes to the asthmatic diathesis, but does not sustain it. Like other thermal causes of bronchial narrowing, it is free of secondary sequelae [15,23,24].

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