Airway response to emotional stimuli in asthma: the role of the cholinergic pathway

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1Department of Psychology, University of Hamburg, Hamburg, Germany; 2Department of Electrical and Computer Engineering, University of Texas at El Paso, El Paso, Texas; 3CareFusion, Höchberg, Germany; and 4Pulmonary Research Institute at Hospital Grosshansdorf, Center for Pneumology and Thoracic Surgery, Grosshansdorf, Germany

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Ritz T, Kullowatz A, Goldman MD, Smith H, Kanniess F, Dahme B, Magnussen H. Airway response to emotional stimuli in asthma: the role of the cholinergic pathway. J Appl Physiol 108: 1542–1549, 2010. First published April 1, 2010; doi:10.1152/japplphysiol.00818.2009.—In asthma, airways constrict in response to emotion and stress, but underlying mechanisms, potential extrathoracic contributions, and associations with airway pathophysiology have not been elucidated. We therefore investigated the role of the cholinergic pathway in emotion-induced airway responses in patients with asthma and the association of these responses with airway pathophysiology. Patients with asthma (n = 54) and healthy participants (n = 25) received either 40 μg ipratropium bromide or a placebo in a double-blind double-dummy cross-over design in two laboratory sessions with experimental emotion induction. Stimuli were preevaluated films and pictures of pleasant, unpleasant, and neutral quality. Respiratory resistance and reactance at 5 and 20 Hz were measured continuously before and during presentations, together with respiration by impedance plethysmography and end-tidal PCO2 by capnometry. In addition, measures of airway inflammation (fraction of exhaled nitric oxide), airway hyper-reactivity (methacholine challenge), and reversibility of obstruction were obtained. Respiratory resistance and reactance at 5 and 20 Hz increased during unpleasant stimuli in asthma patients. This response was blocked by ipratropium bromide and was not substantially associated with asthma severity, airway inflammation, hyperreactivity and reversibility, or pattern of ventilation and PCO2. Under the placebo condition, changes in resistance during unpleasant films were positively correlated with patients’ reports of psychological asthma triggers. In conclusion, airway constriction to unpleasant stimuli in asthma depends on an intact cholinergic pathway, is largely due to the central airways, and is not substantially associated with other indicators of airway pathology. Its link to the perceived psychological triggers in patients’ daily lives suggests a physiological basis for emotion-induced asthma.

respiratory resistance; emotion; airway hyperreactivity

THE ROLE OF PSYCHOSOCIAL FACTORS in patients with bronchial asthma has been studied extensively, with substantial evidence demonstrating effects on the management of this chronic disease (27, 33, 59). However, the relationship between psychosocial stimuli and the regulation of airway tone is not fully understood. Some studies that used diary-assessment techniques have shown an association between impairment of lung function change or asthma exacerbations and mood states or life events (45, 49). Experimental studies that used emotion induction techniques have suggested a uniform tendency of the airways to constrict during unpleasant stimulation (22, 31, 40, 42, 47, 55). However, little is known about the mechanisms underlying emotion-induced airway constriction. Cholinergic effects on muscarinic receptors by vagal motor activity are known to be the major autonomic pathways of bronchoconstriction (3, 9). Early research exploring effects of psychological factors on the airways used the paradigm of bronchoconstrictive suggestion, in which participants inhale an inert substance that is presented as a bronchoconstrictive agent (22). Typically, this paradigm induced bronchoconstriction, which was shown to be abolished by atropine (34), but the extent to which this experimental paradigm informs about emotional processes has remained unclear (7). Exploration of autonomic pathways that mediate emotion-induced bronchoconstriction is also important because such bronchoconstrictions constitute an important paradox (1, 53). Stronger negative emotions such as fear and anger are typically accompanied by a fight-flight pattern with sympathetic activation. Consequently, bronchodilation would be expected if these adrenergic effects predominated in the airways. However, experimental studies using negative emotion induction have so far mostly shown bronchoconstriction (22, 31, 40, 42), which supports clinical and patients’ reports of emotion-induced asthma symptoms (e.g., Refs. 38, 39, 46).

Studies demonstrating respiratory system resistance (Rrs) increases to emotional stimuli have so far not addressed the question of localization of airway constriction. Most importantly, because Rrs is measured with the use of traditional forced oscillation methods for the whole respiratory tract, narrowing of the extrathoracic airways could significantly contribute to the observed Rrs increases, thus possibly reducing the significance of findings for asthmatic bronchoconstriction. However, the use of anticholinergic bronchodilators, such as ipratropium bromide, which block muscarinic receptors in the bronchi (8, 51), could demonstrate the importance of extrathoracic vs. intrathoracic central airway constriction in emotion induction. Because laryngeal constriction relies on nicotinic transmission (57), it would not be affected by blockade with ipratropium. Thus, if emotion-induced airway constriction persisted after blockade by ipratropium, this would be more supportive of a constriction in the extrathoracic airways (such as the larynx), or, alternatively, it would support the notion of peripheral airway constriction. We obtained additional information on the role of the peripheral vs. central airway obstruction in this study by using impulse oscilometry (52), which allows limited inferences on central vs. peripheral airway contributions to any observed resistance change by interpreting the frequency dependence of resistance (18) and the parameters derived from low-frequency reactance.

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In the present study, we explored the effects of experimental emotion induction on Rrs and respiratory system reactance (Xrs) in patients with asthma and in nonasthmatic individuals. We compared the effects of inhaled ipratropium bromide with placebo to explore the dependency of Rrs increases on an intact cholinergic pathway. We also investigated whether emotion-induced airway responses are an independent aspect of airway reactivity that would justify adding experimental emotion induction to the variety of direct and indirect airway challenge methods (13, 24). For that, observed airway responses should not be epiphenomena of pathophysiological processes at the organ level, such as nonspecific airway hyperreactivity, reversibility of airway obstruction, or airway inflammation, and should not reflect respiratory changes that are known to occur in emotion (6, 12, 28). For example, hyperventilation is known to lead to bronchoconstriction in asthma (51), and it has been suspected of being a major mechanism in stress-induced asthma (12, 43). On the other hand, deep breaths can dilate the airways in healthy patients and in patients with milder forms of asthma (50). Experimental studies have been equivocal with regard to ventilatory contributions (47, 48) and the role of nonspecific hyperreactivity to psychologically induced airway constriction (21, 30). No research has explored associations with reversibility and inflammatory markers to date.

METHODS

Participants

Participants were recruited from the Pulmonary Research Institute at the Hospital Grosshansdorf (Grosshansdorf, Germany) and by advertisements at the University of Hamburg. Inclusion criteria were a diagnosis of asthma (or no lung disease in healthy controls), nonsmoker for at least 6 mo (<10 life-time pack-years), and current stable mental and physical health. Excluded were individuals who had used oral corticosteroids in the previous 3 mo. This study was approved by our local ethics committees, and participants gave informed consent.

Diagnostic evaluations by a pulmonologist included asthma history, physical examination, lung function assessment, methacholine testing, exhaled nitric oxide, and allergy skin testing. Asthma severity was then rated according to relevant guidelines (36). Patients were instructed to stay on a stable dose of their asthma medication during the study. Before each assessment, short-acting bronchodilators were to be discontinued for 6 h, long-acting β-agonists for 12 h, and leukotriene inhibitors for 3 days. Inhaled corticosteroids were continued as prescribed if not combined with long-acting β-agonists. Mental health was explored by a clinically trained psychologist who used a structured interview (58). Participants with episodes of major depression, high likelihood of suicide, schizophrenia, or substance abuse were excluded.

Measurements

Impulse oscillometry (IOS MasterScreen, Jaeger/CareFusion) was used to measure Rrs and Xrs and tabulated Rrs at 5 and 20 Hz (Rrs5, Rrs20) and Xrs at 5 and 20 Hz (Xrs5, Xrs20) in an attempt to discriminate between central vs. peripheral resistance (and elastic properties) of the respiratory system. Xrs in the low-frequency range reflects elastic properties and primarily peripheral rather than central airway properties, whereas Xrs in the high-frequency range reflects primarily the effects of inertial forces in the central airways (52). We also tabulated the integrated low-frequency reactance area (AX), which may be less influenced by methodological “noise” than individual values of low-frequency Xrs (16, 17), as well as changes in resonance frequency (fres). In addition, to help distinguish changes in the central vs. peripheral airways, we included Rrs5-Rrs20 as a measure of frequency dependence of resistance (15, 18). The impulse oscillometry pneumotachograph was calibrated daily with a 3-liter syringe, after which measurements were taken with a standard reference impedance to ensure stability of pressure channel gain. Chin straps with attached padding to stabilize cheeks were used during the recordings to reduce upper airway shunt. The device had been customized by the manufacturer to accommodate continuous measurements for the maximum duration of stimulus presentation trials in this study (390 s). Artifacts due to swallowing were manually excluded from the analyzed recordings.

We performed spirometry (forced expiratory volume in the first second) using the pneumotachograph, and our test results were compared with patients’ percent predicted values. The methacholine inhalation test was administered according to a standard protocol (25).

Tidal volume (VT) and respiration rate (RR) were measured using a respiratory inductance plethysmograph (LifeShirt System, Vivometrics, Ventura, CA) calibrated with a fixed-volume breathing bag of 800 ml. VT and RR measurements failed in one patient due to technical difficulties.

The end-tidal PCO2 was measured continuously with a side-stream capnometer (Capnocount, Weinmann, Mannheim, Germany). The sampling tube was connected to the impulse oscillometry mouthpiece. This measure was only available for parts of the sample (n = 34 patients and n = 14 controls).

We determined airway inflammation by the fraction of exhaled nitric oxide (FeNO, in ppb), using a chemiluminescence analyzer (NIOX; Aerocrine, Solna, Sweden) at the beginning of each session and following relevant guidelines (2). The average of nine consecutive valid breaths was used in the analysis.

Physical symptoms (shortness of breath, chest tightness, dizziness, light-headedness, nausea, heart pounding, and weariness) were rated on an 11-point scale (0–10) anchored with “not at all” and “quite strong.” For emotional dimensions of unpleasantness-pleasantness and calmness-arousal, nine-point (0–8) bipolar pictorial rating scales were used (20). Ratings of symptoms were incomplete for 1 control participant, and ratings of emotion were incomplete for four patients and three control participants.

Before the session, asthma patients also completed a questionnaire on frequency of perceived asthma triggers (Asthma Trigger Inventory) (44, 46), with subscales for psychological triggers, allergens, physical activity, air pollution/irritants, and infection.

Experimental Stimuli

Participants viewed emotional stimulation material that had been successfully used in previous experimental studies. These materials included two parallel sets of affective picture blocks (9 pictures per block, each shown for 20 s) and preevaluated emotion-evoking film sequences of a pleasant, neutral, or an unpleasant emotional quality (length of 3–5 min each) (19, 47). Pictures were selected from the International Affective Picture System (10). (See supplemental data for reference number of pictures. Supplemental data are available in the online version of this article.)

Film sequences were extracted from commercially available movies, medical education materials, and archive materials of the University of Hamburg. The following film sequences were presented: for pleasant, British comedic I and British comedic II; for neutral, medical education materials, and archive materials of the University of Hamburg; for unpleasant, emotional clips. Pictures were rated for perceived pleasantness, neutral, and unpleasant emotional quality (length of 3–5 min each) (19, 47). Pictures were selected from the International Affective Picture System (10). (See supplemental data for reference number of pictures. Supplemental data are available in the online version of this article.)

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**Table 1. Basic demographics and lung function for asthma patients and healthy controls**

<table>
<thead>
<tr>
<th>Asthma Patients</th>
<th>Healthy Volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, % female</td>
<td>64.0</td>
</tr>
<tr>
<td>Age, years</td>
<td>27.5 ± 6.8</td>
</tr>
<tr>
<td>Education, % Abitur§</td>
<td>86.5</td>
</tr>
<tr>
<td>Family status, % unmarried</td>
<td>71.2</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>99.8 ± 13.7</td>
</tr>
<tr>
<td>Rrs₅ change to ipratropium, % of baseline</td>
<td>−24.0 ± 18.6</td>
</tr>
<tr>
<td>Feso₄ ppb</td>
<td>49.9 ± 34.1</td>
</tr>
<tr>
<td>Methacholine test, % positive</td>
<td>75.9</td>
</tr>
<tr>
<td>Skin prick test, % positive</td>
<td>98.1</td>
</tr>
</tbody>
</table>

Values are means ± SD. FEV₁, forced expiratory volume in the first second; Feso₄, fraction of exhaled nitric oxide; Rrs₅, respiratory system resistance at 5 Hz. *P < 0.05, †P < 0.01, ‡P < 0.001. §German certificate of high school education, guarantees university access.

**Protocol**

Subsequent to a diagnostic intake visit, which included skin testing and methacholine challenge, two laboratory visits were scheduled within 3–8 days. Before each presentation protocol, initial impulse oscillometry measurements were taken, and participants were administered a dose of ipratropium bromide (Atrovent, two actuations of 20 μg) or placebo delivered by dry powder inhalers under nurse supervision. Both the participants and the experimenter remained blind to the type of substance administered. After a 20-min rest period, a 90-s impulse oscillometry baseline period was recorded, which served to quantify reversibility of constriction [spirometry was not implemented at this point due to the known influences of the forced expiratory maneuver on airway tone (41)]. Participants then viewed the stimulus material sitting upright in a light- and temperature-controlled room. Physiological measures were recorded continuously before (90 s) and during each presentation. Participants breathed ambient air through a mouthpiece connected to the impulse oscillometry measurement head with a small terminal resistor of 0.1 kPa·l⁻¹·s while their nose was occluded. Participants were instructed to breathe normally, keep their eyes open, and avoid excessive body movements. After each film and picture block, participants rated their symptoms and emotion.

**Data Analysis**

Effects of ipratropium on prestimulation baseline were analyzed with the use of two-way ANOVA with two conditions (ipratropium vs. placebo) and two groups (asthma vs. control), with levels of resistance and reactance as dependent variables. To study effects of emotion induction under ipratropium vs. placebo conditions, difference scores of physiological parameters for each film and picture block were calculated by subtracting the 90-s premeasurement periods. Four-way repeated-measures ANOVAs with two conditions (ipratropium vs. placebo), two methods (film, pictures), three emotions (unpleasant, neutral, pleasant), and two groups (asthma patients, healthy individuals) as independent variables were calculated with resistance, reactance, respiration, and rating scales as dependent variables. For all repeated-measures ANOVAs, Greenhouse-Geisser correction on dfs was performed to account for violations of the sphericity assumption. Partial eta squared (η²) was used as a measure of effect size. A priori contrasts tested the hypothesis that increases in Rrs₅ and Rrs₂₀ were stronger during unpleasant than during neutral stimulations under placebo vs. ipratropium conditions. Additional post hoc comparisons of means were calculated using the Newman-Keuls procedure (P < 0.05). For correlations, Spearman’s rho was calculated. To estimate the potential clinical relevance of changes in Rs, we compared results with typical thresholds for just noticeable differences, as found in prior added resistive load studies (14); criteria were 0.076 kPa·l⁻¹·s for asthma patients and 0.061 kPa·l⁻¹·s for controls.

**RESULTS**

**Baseline Sample Characteristics**

Eighty-two participants were invited to participate; three of these were excluded because of pregnancy (n = 1), scheduling problems (n = 1), or technical problems (n = 1). Thus 79 participants (54 patients with asthma, 25 controls) were included in the final analysis. In patients, asthma severity was rated as intermittent for 48.1%, mild persistent for 32.5%, and moderate persistent for 20.4%. Forced expiratory volume in the first second at baseline was lower and the reversibility of Rrs₅, the percentage of positive skin tests, and FeNO were higher in patients than in controls (Table 1). Common criteria for hyperresponsiveness in methacholine testing were met by 41 patients and 3 healthy controls. Both groups were equivalent in basic demographics, including age, sex, family status, and educational level. Asthma onset before the age of 17 years was reported by 76% of the patients, seasonal asthma symptoms by 50%, night-time symptoms at least twice monthly by 42.6%, and a family history of atopy by 64.8%. Inhaled corticosteroids were taken by 29.6% of the patients, short-acting bronchodilators by 37%, long-acting bronchodilators by 24.1%, cromoglycate by 20.4%, and other medication (leukotriene inhibitors, antihistaminics, theophylline) by 11.1%. One-third of the patients were not taking anti-asthmatic medication. There were no overall group differences in initial baseline measures (Table 2).

**Effects of Ipratropium on Prestimulation Baseline**

Rrs₅, Rrs₂₀, and f₉es were reduced by ipratropium in both groups. Reductions in Rrs₅ and f₉es were particularly seen in the

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**Table 2. Results and ANOVA effects (df = 1,76) of preexperimental baseline values for Rrs, Xrs, AX, and f₉es under placebo and ipratropium conditions for asthma patients and healthy controls**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>Ipratropium</th>
<th>F</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rrs₅</td>
<td>0.448 ± 0.18</td>
<td>0.366 ± 0.12</td>
<td>0.416 ± 0.12</td>
<td>0.383 ± 0.11</td>
</tr>
<tr>
<td>Rrs₂₀</td>
<td>0.300 ± 0.11</td>
<td>0.257 ± 0.09</td>
<td>0.317 ± 0.12</td>
<td>0.297 ± 0.12</td>
</tr>
<tr>
<td>Xrs₅</td>
<td>−0.106 ± 0.15</td>
<td>−0.081 ± 0.06</td>
<td>−0.080 ± 0.05</td>
<td>−0.081 ± 0.04</td>
</tr>
<tr>
<td>Xrs₂₀</td>
<td>0.104 ± 0.06</td>
<td>0.122 ± 0.06</td>
<td>0.104 ± 0.08</td>
<td>0.112 ± 0.07</td>
</tr>
<tr>
<td>AX</td>
<td>0.405 ± 0.93</td>
<td>0.214 ± 0.38</td>
<td>0.201 ± 0.29</td>
<td>0.235 ± 0.43</td>
</tr>
<tr>
<td>f₉es</td>
<td>10.2 ± 4.0</td>
<td>9.1 ± 2.9</td>
<td>9.6 ± 3.0</td>
<td>9.7 ± 4.4</td>
</tr>
</tbody>
</table>

Values are means ± SD. Rrs₂₀, Rrs at 20 Hz; Xrs₅ and Xrs₂₀, respiratory system reactance at 5 and 20 Hz, respectively; AX, reactance area; f₉es, resonance frequency; η², partial eta squared. *P < 0.05, †P < 0.01, ‡P < 0.001.

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asthma group. Xrs5 and AX were smaller in magnitude after ipratropium in asthma patients, but changes were not significant.

Effect of Emotion Induction on the Airways and Its Modulation by Ipratropium Bromide

Group effects. Patients with asthma showed overall stronger increases in resistance across protocols of both sessions [group effects were $F(1,77) = 3.96$ and $2.62, P = 0.050$ and 0.109, and $\eta^2 = 0.058$ and 0.033, respectively, for Rrs5 and Rrs20, respectively].

Effect of emotion induction. Relatively uniform changes of resistance were observed across the frequency spectrum with emotion induction. Across all conditions and methods, unpleasant stimuli were associated with the strongest increases in resistance, with significant emotion effects of $F(2,154) = 13.81$ and 12.26, both $P < 0.001$, $\varepsilon = 0.92$ and 0.90, and $\eta^2 = 0.152$ and 0.137 for Rrs5 and Rrs20, respectively.

Effect of placebo vs. blockade. Increases in Rrs5 during unpleasant stimuli were generally greater under placebo than under ipratropium conditions, as suggested by a significant condition-by-emotion interaction [$F(2,154) = 6.04, P = 0.003, \varepsilon = 0.98, \text{and } \eta^2 = 0.073$] (Fig. 1). (See also supplement for more details. Supplemental data are available in the online version of this article.) Both Rrs5 and Rrs20 showed condition-by-emotion-by-group interactions [$F(2,154) = 2.41$ and 3.86, $P = 0.094$ and 0.023, $\varepsilon = 0.98$ and 0.96, and $\eta^2 = 0.030$ and 0.048], although the former was only a statistical trend. A priori contrasts suggested that, for asthma patients only, increases in Rrs5 and Rrs20 during unpleasant stimuli were higher than during neutral stimuli under placebo vs. under ipratropium conditions [$F(1,77) = 14.75$ and 6.86, $P < 0.001$ and 0.011, respectively]. Post hoc testing also showed significantly stronger increases in Rrs5 and Rrs20 during unpleasant stimuli and placebo condition than during any other combination of emotion, condition, and group. After ipratropium, Rrs increases were still visible during unpleasant stimuli but they were not significant. Healthy participants only showed significantly or marginally (post hoc tests, $P < 0.11$) stronger increases during negative stimuli vs. during neutral and positive stimuli in the placebo condition.

Figure 2 shows percent changes in Rrs5 and Rrs20 from prestimulus levels for unpleasant stimuli in both groups and the number of participants exceeding typical thresholds for just noticeable differences in prior added resistive load studies.

Evidence for central vs. peripheral effects on the airways. Although airway constriction to unpleasant stimuli was observed across impulse frequencies, they were smaller at higher frequencies. Rrs5-Rrs20 showed significant effects of emotion and condition by emotion [$F(2,154) = 6.46$ and 10.89, $P = 0.003$ and 0.001, both $\varepsilon = 0.90$, and $\eta^2 = 0.077$ and 0.124, respectively], with post hoc test showing that increases in Rrs5-Rrs20 were greater for unpleasant stimuli under placebo but not under ipratropium conditions. The increase in Rrs5-Rrs20 is consistent with the possibility of some increase in peripheral airway resistance.

No effects were found for Xrs5. Additional effects were observed for AX, but they did not reflect specific changes observed with Rrs for negative stimuli and ipratropium vs. placebo conditions. (See supplement for more details. Supplemental data are available in the online version of this article.)

Changes in Emotion and Symptoms

Ratings of pleasantness-unpleasantness and calmness-arousal both showed a clear distinction between emotional and neutral stimuli. Additional method-by-emotion effects were due to significantly greater unpleasantness for unpleasant pictures and greater pleasantness and arousal for pleasant films.

Asthma patients reported significantly higher overall levels of chest tightness and a tendency toward increased breathlessness and dizziness. Overall, the sensation of dizziness was stronger with ipratropium than with placebo for asthma pa-

As a supplementary analysis, we also calculated a five-way repeated-measures ANOVA, including resistance (Rrs5 and Rrs20) as 2 levels of an additional repeated-measures variable. This analysis yielded a condition by emotion by resistance interaction, which indicated that reductions in resistance during ipratropium were stronger for Rrs5.
tients. Symptoms were generally stronger for unpleasant stimuli than for others, regardless of whether ipratropium or placebo was used.

Correlations between emotions or symptoms and Rrs change were not significant, except for nausea levels, which showed consistently positive associations with Rrs5 and Rrs20 changes in asthma patients. (For more detailed findings, see supplement. Supplemental data are available in the online version of this article.)

Changes in Ventilation

PCO2 and RR, but not VT, showed smaller changes to film than to picture stimulation and emotional qualities. Significant increases in PCO2 were found that were generally stronger during pictures, as well as increases in RR that were stronger during pleasant and unpleasant films than during neutral films. In addition, RR changes were negatively correlated with Rrs5 and Rrs20 for some pleasant and neutral stimulus presentations in healthy participants only. None of the effects reflected the increases observed in Rrs5 and Rrs20 during unpleasant stimuli and their attenuation during ipratropium. (See supplement for more detailed findings. Supplemental data are available in the online version of this article.)

Association of Airway Responses with Demographics, Asthma Manifestation, and Medication

No significant associations were found for Rrs5, Rrs10, Xrs5, and AX with age or gender. fes increased more for women than for men [r(49–50) = 2.10, 2.40, and 1.98; P = 0.041, 0.020, and 0.053, respectively] (see also supplement, available in the online version of this article). Asthma severity and age of asthma onset were not significantly associated with airway responses, nor was currently prescribed medication (inhaled corticosteroids vs. other medication, short-acting bronchodilator or no medication vs. other medication).

Association of Airway Responses with Nonspecific Hyperreactivity, Reversibility, and Airway Inflammation

In asthma patients, only airway responses to neutral pictures under placebo conditions were negatively associated with methacholine PC20 [r(52) = −0.41, P < 0.001], where PC20 is the concentration of drug that induces 20% decline in forced expiratory volume in the first second. The remaining coefficients were not significant. There were no substantial associations of Rrs5 or Rrs20 changes with reversibility or basal FeNO assessed before each session (for more detailed findings, see supplement, available in the online version of this article).

Association of Airway Responses with Self-Reported Psychological Triggers of Asthma

Patients who reported more frequent psychological triggers in their daily lives, as measured by the respective Asthma Trigger Inventory subscale, showed larger increases in Rrs5 and Rrs20 during unpleasant films under placebo conditions [r(51) = 0.39 and 0.34, P = 0.008 and 0.013, respectively] (for more detailed findings, see supplement, available in the online version of this article).

DISCUSSION

Airway Response to Emotional Stimulation and Its Attenuation by Ipratropium

In this study, we demonstrated airway constriction to unpleasant emotional stimuli in asthma patients, which was attenuated significantly by cholinergic blockade. Whereas airway constriction to negative stimuli and stress has been shown in asthma patients before (22, 40, 42), this is the first study to demonstrate an involvement of the cholinergic pathway in such responses. It confirms earlier speculations about involvement of the cholinergic pathway in psychologically induced bronchoconstriction (e.g., Refs. 22, 35). Because stronger airway responses to emotional stimuli were not correlated with methacholine PC20, such responses do not seem to be a function of greater sensitivity of the airways to a normal level of cholinergic stimulation. Rather, stronger centrally mediated vagal excitation would be a more likely explanation for increases in resistance observed during unpleasant stimulation.

The alternative explanation that the observed bronchoconstriction might be due to sympathoadrenergic mechanisms is unlikely for the following reasons. First, there is no direct functional sympathetic innervation in humans (3, 9), and, although possible sympathetic modulation of cholinergic activity at the ganglia might occur, its extent is not well explored. Stress-induced sympathetic influences on the airways would thus mainly cause an effect via circulating epinephrine, which leads to relaxation of the airway smooth muscles. Second, sympathetic withdrawal rather than excitation or reductions in circulating catecholamines rather than increases would need to have occurred under negative emotion induction; however, this is a more unlikely scenario in the arousal of unpleasant affect (5). Third, the abolition of bronchoconstriction to negative emotional stimuli by cholinergic blockade strongly suggests a cholinergic pathway of constriction.

The number of asthma patients responding with Rrs5 and Rrs20 increases that approach typical thresholds for just noticeable change [as defined by added resistive load studies (14)] was largely comparable to results shown in earlier research with similar stimulation material (40), with 19% and 13% of patients exceeding such thresholds for films and pictures, respectively. Research on bronchoconstrictive suggestion has typically found that 20–40% of patients report to stimulation, depending on samples and varying criteria of clinical significance. Thus a subset of asthma patients will be particularly susceptible to psychological stimulation. Beyond that, it should be noted that responding was not discrete but a continuous variable. It is conceivable that unpleasant psychosocial situations that only lead to weak airway constrictions may nevertheless contribute to symptoms or asthma exacerbations if these airway constrictions are superimposed on the effects of other bronchoconstricting triggers such as exercise, infections, or allergens.

Resistance increases during unpleasant stimuli in healthy controls were similar to results shown in asthma patients, although more marginal in size. In contrast to asthma patients, decreases in resistance were observed during neutral and pleasant stimuli in healthy controls, with a notable consistency and magnitude that exceeded prior findings (40). Further exploration of underlying mechanisms may yield interesting new
insights into factors that may dilate the airways in health and disease.

**Association with Indicators of Airway Pathology, Asthma Severity, and Ventilatory Adjustments**

Our findings suggest that stimulation of the airways by experimental emotion induction is a relatively independent challenge procedure that yields an index of airway responsiveness that can be distinguished from indexes of local airway pathophysiology, such as nonspecific hyperresponsiveness (PC_{20} of methacholine), bronchodilator response to ipratropium, and airway inflammation (FeNO). The associations of airway responses to emotional stimuli with these indicators of airway pathophysiology were mostly nonsignificant in asthma patients, under both placebo and blockade conditions. Thus we suggest that emotional responsiveness of the airways in asthma is not just an epiphenomenon of underlying variations in the pathophysiological status of the airways, nor is it strongly linked to asthma severity within the limited range tested here. However, it informs about an aspect of airway reactivity that has relevance to a patient’s daily life: patients who reported before the experiment that psychological states are more frequently triggering asthma symptoms and exacerbations showed under unblocked conditions stronger responses to emotionally unpleasant film material. This replicated early findings with different film material (46) and provides a physiological basis to frequent claims of emotion- or stress-induced asthma.

The fact that these associations were tested between patients does not rule out that changes in life events, stress, and emotion, which may occur within patients over longer periods of time, could be associated with change indexes of airway pathophysiology, such as inflammatory status. In one recent study, our group (28) observed that changes in negative stimuli and daily hassles over a 3-mo period were systematically associated with changes in lung function and that this association was mediated by changes in inflammation. Thus, although vagal excitation was the major pathway of the observed airway constriction to brief experimental stimuli, certain forms of psychological stress will affect asthma by their effects on airway inflammation, a conclusion supported by experimental research with asthma patients (e.g., Refs. 26, 32) and animal models of asthma (e.g., Refs. 23, 37). Short-term bronchoconstriction as observed in this study could add to or interact with the load exerted on the airways by exacerbation of inflammation.

Patients’ airway responses to unpleasant stimuli were also not substantially associated with breathing parameters. This would argue against the possibility that Rrs increases were epiphenomena of ventilatory adjustments, but we tested this association only between subjects, not within. It should be noted that some associations were observed in healthy controls during neutral and pleasant pictures, but none explained the pattern of response to unpleasant stimuli. Prior experimental research using film or picture stimuli has also yielded little consistent evidence for substantial contributions from ventilation (40). Ventilatory adjustments may be a more systematic factor in daily states of emotion or distress that can be more intense than experimentally induced emotional states.

**Localization of Airway Response to Emotional Stimulation**

The significant attenuation of airway constriction with ipratropium inhalation suggested that a substantial part of the response can be attributed to the central intrathoracic airways. Extrathoracic airway responses, such as narrowing of the larynx or partial closures of the glottis alone would not have been affected directly by blockade of muscarinic receptors (57). Increases in Rrs were typically observed across the frequency spectrum from 5 to 20 Hz, indicating that the central airways contributed as a main site to the observed constriction during unpleasant stimuli in unblocked conditions. In addition, the substantially larger increases in Rrs than in Rrs_{20} (i.e., increase in Rrs_{5}-Rrs_{20}) and increases in the magnitude of AX could suggest that the peripheral airways were also affected by unpleasant stimulation. Because the peripheral airways are less susceptible to ipratropium bromide (3), the small, albeit insignificant, increases shown for unpleasant stimuli under blockade could be attributed to this airway site, to extrathoracic airway contributions, or to incomplete blockade due to variations in inhaler technique. However, even subtle laryngeal aperture changes such as in subvocalization lead to much larger changes in resistance (Goldman, unpublished observations), making this extrathoracic pathway an unlikely contributor to the present findings. On a cautionary note, inferences about localization are far from perfect with indirect techniques, such as impulse oscilometry used in this study. However, although direct methods may have the potential of yielding more conclusive findings regarding sites of airway constriction, they can also be expected to interfere substantially with the process of emotional experience and thus compromise the validity of the experimental procedure.

**Limitations**

Limitations of this study include the predominance of intermittent to mild persistent asthma in our patient sample. Lung function measures, including basal Rrs, Xrs, and f_{res}, also suggested that asthma was well controlled in these patients; also, one-third of the participants were not taking any antiasthmatic medication. Psychosocial factors have been shown to be important in patients with more difficult or more severe asthma (11, 56). We decided to exclude patients who had more severe asthma and who had recently required systemic corticosteroids because of the profound steroid effects on airway reactivity and inflammation. Consequently, generalization of our findings to severe or uncontrolled asthma is not possible. However, within the restricted range of severity grades sampled in this study, no dependency of emotion-induced airway response on asthma severity was observed. Our sample was also limited with respect to demographic variables in that patients were relatively young and were highly educated on average. Although the findings in terms of resistance increases during unpleasant stimuli concur with earlier research on samples with different demographics (47), a systematic comparison of emotion-induced airway reactivity across demographic subpopulations of patients would be needed. Finally, because the major focus of this study was on changes in airway mechanics, we had not selected healthy controls for nonatopic status, resulting in half of the control sample presenting with positive allergy skin tests. This may also have affected FeNO values in this sample, which on average slightly exceeded 20.
ppb as the commonly applied threshold for clinically relevant inflammation. Similarly, our asthma group also included patients with FeNO or PC20 below the clinical threshold, which could be due to less severe (intermittent) or well-controlled asthma (13). However, wider ranges in FeNO and PC20 values and limited overlap in atopic status and hyperreactivity probably resulted in a more conservative test for differences between patients and healthy controls and for associations between these parameters and emotion-induced airway responsiveness. Recalculation of the analyses with only methacholine-positive patients did not substantially change the main findings.

In conclusion, asthma patients showed significant airway constriction to unpleasant stimuli, which was significantly attenuated by anticholinergic bronchodilators. In addition to central cholinergic airway constriction, peripheral airways may also contribute to increased resistance. Up to one-fifth of patients showed resistance increases that reached clinically relevant levels if not medicated. These patients did not show parameters and emotion-induced airway responsiveness. Recalculation of the analyses with only methacholine-positive patients did not substantially change the main findings.

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