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Role of Autonomic Nervous System and the Cough Reflex in the Increased Responsiveness of Airways in Patients with Obstructive Airway Disease *

B. G. SIMONSSON,‡ F. M. JACOBS,§ AND J. A. NADEL ||

(From the Cardiovascular Research Institute and the Department of Medicine, University of California San Francisco Medical Center, San Francisco, California)

Abstract. Inhalation of aerosols of citric acid, histamine phosphate, or carbon dust, or air cooled to − 20°C or rapid respiratory maneuvers (inspiration or expiration) results in an increase in airway resistance in some patients with asthma or bronchitis. It has been shown previously in animals that stimulation of cough receptors results in bronchoconstriction through efferent cholinergic pathways. In the patients studied, the administration of atropine sulfate, which would block such pathways, abolished the bronchoconstrictor effects of all the stimuli except large doses of histamine, which may exert a direct effect on airway smooth muscle. These data suggest that sensitized cough receptors may be involved in triggering reflex airway constriction in such patients.

Introduction

Irritation of the conducting airways with a catheter (1), chemically inert dust (2), or sulfur dioxide (3) stimulates cough but also causes reflex bronchoconstriction in animals. The responsible receptors appear to be subepithelial irritant or "cough" receptors in the airways, and the efferent pathways are via the vagus nerves. In healthy humans, these irritants also increase airway resistance; this bronchoconstriction can be prevented by prior i.v. injection of atropine sulfate, which suggests that cholinergic efferent pathways are also involved in the response in humans. There is evidence in animals that alterations in the airways "sensitizes" the cough receptors so that they discharge at a lower threshold. Thus, in cats that have suppurative lung infections or have inhaled ammonia gas, pulmonary branches of the vagus nerves distributed to the bronchi show an inspiratory rhythm. This finding indicates that some receptors (presumably cough receptors) are stimulated by lung inflation (4) and that this stimulation results in increased efferent activity in the vagi (and increased bronchomotor tone) (5). Since patients with asthma (6, 7) and some patients with other chronic obstructive airway diseases (8, 9) increase their airway resistance and cough (10, 11) to a greater extent in response to smaller doses of various inhaled substances than do healthy individuals, we proposed that the increased "responsiveness" of the airways in this group of patients was due to sensitization of the cough receptors in the airways, and that many stimuli that elicit cough may cause bronchoconstriction by stimulating these receptors (12). We have tested this hypothesis, before and after i.v. injection of atropine sulfate (which blocks the efferent cholinergic pathways), by studying the response of the airways to various stimuli known to cause cough in patients with airway obstruction.

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|| Address requests for reprints to Dr. J. A. Nadel, Cardiovascular Research Institute, University of California San Francisco Medical Center, San Francisco, Calif. 94122.

Methods

Patients. The subjects included 13 male and 9 female patients with obstructive airway diseases (ages, 13–64 yr). 13 patients had bronchial asthma, diagnosed on the basis of clinical history, presence of eosinophilia in the sputum, and evidence that the disease was completely reversible after prolonged therapy. Nine patients had chronic bronchitis, diagnosed on the basis of clinical history of cough and sputum for at least 3 months of the year for at least 2 yr. The patients had decreased 1 sec-timed vital capacity, decreased maximal expiratory airflow rates, and increased airway resistance at the time of one study. Three of the patients were also studied when their airway resistance was normal. No patient received treatment on the day of the study.

Measurement of resistance to airflow. We measured both the amount of constriction in response to each stimulus and the changes in the response with time. We performed studies measuring the response of the airways to the various stimuli before and after atropine, while each subject sat in a closed 900 liter body plethysmograph. The patient panted through a flowmeter for several seconds at a frequency of 2 cycle/sec; during this time we measured his airway resistance at flow rates of 0.5 liter/sec (13). A shutter closed between the mouthpiece and the flowmeter and we measured the patient's thoracic gas volume (14). The patients panted at a convenient lung volume during the control measurements of airway resistance, but we attempted to compare the effect of various maneuvers on airway resistance at similar levels of lung inflation. Each test consisted of four consecutive measurements of airway resistance and thoracic gas volume. The resistance of the apparatus, 0.2 cm of H_2O/liter per sec, was subtracted from each value of airway resistance. The average of the four corrected values was converted to its reciprocal (1/resistance), which is airway conductance. All data from plethysmographic studies are expressed as airway conductance/thoracic gas volume (G_A/TGV) in order to correct for small variations in lung volume during testing (15). After making control measurements, we opened the door of the plethysmograph and exposed the patient to the stimulus and repeated the measurements. The sequence of procedures was varied to avoid the possibility of tachyphylaxis during an experiment. Later, we repeated the procedures 10 min after administering 1.0–2.0 mg of i.v. atropine sulfate, or, in the study of inhalation of cold air, after 5–10 breaths of 0.5% atropine sulfate aerosol delivered from a Vaponefrin nebulizer (Vaponefrin Co., New York, N. Y.). To study the time course of the changes in airflow resistance we introduced an esophageal balloon into the lower third of the patient's esophagus, and measured the difference between pressures there and at the mouth as a reflection of transpulmonary pressure. Patients were seated, wore a noseclip, and breathed through the mouth during all procedures. We measured airflow with a Fleisch pneumotachograph (Instrumentation Associates, New York, N. Y.) and Statham differential strain gauge (Statham Instruments, Inc., Los Angeles, Calif.), and obtained a volume signal by integrating the airflow signal electrically. We determined pulmonary resistance, which equals airway resistance plus viscous resistance of

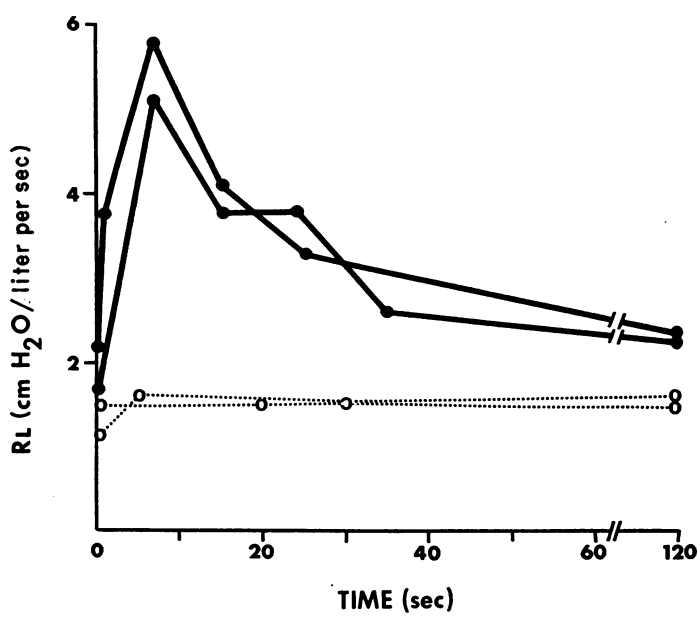

FIG. 1 *a*. TIME COURSE OF CHANGES IN TOTAL LUNG RESISTANCE (*RL*) AFTER INHALATION OF ONE BREATH OF 20% CITRIC ACID AEROSOL IN ONE PATIENT. The procedure was performed twice before (solid line) and twice after (dotted line) injection of 2.0 mg of atropine sulfate.

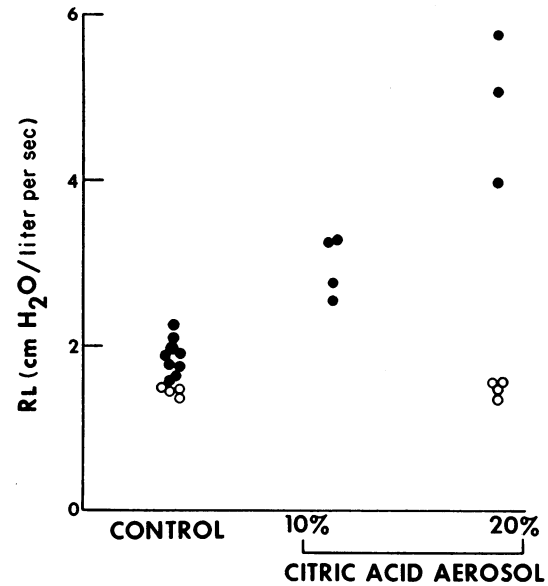

FIG. 1 *b*. EFFECT OF CONCENTRATION OF CITRIC ACID AEROSOL ON CHANGES IN TOTAL LUNG RESISTANCE (*RL*) IN ONE PATIENT BEFORE (SOLID CIRCLES) AND AFTER (OPEN CIRCLES) I.V. INJECTION OF 1.5 MG OF ATROPINE SULFATE. Each point represents a single measurement. The patient inhaled one breath of the aerosol at each concentration.

lung tissue, by a method of electrical subtraction (16). By this means we were able to study changes in airflow resistance from breath to breath.

Stimuli. Aerosols of citric acid (10–20%) and histamine phosphate (various concentrations, reported as percentage histamine base) were delivered from a Vaponefrin nebulizer. The patient inhaled normal tidal volumes from the nebulizer. Charcoal dust, 4–10 mesh, was delivered by a steady airstream, 20 liters/min, after elutriation through three bottles. Cold air flowed through a copper coil submerged in a mixture of acetone and dry ice; the air temperature at the mouthpiece was −20 to −25°C.

To study the effect of respiratory maneuvers, we measured the control airway conductance at the lung volume chosen by the patient. Then we instructed the patient to take either a rapid deep inspiration or rapid forced expiration and return to the control lung volume; we repeated the measurements within 15 sec.

Results

Citric acid aerosol. Inhalation of five breaths of citric acid aerosol decreased G_A/TGV in each of five patients (mean decrease, 30%; $P < 0.025$). Changes in resistance to airflow (RL) were present as early as we were able to make measurements (less than 5 sec after inhalation), reached a maximum within 30 sec, and returned to control values in 1–3 min (Fig. 1 *a*); increasing the dose increased the response of the airways (Fig. 1 *b*). After i.v. atropine sulfate, inhalation of citric acid aerosol no longer decreased G_A/TGV (mean decrease, 4%; $P > 0.2$), although the patients still wanted to cough.

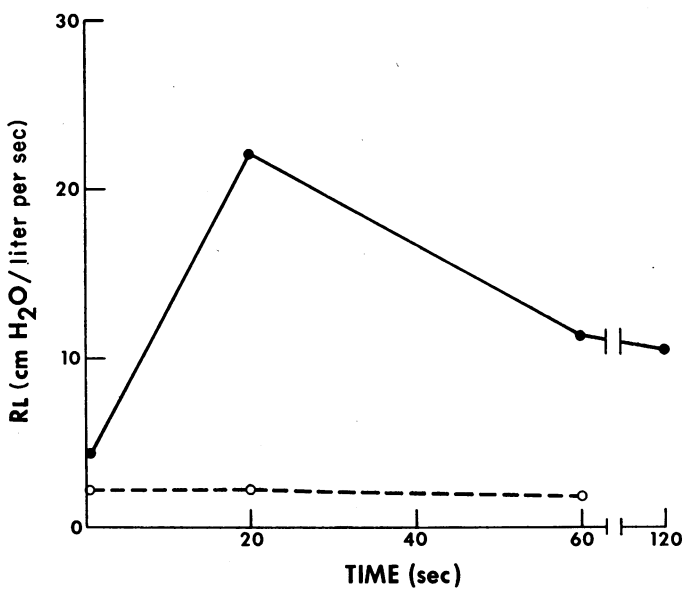

FIG. 2. TIME COURSE OF CHANGES IN TOTAL LUNG RESISTANCE (*RL*) AFTER INHALATION OF COLD AIR IN ONE PATIENT. The study was performed before (solid line) and after (dashed line) i.v. injection of 2.0 mg of atropine sulfate.

Maximal inspiration and maximal expiration. After a single rapid maximal inspiration, G_A/TGV measured at lung volumes comparable to those of the control state decreased temporarily in each of six patients (mean decrease, 38%; $P < 0.001$); after atropine, rapid inspiration no longer resulted in a significant decrease in G_A/TGV (mean increase, 4%; $P > 0.1$). After a single rapid maximal expiration, G_A/TGV decreased in each of six patients (mean decrease, 49%; $P < 0.001$). After atropine, further maximal expiratory maneuvers no longer resulted in a significant change in G_A/TGV (mean increase, 13%; $P > 0.5$). Rapid maximal inspiration frequently stimulated a desire to cough, both before and after atropine.

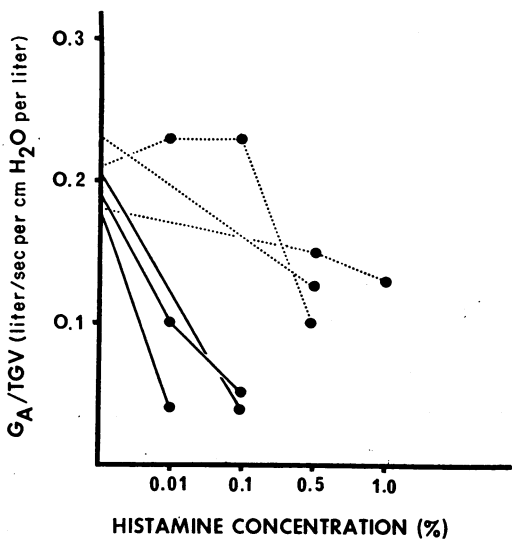

FIG. 3. COMPARISON OF EFFECT IN THREE HEALTHY SUBJECTS AND IN THREE ASTHMATIC PATIENTS OF INHALATION OF 10 BREATHS OF VARIOUS CONCENTRATIONS OF HISTAMINE PHOSPHATE AEROSOL ON AIRWAY CONDUCTANCE/THORACIC GAS VOLUME (G_A/TGV). Healthy subjects, dotted line; asthmatic patients, solid line.

Inhalation of charcoal dust. Inhalation of 10 breaths of charcoal dust decreased G_A/TGV in each of six patients (mean decrease, 45%; $P < 0.001$). Atropine stopped the response in five of the six patients (mean decrease, 15%; $P > 0.05$). Inhalation of dust, before and after atropine, stimulated a sensation of tickling in the throat and a desire to cough in most patients.

Inhalation of cold air. Breathing cold air for 2 min decreased G_A/TGV in each of nine patients (mean decrease, 27%; $P < 0.001$). Resistance

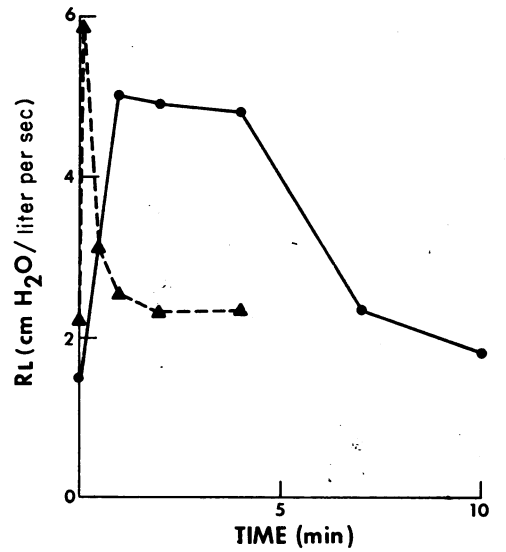

FIG. 4. COMPARISON OF TIME COURSE OF CHANGES IN TOTAL LUNG RESISTANCE (R_L) AFTER INHALATION OF ONE BREATH OF 20% CITRIC ACID AEROSOL (DASHED LINE) AND AFTER INHALATION OF 10 BREATHS OF 0.01% HISTAMINE PHOSPHATE AEROSOL (SOLID LINE) IN ONE PATIENT.

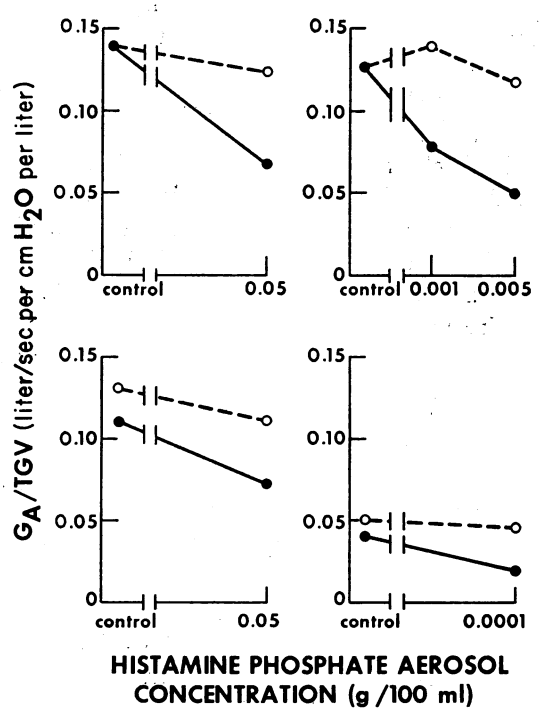

FIG. 5. EFFECT OF INHALATION OF 10 BREATHS OF VARIOUS. CONCENTRATIONS OF HISTAMINE PHOSPHATE AEROSOL ON AIRWAY CONDUCTANCE/THORACIC GAS VOLUME (G_A/TGV). In four asthmatic patients the study was performed before (solid line) and after (dashed line) i.v. injection of a 2 mg of atropine sulfate.

to airflow increased within 20 sec after inhalation of cold air and returned to control levels within 2–3 min (Fig. 2). Atropine abolished the response (mean increase, 6%; $P > 0.2$).

Inhalation of histamine phosphate aerosol. We compared the effect of inhalation of different doses of histamine in three healthy subjects with its effect in three asthmatic patients who had normal G_A/TGV at the time of the study: asthmatic patients required a much smaller dose of histamine for significant decrease in G_A/TGV than did the healthy subjects (Fig. 3). Resistance to airflow (R_L) returned to control levels more slowly after histamine aerosol than after citric acid aerosol (Fig. 4) or after inhalation of cold air. Atropine decreased the response to histamine in four patients (Fig. 5).

Discussion

Atropine sulfate decreased or prevented the bronchoconstriction that usually occurred in patients with chronic obstructive airway disease after introduction of various stimuli known to stimulate cough. This finding suggests that the response of the airways to these stimuli is mediated by efferent cholinergic pathways. If the response is due to a reflex, what are the responsible receptors? Each of the stimuli we chose is known to stimulate cough receptors. Various inhaled "irritants" that stimulate cough, including mechanical irritation of the airway (1), chemically inert dust (2), and sulfur dioxide (3), reflexly constrict the airways in animals and in healthy humans. The afferent and efferent pathways are the vagus nerves and the responsible receptors are believed to be cough or subepithelial receptors in the airways. Therefore, we suggest that the airway responses in our studies are due to stimulation of "sensitized" cough receptors in patients with obstructive airway disease. Patients with asthma and some patients with other obstructive airway diseases do seem to respond more readily to cough-provoking substances (10, 11). Curiously, the investigators who have demonstrated this decreased threshold for cough have used as stimuli the same substances shown to cause bronchoconstriction by other investigators (i.e., histamine and citric acid). We suggest that the increased responsiveness in terms of airway size and in terms of cough is due to stimulation of the same receptors, i.e., the cough receptors. The lowered threshold could be due to irritation of the airway mucosa by such things as inflammation, abrasion, or antigen-antibody reactions.

Atropine sulfate abolished or decreased the bronchoconstriction but had no significant effect on the cough in response to various stimuli. This suggests that the drug was acting on the efferent arc of the bronchoconstriction reflex, rather than on the cough receptors. The dose of atropine sulfate used in our study was larger than the dose usually given as medication to induce dryness of the mouth (17), but the dose we used is far less than the pharmacologic dose required in animals to prevent the effects of electrical stimulation of the peripheral ends of the cut vagi (0.5 mg/kg).

The physical and chemical characteristics of the stimuli we used were very different and this was reflected in the responses evoked. The airway response to citric acid aerosol was rapid and brief: the stimulus may have been due to the low pH, and rapid buffering of the acid in the airway could explain the rapid return of airway size to the control state. Inhalation of cold air also had a brief effect. It is curious that inhalation of cold air narrows the airways since normally the air is warmed rapidly in the large conducting airways before it reaches the small airways responsible for most of the total resistance to airflow. This in itself suggested the possibility that a reflex was involved and that the receptors were located in the upper airways. The rapid warming of the air may explain the short-lived nature of the response. Inhalation of chemically inert dust resulted in bronchoconstriction in our patients as it did in healthy subjects (13); in both cases, the responses were prevented by atropine sulfate.

After temporary rapid maximal inspiration, the airways either temporarily narrow only slightly (18) or not at all (19) in healthy subjects; in our patients, this maneuver caused marked narrowing of the airways. Rapid expiratory maneuvers had similar effects. Both rapid inspiration and rapid expiration stimulate cough receptors, particularly when these receptors have been "sensitized" by infection or by inhalation of ammonia gas (4).

Histamine caused a more prolonged bronchoconstriction than citric acid. This could be due to a less rapid disappearance or neutralization of the histamine from the airway. Histamine is gen-

erally considered to constrict the airways solely by its local effect on airway smooth muscle. However, most studies testing with this substance have used isolated muscle strips, and the results may not be wholly true for muscles in situ: that the bronchoconstriction resulting from small doses of histamine injected into a bronchial artery (and therefore distributed primarily to the conducting airways) can be abolished completely by bilateral cervical vagotomy or by prior administration of i.v. atropine sulfate indicates that cholinergic efferent pathways are involved (20). That study also indicated that the afferent pathways were in the pulmonary vagi. We suggested that histamine stimulated cough receptors (inhalation of histamine aerosol is followed by coughing), which initiated reflex bronchoconstriction. When the dose of histamine injected into the bronchial artery of dogs was increased, part of the effect was shown to be present after vagotomy, which suggested that an additional local effect of histamine was now also present. In our present experiments histamine was less effective after atropine, which suggested that part of the effect was due to a reflex.

Our findings are compatible with those of a previous study, which showed that hexamethonium bromide decreased the responsiveness of asthmatic patients to histamine to nearly normal levels, suggesting that autonomic ganglia were involved in the response (21).

The most common single factor which precipitates acute attacks of asthma during operation on an asthmatic patient is the introduction or presence of an endotracheal tube (22). We suggest that this may be due to stimulation of cough receptors. Otherwise healthy individuals may show increased responsiveness of their bronchi during or shortly after acute infections of the upper respiratory tract (23). This gives further evidence that alteration of the airways by many different forms of "irritation" may result in increased responsiveness of the airways.

All the present studies are compatible with our hypothesis that increased responsiveness of the airways to various stimuli which cause cough and bronchoconstriction is "specific" in that it is due to increased sensitivity of the cough receptors, but "nonspecific" in that the increased sensitivity of the cough receptors may be caused by many different processes.

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