Handgrip-induced airway dilation in asthmatic patients with bronchoconstriction induced by MCh inhalation

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Dipartimento di1 Area Critica Medico Chirurgica, 2Scienze Fisiologiche, and 3Fisiopatologia Clinica, Università degli Studi di Firenze, I-50134 Florence, Italy; and 4Department of Respiratory Paediatrics, Barts and The London NHS Trust, London E1 1BB, United Kingdom

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Fontana, Giovanni A., Tito Pantaleo, Federico Lavorini, Fulvia Bongianni, Massimo Mannelli, Peter D. Bridge, and Massimo Pistolesi. Handgrip-induced airway dilation in asthmatic patients with bronchoconstriction induced by MCh inhalation. J Appl Physiol 93: 1723–1730, 2002—We investigated the effects of static and rhythmic handgrip on the time course of recovery of airway resistance measured with the interrupter technique (Rint) following bronchoconstriction induced by methacholine (MCh) inhalation in 17 asthmatic patients. On three separate occasions, a 100 ± 5% increase in baseline Rint was induced by MCh inhalation. Subsequently, patients either rested (control trials [CTs]) or performed 3-min bouts of static or rhythmic handgrip. Respiratory and cardiovascular variables were continuously monitored. Rint changes were assessed at 1-min intervals for 30 min after rest and both types of handgrip. Plasma catecholamine concentrations were also determined at scheduled intervals. Bronchoconstriction increased ventilation (P < 0.01) but did not affect cardiovascular variables and plasma catecholamine concentrations. Handgrip provoked an increase in cardiovascular variables (P < 0.01) and plasma norepinephrine concentrations (P < 0.05) but caused no additional changes in ventilation. Rint only partially recovered within 30 min after CTs, whereas it consistently decreased 1 min after both handgrip paradigms and remained lower than after CTs (P always <0.01) for the whole 30-min observation period. Sympathetic activation and withdrawal of cholinergic input to the airway smooth muscle reflexly induced by activation of skeletal muscle and carotid sinus receptors may be the primary events accounting for the bronchodilator response induced by handgrip. Mediators co-released in response to sympathetic activation may also have contributed.

interrupter technique; pattern of breathing; exercise

ADDITION OF AEROSOLIZED bronchoconstrictor agents, such as histamine and methacholine (MCh), is widely used to document nonallergic bronchial hyperresponsiveness. Despite the large amount of work devoted to the study of the airway constrictor response evoked by inhalation of these and other agents, the time course of recovery of airway resistance after induced bronchoconstriction has received much less attention (11, 14). Spontaneous recovery from intense bronchoconstriction induced by MCh inhalation has been shown to occur slowly; up to 3 h may be required for its completion (11). Besides the natural degradation of the agonist and its clearance by the bronchial circulation (47), additional factors may be of importance in determining the time course of recovery. For instance, bronchoconstriction causes reflex increases in ventilation (24), which, in turn, may reflexly cause airway smooth muscle relaxation (13). Studies in the anesthetized rabbit have shown that increases in the amplitude and rate of mechanical ventilation decrease airway narrowing provoked by intravenous MCh administration, a phenomenon likely due to effects of stretching of the airway smooth muscle on force generation (41).

It is well established that the adaptive responses evoked by exercise also include prominent increases in cardiorespiratory activity (48) and bronchodilation (45), which are to be ascribed partly to the reflex and mechanical effects exerted by the exercise hyperpnea (45). However, additional exercise-specific bronchodilator mechanisms have also been implicated. Submaximal exercise is associated with increased sympathetic activity (43); thus bronchodilation could be related to the increases in plasma catecholamine concentrations that occur during exercise (4), as well as to the release of inhibitory nonadrenergic noncholinergic neurotransmitters that are colocalized with norepinephrine (NE) in sympathetic motor nerves (52). Noticeably, epinephrine (E) infusions producing plasma concentrations similar to those achieved during intense exercise have been shown to induce bronchodilation and protection against induced bronchoconstriction, both in patients with bronchial asthma (25, 38) and in normal subjects (38). Animal experiments indicated that signals conveyed by thin myelinated (group III) and unmyelinated (group IV) muscle afferents, which have been shown to participate in the reflex cardiorespiratory adjustments induced by exercise (21), also influence airway smooth
muscle tone. In fact, an inhibitory bronchomotor reflex has been demonstrated in the anesthetized animal; a decrease in tracheal smooth muscle tension is produced when chemical stimulants of group III and IV muscle afferents are injected into the arterial supply of hindlimb muscles (22) or when isometric contractions of hindlimb muscles are evoked by electrical stimulation of the appropriate ventral roots (23, 28). Bronchodilator responses of similar intensity may also originate from receptors located in the carotid body in response to pressor stimuli, such as those that are commonly observed during isometric exercise (39).

Previous human studies (17, 18) have shown that sustained static muscular exercise of forelimb muscles (handgrip) elicits pressor and ventilatory responses. Rhythmic (intermittent) handgrip has been shown to induce cardiovascular responses similar to those of sustained static handgrip (2), but the respiratory adjustments evoked by this form of exercise have been less extensively investigated (20). So far, no attempts have been made at evaluating the influence of handgrip on airway tone, neither in normal subjects nor in patients with airway diseases.

We observed in preliminary trials that, in normal (n = 4) and asthmatic (n = 5) subjects with normal baseline airway tone, 3-min static handgrip bouts at 30% of the maximum voluntary contraction (MVC) (shG30) caused in most of them changes in airway tone ranging from 0 to −45% of baseline. Because, in some instances, handgrip-induced bronchodilation may be difficult to appreciate, especially when control airway caliber is within the normal range, we preferred to evaluate asthmatic patients in whom bronchoconstriction of similar degree (approximately +100% of baseline) had been induced experimentally. This approach also allowed us to minimize the confounding effects of differences in baseline airway smooth muscle tone that may be present in patients with natural asthma. Therefore, the present experiments were undertaken to investigate the effects of static and rhythmic handgrip on the time course of recovery of airway resistance after bronchoconstriction induced by MCh inhalation in asthmatic patients.

METHODS

Patients. Seventeen asthmatic outpatients (10 men, and 7 women, median age 27.0 yr, range 20–36 yr) participated in the study. All patients were nonsmokers and had allergic seasonal or perennial asthma, i.e., the presence of at least one positive immediate skin reaction to a battery of common inhaled allergens. They were in a stable clinical and functional state and were not on maintenance treatment with oral bronchodilators or corticosteroids. None of them had suffered from recent (within 4 wk) respiratory infections. They did not participate in competitive sports or take part in training programs that could alter their catecholamine response to physical exertion (19). All had normal arterial blood pressure (<140/90) and no history of cardiovascular diseases. They had participated in previous asthma studies and were fully familiarized with the laboratory equipment and provocation procedures. Patients’ baseline lung function data are summarized in Table 1. The study protocol adhered to the recommendations of the Declaration of Helsinki for Human Experimentation and was approved by the local ethics committee; informed consent was obtained from each participant.

Recording procedures. We measured airway resistance with the interruption method (Rint). Airway resistance is the ratio of the pressure gradient between the alveoli and the airway opening to the airflow. Pressure and flow were measured by means of a portable device (MicroRint, Micro Medical, Rochester, UK) consisting of an interrupting valve, a screen pneumotachograph, and a pressure transducer connected to a palmtop dedicated computer. This method for assessing airway resistance is based on the assumption that an imperceptible, brief airway occlusion during tidal breathing results in a pressure vs. time function that can be measured at the airway opening and used to estimate the alveolar pressure at the moment of the occlusion. The screen pneumotachograph, located between the pressure sensor and interrupter shutter, measures flow during tidal breathing. The ratio of the pressure difference between the estimated alveolar pressure at the moment of airway occlusion and the open-circuit pressure before occlusion to the flow measured immediately before airway occlusion yields the resistance of the conducting airways (Ref. 1, see also for further references). A brief interruption of expiratory flow was obtained by means of a rotating elliptical shutter. This design of shutter maximizes completeness of occlusion with a minimum of friction and loss of rapidity of closure. Manufacturer’s specifications of the shutter state that closure occurs within 5–6 ms, with an occlusion period of 100 ms. Interruption was at peak expiratory flow, the preProgrammed manufacturer’s default setting. This should correspond, approximately, to midexpiratory tidal volume (VT), thus minimizing the influence of breath-to-breath variations in lung volume and, hence, in airway resistance (33). Interruptions occurred after a random number of breathing cycles (one to four), to prevent patients from anticipating shutter closure. The screen of the palmtop computer connected to the interrupter head displays the flow pattern during tidal breathing between interruptions. After a set of interruptions has been completed, this display can be used to validate mouth pressure and time functions (10) and to show simple summary statistics. Measurements were undertaken with the patient breathing through a disposable flanged mouthpiece and barrier filter (MicroGard, Sensormedics, Yorba Linda, CA) positioned between the patient’s mouth and measuring device. Filter resistance was preliminarily checked in five pieces randomly selected from the available stock by means of a rotameter and a pressure transducer. Mean (±SD) filter resistance value was 0.035 ± 0.006 KPa·l⁻¹·s⁻¹. This value was similar to that incorporated in the software of the device. Rint measurements are likely to be influenced by face and neck positioning, and, therefore, an arm supporting the measuring device was used to ensure standardized positioning of the patient’s head and mouthpiece on a horizontal plane, with the neck

<table>
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<tr>
<th>FVC</th>
<th>FEV₁</th>
<th>FEV₁/FVC</th>
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<td>Mean</td>
<td>95.72</td>
<td>93.82</td>
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<td>SE</td>
<td>2.37</td>
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Values are percent predicted. FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; FEV₁/FVC, ratio of FEV₁ to FVC; FRC, functional residual capacity.
slightly extended (5). Rint measurements were performed with a technician supporting the patient's cheeks and pharynx to reduce cheek and upper airway compliance (5).

Breathing pattern was recorded by means of the respiratory inductive plethysmograph (RIP: Respiracite, Non-invasive Monitoring System, Ardsley, NY). The device was calibrated according to the procedure devised by Sackner et al. (36); validity of calibration was evaluated both by analyzing RIP waveforms during an isovolume maneuver and by comparing changes of VT amplitude and end-expiratory lung volume measured by spirometry with RIP values (36). The sum of rib cage and abdominal RIP signals, which closely reflects the VT measured at the airway opening, was fed to an eight-channel chart recorder (HP 7758A, Hewlett Packard, Palo Alto, CA). On paper recordings, we measured, on a breath-by-breath basis, the VT, the duration of inspiratory (Ti) and expiratory times, and the total duration of the respiratory cycle (Tt). The respiratory rate (f = 60/Tt), the respiratory drive (VT/Ti), and the inspiratory minute ventilation (VT × f = VT) were subsequently calculated. Augmented breaths, i.e., the breaths approximating or exceeding twice the control VT observed during handgrip and control trials (CTs) were counted. The fractional end-tidal CO2 (FETCO2) was also continuously monitored (Normocap CD 2300, Datex, Helsinki, Finland).

Static and rhythmic handgrip were performed by using the dominant hand, which grasped an isometric dynamometer connected to a strain-gauge transducer. The transducer signal was continuously displayed on an oscilloscope positioned in front of the patients to help them to maintain the desired level of contraction. Mean arterial blood pressure (MAP) and heart rate (HR) were continuously monitored noninvasively by using finger photoplethysmography (Finapres BP Monitor 2300, Ohmeda, Englewood, CO) from the second phalanx of the middle finger of the nonexercising hand, as previously reported (17, 18). The MAP and HR signals were also displayed on the chart recorder.

MCh-induced bronchoconstriction. MCh inhalations were carried out with a technique similar to that employed in previous studies (16). In brief, patients inhaled doubling MCh concentrations ranging from 0.125 to 16.00 mg/ml through a DeVilbiss no. 646 nebulizer (DeVilbiss, Somerset, PA) driven by a constant airflow (8 l/min). Each challenge was preceded by inhalation of 0.9% saline as a control solution. Both saline and MCh were inhaled during tidal breathing for 2 min (but see Protocol); a 5-min interval was allowed between each inhalation period. The bronchial response was assessed by measuring 8–10 Rint values 90 s after inhalation of either saline or each MCh concentration. The highest and lowest recorded Rint values were always discarded, as well as those whose pressure-time curves were not consistent with those reported in the literature, e.g., showing a negative gradient after shutter closure, indicating artifacts due to air leakage (10). The remaining six to eight Rint values had a coefficient of variation <10%, and the mean value was used for data analysis (6). MCh inhalation was discontinued when Rint values increased by 100 ± 5% of the corresponding postsaline value.

Blood samples and laboratory assays. Samples of venous blood for catecholamine measurements were drawn from the cannulated large forearm vein of the nonexercising forearm. In all instances, an initial 3-ml sample of blood was discarded; 10-ml samples of blood were drawn into vacutainers containing 100 μl of a solution of glutathione (60 mg/ml) and EGTA (90 mg/ml). Blood samples were put immediately in an ice-water bath, centrifuged at 4°C, and stored at ~70°C until assayed. Plasma E and NE concentrations were measured in duplicate and in the same assay for each patient by a radioenzymatic method previously described (30), using a CAT-A-Kit (Amersham, Buckinghamshire, UK) and according to the basic principles of Passon and Peuler (34). The sensitivity of the method was 20 and 15 pg/ml for NE and E, respectively; the between-assay variability was 10 and 7.5% for NE and E, respectively.

Protocol. Patients attended the laboratory on three separate occasions separated by an interval of ~48 h. They were requested to abstain from all medications for the whole duration of the study and from caffeine-containing food for at least 12 h before each study day. After positioning of the RIP belts, patients were comfortably seated on a dentist's chair and were requested to relax fully with their head positioned in a slightly extended position. To this purpose, a soft cushion was placed between the patient's neck and the head rest. Patients were then connected to the airway resistance measuring device and were allowed to familiarize themselves with the equipment for 4–6 min. Subsequently, baseline measurements of Rint and cardiorespiratory variables were obtained during 3 min of tidal, quiet breathing, which was judged by inspection of the RIP signals. Care was taken to ensure that patients' baseline Rint values did not significantly vary between each study day. If Rint values turned out to be outside the accepted variability range (±15% compared with the first study day), the experimental session was rescheduled. If baseline Rint values proved to be within the accepted variability range, a 18- or 20-gauge Teflon catheter-over-needle intravenous line was inserted into a large forearm vein after local anesthesia, with injection of 1% lidocaine to the skin. This intravenous catheter was attached to a three-way stopcock apparatus, with one port available for blood sampling and the other connected to a 0.9% saline solution to keep the vein patent. After insertion of the venous line, each patient was allowed to relax for at least 30 min. A blood sample for baseline assessment of baseline catecholamine concentration was subsequently collected. Patients were then administered doubling MCh concentrations, preceded by inhalation of 0.9% saline as a control solution, while cardiorespiratory variables were continuously monitored. Changes in Rint were reassessed 90 s after inhalation of saline and each MCh concentration. To obtain, in each patient, a Rint increase as close as possible to +100% of the corresponding postsaline value, the last MCh administration could be tapered by reducing the inhalation time. Once the desired degree of bronchoconstriction had been achieved, an additional blood sample for measuring catecholamine plasma level was obtained. Then patients were randomly requested to rest for 3 min (CTs) or to perform either a 3-min sHG30 or a 3-min rhythmic (twelve 2-s contractions repeated every 3 s) handgrip at 60% of their MVC (rHG60). MVC values were determined as the mean value (coefficient of variation <5%) of the peak force developed during three consecutive MVCs lasting at least 3 s and performed at 5-min intervals. These handgrip paradigms producing the same total work output (9) were selected because, in previous studies (17, 18) and/or in preliminary trials, they were found to induce relatively intense cardiorespiratory responses and to be tolerated by the subjects without pain or discomfort. Changes in Rint values and in cardiovascular and respiratory variables were reassessed, at 1-min intervals, for 30 min after the completion of each 3-min period of rest or exercise. Additional blood samples for catecholamine assays were obtained 1 and 12 min after rest or exercise.

Data analysis. To analyze changes in breathing pattern variables observed during MCh inhalation, CTs, sHG30, and rHG60 bouts, all recorded breaths were considered, except
formed. All reported values are means obtained at each interval similarly per-
period. Comparisons of plasma NE and E concentrations are made as mean (±
variation of postsaline (control) values. Increases in baseline Rint observed at maximum metha-
line, at the predetermined level of MCh-induced bronchocon-
changes in HR and MAP values recorded at base-
served after CTs and shHG30 and rHG60 runs were −13.6 ± 1.1, −36.1 ± 1.7,
and −32.7 ± 0.7% respectively (Fig. 2).
changes in Rint values after sHG30 did not signif-
ance (P < 0.01). Mean control \( F_{ETCO_2 \text{}} \) diminished from 5.9 ± 0.1 to 4.6 ± 0.1% (P < 0.01). During both shHG30 and rHG60 bouts, Vi displayed further, slight increases, mainly due to ad-
additional rises in VT; these handgrip-induced increases in Vi did not reach the level of statistical significance and did not cause additional changes in \( F_{ETCO_2 \text{}} \). After exercise, overall mean (30-min periods) Vi and Vt/Ti/
values remained significantly higher (P always < 0.05) than the corresponding postsaline values. No differ-
ences were observed between changes in the pattern of breathing recorded after shHG30 and rHG60 runs. The number of augmented breaths was 2.0 ± 0.6 (range 0–8), 2.8 ± 0.7 (range 0–8), and 4.2 ± 0.6 (range 0–6).

**RESULTS**

After MCh inhalation, mean percent increases in postsaline Rint attained before CTs and shHG30 and rHG60 runs were 102.0 ± 1.8, 103.7 ± 1.7, and 103.9 ± 2.1%, respectively. No significant differences were found among these values. The time course of mean percent changes in Rint observed after the completion of CTs as well as of shHG30 and rHG60 bouts is depicted in Fig. 1. Within 1 min after sHG30 and rHG60 runs, mean Rint values significantly decreased to similar extents (60.3 ± 4.0% after shHG30, and 65.3 ± 2.3% after rHG60) of the respective post-MCh values (P always < 0.01). Three minutes after the completion of shHG30 and rHG60 runs, mean Rint values consistently displayed moderate increases up to levels corresponding to 74.1 ± 4.3 and 77.9 ± 2.9% of the respective post-MCh value (Fig. 1). In all experimental conditions, Rint values recorded from the 3rd min to the completion of the observation period proved to decrease in an approximately linear fashion, although those recorded after both types of handgrip consistently displayed levels lower than those recorded after CTs (Fig. 1).

Compared with post-MCh values, the overall (30-
min periods) mean percent reductions in Rint after CTs and shHG30 and rHG60 runs were −13.6 ± 1.1, −36.1 ± 1.7, and −32.7 ± 0.7%, respectively (Fig. 2).

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Analysis of variance revealed that both shHG30 and rHG60 bouts caused more marked mean percent Rint decreases than CTs (P always < 0.01), and that the reduction in Rint observed after shHG30 did not significantly differ from that attained after rHG60 (Fig. 2).

On each study day, mean baseline \( V^\text{ti} \) values (Fig. 3A) were similar and corresponded to 9.25 ± 0.70, 9.95 ±
75.5, and 9.50 ± 0.74 l/min, respectively, on CTs and on shHG30 and rHG60 study days. In all experimental conditions (Fig. 3A), when Rint had augmented by
100% after MCh inhalation, mean \( V^\text{ti} \) significantly rose from the corresponding control value (P always < 0.01). The increase in \( V^\text{ti} \) could be achieved, in some occasions, by prevailing increases in VT or, more frequently, by increases in both VT and f. In all instances, \( V^\text{ti}/T^\text{ti} \) also increased significantly (P < 0.01). Mean control \( F_{ETCO_2 \text{}} \) diminished from 5.9 ± 0.1 to 4.6 ± 0.1% (P < 0.01). During both shHG30 and rHG60 bouts, \( V^\text{ti} \) displayed further, slight increases, mainly due to ad-
additional rises in VT; these handgrip-induced increases in \( V^\text{ti} \) did not reach the level of statistical significance and did not cause additional changes in \( F_{ETCO_2 \text{}} \). After exercise, overall mean (30-min periods) \( V^\text{ti} \) and \( V^\text{ti}/T^\text{ti} \) values remained significantly higher (P always < 0.05) than the corresponding postsaline values. No differ-
ences were observed between changes in the pattern of breathing recorded after shHG30 and rHG60 runs. The number of augmented breaths was 2.0 ± 0.6 (range 0–8), 2.8 ± 0.7 (range 0–8), and 4.2 ± 0.6 (range 0–6).
and C). There was no significant difference between mean peak HR and MAP values recorded during sHG30 and rHG60 runs. With the cessation of exercise, HR and MAP consistently resumed their control values within 2 min (Fig. 3, B and C) and did not display significant changes during the remaining 28 min of the observation period.

As shown in Fig. 4, mean venous blood E and NE concentrations observed at baseline in CTs, as well as on sHG30 and rHG60 study days, were similar. MCh-induced bronchoconstriction did not induce significant changes in these variables. In contrast, 1 min after the completion of both sHG30 and rHG60 bouts, venous blood NE concentrations attained similar values that were higher than those recorded in control conditions and at maximum bronchoconstriction (P always <0.05). In all instances, NE concentrations measured 12 min after completion of each motor task were similar to those of control conditions; changes in venous blood E concentrations were small and inconsistent. No variations in plasma catecholamine concentrations were recorded during CTs.

DISCUSSION

This study in asthmatic patients analyzes the time course of recovery of Rint values after bronchoconstriction induced by MCh inhalation occurring either spontaneously or after 3-min bouts of static and rhythmic handgrip. The results of CTs indicate that the magnitude of the bronchoconstrictor response decreases with

during CTs, sHG30, and rHG60, respectively; no significant differences were found among these values.

On each of the 3 study days, baseline HR (70.73 ± 5.90, 69.48 ± 6.14, and 70.73 ± 5.60 beats/min) and MAP (80.31 ± 4.89, 77.60 ± 5.22, and 79.67 ± 5.22 mmHg) values did not significantly differ and showed only minimal, nonsignificant increases after MCh-induced bronchoconstriction (Fig. 3, B and C). As expected, cardiovascular variables did not change during CTs, and their values were significantly different (P always <0.01) from those observed during handgrip. In fact, during the 3-min exercise runs, both cardiovascular variables displayed progressive, significant increases up to peak values that were consistently attained by the end of the 3rd min of exercise (Fig. 3, B and C). There was no significant difference between mean peak HR and MAP values recorded during sHG30 and rHG60 runs. With the cessation of exercise, HR and MAP consistently resumed their control values within 2 min (Fig. 3, B and C) and did not display significant changes during the remaining 28 min of the observation period.

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time in an approximately linear fashion, whereas the results of handgrip runs show that the recovery from induced bronchoconstriction follows a biphasic pattern. In the early postexercise phase (within 1 min), Rint displays a clear reduction, followed by a partial rebound toward higher values at 3 min (Fig. 1). Subsequently, i.e., during the remainder of the 30-min observation period, postexercise Rint progressively decreases at about the same rate as that observed after CTs, although consistently displaying lower levels. In addition, the magnitude of the overall bronchodilator response was similar after both handgrip paradigms and significantly greater than that observed after CTs (Fig. 2).

We have monitored changes in airway resistance by means of the interrupter technique. The physiological basis and clinical utility of the interrupter technique have been reevaluated (e.g., Refs. 12, 27), and the theoretical analysis by Bates et al. (1) has validated the technique. This technique has recently been proved to provide reliable estimates of airway resistance after MCh-induced bronchoconstriction (35), as well as to accurately assess the response to bronchodilators in the presence of preexisting bronchoconstriction (29). The interrupter technique is noninvasive, requires only passive cooperation, provides repeated estimates of airway resistance within a relatively short time interval, and, perhaps more importantly, allows the simultaneous assessment of other relevant variables, such as those derived from prolonged and undisturbed recordings of the breathing pattern. The use of variables derived from forced expirations for assessing changes in bronchial tone has been discarded, because these maneuvers require full inspirations that have been shown to alter airway smooth muscle tone (8, 40, 42).

After CTs, recovery from induced bronchoconstriction within the selected time frame was partial (Fig. 1). This finding is in keeping with previous observations in asthmatic patients showing limited recovery 30 min after MCh-induced bronchoconstriction (10, 14). Spontaneous recovery from induced bronchoconstriction reflects not only natural degradation of the agonist and its clearance from the bronchial circulation (47) but also the reflex effects evoked by airway smooth muscle contraction and the mechanical action exerted by increased ventilation (7, 37, 40, 42). Responses specifically evoked by exercise likely contributed to define the magnitude and time course of bronchodilation after handgrip.

In agreement with previous findings (24), the results show that, in asthmatic patients, MCh inhalation is accompanied by obvious increases in ventilation involving, as a rule, both the timing and drive components of the breathing pattern. These response are known to be reflex in origin (13) and can be ascribed to both direct (31) and indirect (13) airway receptor stimulation. The increases in Vt and Vl brought about by bronchoconstriction may have resulted in activation of other receptors, located both within and outside the respiratory tract. Signals arising from receptors located in the diaphragm that have been implicated in sympathetic activation during high-resistance breathing (43) may have reflexly influenced the time course of recovery from induced bronchoconstriction. In addition, feedback from slowly adapting pulmonary “stretch” receptors during the prolonged MCh-induced period of hyperventilation may have inhibited (32) the vagal bronchomotor neurons (vagal withdrawal). However, recent animal experiments indicate that vagotony does not prevent suppression of MCh-induced airway narrowing caused by increases in the volume and frequency of mechanical ventilation (41) and suggest that maintenance of airway patency in vivo may depend on the static interactions between lung volume and the degree of smooth muscle activation, as well as on the stress exerted by the lung parenchyma on the airways during breathing (7, 37, 49). These mechanical events have been implicated in the reversal of MCh-induced bronchoconstriction by large lung inflation to near total lung capacity in both normal subjects (42) and patients with bronchial asthma (40). Inspiratory excursions approximating or exceeding twice the control VT were occasionally recorded in our experiments and occurred during both CTs and HG runs. The effects of these “augmented breaths” were homogeneously distributed over all of the experimental conditions considered in the present study; thus they unlikely account for the bronchodilator responses observed immediately after handgrip cessation. Nevertheless, we can hypothesize that increases in ventilation of similar degrees can differentially affect the time course of Rint changes, depending on the level of airway smooth muscle tone on which they exert their mechanical action. Because handgrip consistently decreased Rint, the stretching effects of increased ventilation on dilated airways could have contributed in maintaining their caliber at a lower level throughout the whole 30-min observation period.

The results confirm (17, 18, 20) that static and rhythmic handgrip paradigms producing the same total work output (9) evoked prominent rises in MAP and HR (Fig. 3). The cardiovascular responses elicited by isometric exercise are thought to be mediated by both an increase in efferent sympathetic nerve activity and a decrease in efferent vagal cardiac nerve activity (17, 18, see also for further references). Because handgrip caused no significant increase in circulating E but markedly increased HR, it is most likely that vagal withdrawal was the main mechanism involved not only in the mediation of tachycardia but also in the genesis of airway smooth muscle relaxation.

Handgrip-induced cardiovascular responses were accompanied by slight, nonsignificant, additional increases in Vt and Vl compared with those already attained after MCh inhalation. This finding is not surprising, because it seems obvious that the intense ventilatory response evoked by prior MCh inhalation did not warrant the development of the full range of ventilatory adjustments normally elicited by static (17, 18) and rhythmic (20) handgrip (occlusion phenomena).
Animal studies have demonstrated that static contractions of the hindlimb muscles induced by electrical nerve stimulation (23, 28), as well as injections of algesic substances into the arterial supply of the muscle (22), are accompanied by a reflex reduction in airway smooth muscle tone. It seems conceivable that the same mechanisms are implicated in the bronchodilator response evoked by both forms of handgrip. Whether supraspinal mechanisms, the so-called “central command” (48), have a role in the regulation of airway smooth muscle tone during voluntary exercise remains to be investigated. The reflexogenic drive arising from the working muscles, along with the central command, has also been implicated in sympathetic activation (43), which may occur also in response to prolonged, low-intensity (25% MVC) rhythmic handgrip causing no apparent stimulation of chemosensitive muscle endings (2).

In agreement with previous findings (38), we found no significant changes in venous catecholamine concentrations in response to bronchoconstriction (Fig. 4). The finding of selective increases in NE plasma levels in response to isometric exercise is in keeping with previous observations obtained in normal subjects who performed static handgrip runs at the same contraction intensity as that used in the present study (e.g., Refs. 9, 30). Previous studies in normal subjects (46) have reported slight but significant increases in both E and NE plasma levels after handgrip bouts of the same intensity as that used in the present experiments but sustained until exhaustion. Handgrip runs were sustained without difficulty for 3 min by our patients and were not accompanied by muscle pain or discomfort (18). Whether the increases in circulating NE observed in the present experiments have a role in the genesis of the bronchodilation observed after sHG30 and rHG60 bouts remains unclear. In the light of earlier results showing no change in airway patency in response to NE infusions in asthmatic patients (3, 26), it seems unlikely that the mild, albeit significant, handgrip-induced rise in plasma NE concentration contributed to the postexercise decrease in Rint observed in the present experiments. However, the possibility exists that the action of NE is more evident when the airway smooth muscle is precontracted by MCh inhalation. Because handgrip-induced increases in circulating NE in this and previous experiments (30) have been shown to be short lasting, the effects exerted by this hormone, if any, were most likely confined to the decrease in Rint observed shortly after handgrip cessation. In light of available literature, inhibitory nonadrenergic noncholinergic neurotransmitters, such as nitric oxide and neuropeptide Y, which are coreleased with NE by sympathetic motor nerves (52), may contribute to airway smooth muscle relaxation. Due to its long-lasting activity (51), neuropeptide Y may also have a role in maintaining a decreased airway tone for the whole 30-min observation period (Fig. 1).

Although studies in animal models (50) and in isolated human airway smooth muscle (5) have demonstrated airways dilation with severe hypoxemia, the results of studies performed in normal subjects seem to deny this possibility (15). Thus a significant effect of hypoxemia on the time course of recovery from induced bronchoconstriction appears unlikely and, furthermore, possibly counterbalanced by an opposing effect (44) exerted by the concomitant reduction in PETCO2 provoked by hyperventilation in the present experiments. The carotid baroreflex has an influence on airway smooth muscle extending over the normal range of arterial pressures (39): increases in carotid body pressure decreases tracheal tension, whereas decreasing sinus pressure has the opposite effect (39).

Airway smooth muscle relaxation is likely to represent a normal component of the adaptive response to isometric exercise. In fact, preliminary trials have documented a reduction in baseline airway resistance in most of the normal subjects and asthmatic patients with normal baseline airway caliber who performed 3-min static handgrip runs at the same contraction intensity as that employed in the present study. Additionally, previous studies have demonstrated airway dilation by brief, graded exercise in humans with normal or experimentally constricted airway smooth muscle (see Ref. 13 for references).

In conclusion, we propose that the bronchodilator response induced by handgrip results mainly from the combined action of reflex withdrawal of cholinergic input to airway smooth muscle evoked by the simultaneous activation of skeletal muscle afferents and carotid sinus receptors (52), possibly with some contribution by mediators released in response to sympathetic activation.

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