Exercise-induced bronchodilation in natural and induced asthma: effects on ventilatory response and performance

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We studied whether bronchodilatation occurs with exercise during the late asthmatic reaction (LAR) to allergen and whether this is sufficient to preserve maximum ventilation (VEmax), oxygen consumption (VO2 max), and exercise performance (Wmax). In group 1, partial forced expiratory flow at 30% of resting forced vital capacity increased during exercise, both at control and LAR. Wmax was slightly reduced at LAR, whereas VEmax, tidal volume, breathing frequency, and VO2 max were preserved. Functional residual capacity and end-inspiratory lung volume were significantly larger at LAR than at control. In group 2, partial forced expiratory flow at 30% of resting forced vital capacity increased greatly with exercise during NA but did not attain control values after appropriate therapy. Compared with control, Wmax was slightly less during NA, whereas VO2 max and VEmax were similar. Functional residual capacity, but not end-inspiratory lung volume at maximum load, was significantly greater than at control, whereas tidal volume decreased and breathing frequency increased. In conclusion, remarkable exercise bronchodilation occurs during either LAR or NA and allows VEmax and VO2 max to be preserved with small changes in breathing pattern and a slight reduction in Wmax.

Subjects

We studied two groups of subjects (Table 1) with established diagnosis of bronchial asthma (1) who regularly attended our Asthma Clinic. Subjects of group 1 were under stable control of asthma in the last 4 wk before the study. They were known to be sensitized to house dust mites and to develop a LAR on experimental inhalation of this allergen. Subjects of group 2 had less stable control of asthma and were recruited to the study when they attended the clinic because of deterioration of their disease. The subjects of both groups were taking short-acting β-agonists on demand. All subjects gave a written, informed consent as approved by the local Ethics Committee.

Resting Lung Function Measurements

A Vmax 6200 Autobox (SensorMedics, Yorba Linda, CA) was used to obtain standard spirometry and lung volume measures. Flow was measured at the mouth by a mass flowmeter and numerically integrated to obtain inspired and expired volumes. Spirometry was performed according to the American Thoracic Society recommendations (2). Thoracic gas volume was measured by whole body plethysmography with the subjects panting against a closed shutter at a frequency slightly < 1 Hz, with their cheeks gently supported by their hands. Total lung capacity (TLC) was obtained as the sum of thoracic gas volume and the inspiratory capacity taken immediately after the shutter was open. Functional residual capacity (FRC) was corrected for any difference in volume between the volume at which the shutter was closed and the four preceding end-tidal expirations. Residual volume (RV) was obtained by subtracting vital capacity from TLC. Predicted values are from Quanjer et al. (35). Diffusion capacity for carbon monoxide (DLCO) was measured by a single-breath technique (SensorMedics 2200) (23).

Exercise Test and Measurements

A symptom-limited exercise test was performed on an electronically braked cycle ergometer (Esaote Biomedica, Largo R. Benzi 10, 16132 Genova, Italy (E-mail: brusasco@dism.unige.it)).

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In the present study, RV were repeated as a single set over the last 20 s of each expiratory volume in 1 s; FVC, forced vital capacity; V˙ during inspiration and expiration and numerically integrated through rapid gas analyzers. Flow was continuously measured breath by breath through rapid gas analyzers. Significance was estimated as the difference between the tidal expiratory flow 100 ml above the increased FRC and the partial flow measured at the level of the lowest FRC ever recorded during the test. Thus EFR would become negative when FRC increased with exercise. A schematic representation of the computation of EFR at rest and during exercise is presented in Fig. 1.

Special care was taken to maintain the position of the trunk fairly constant during the test.

**Experimental Protocols**

**Group 1.** Subjects attended the laboratory on a prestudy day for clinical history, physical examination, electrocardiogram, and resting lung function measurements. Then they were coached to perform partial forced expiratory maneuvers and underwent a maximum exercise test.

In the midafternoon of 2 separate study days, subjects were tested for lung function and exercise under two conditions (control or LAR) in a random order. LAR was induced by an allergen challenge started at 9 AM and completed by administering double increasing doses of allergen (11) until Vpart 30, measured 15 min after dosing, was decreased by at least 36% and 0.16 l/s of control. At each step, forced expiratory volume in 1 s (FEV1) and FVC were also recorded immediately after the partial forced expiratory maneuver. Subjects were then monitored hourly until a LAR was manifested with a decrease in Vpart 30 of the same extent as above. Lung function and exercise studies were performed from 3:00

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**Table 1. Anthropometric and functional characteristics of the subjects**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>LAR</th>
<th>Control</th>
<th>NA</th>
</tr>
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<tbody>
<tr>
<td>M/F</td>
<td>10/4</td>
<td>2</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>25 ± 4</td>
<td>34 ± 15</td>
<td>17 ± 7</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>176 ± 7</td>
<td>172 ± 7</td>
<td>23 ± 2</td>
<td>25 ± 3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23 ± 2</td>
<td>26 ± 2</td>
<td>25 ± 3</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. M, male; F, female; LAR, late asthmatic reaction; NA, natural asthma; BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; Vmax 30, V˙max 30, Vpart 30, ratio of Vmax 30 to Vpart 30; TLC, total lung capacity; DLCO, single-breath carbon monoxide diffusing capacity. Significant difference vs. control: *P < 0.05, †P < 0.01, and ‡P < 0.001.

Genoa, Italy) with the subject wearing a nose clip and breathing through the mass flow sensor (dead space, 75 ml) connected to a saliva trap. Heart rate (HR) was continuously recorded (Acta-Plus, Esaote Biomedica, Genoa, Italy). Oxygen uptake (VO2) and carbon dioxide output (VCO2) were measured breath by breath through rapid gas analyzers (Vmax, SensorMedics). Flow was continuously measured during inspiration and expiration and numerically integrated to determine tidal volume (VT). After a 6-min resting measurement and 2-min warm-up, the exercise load was increased by 25 W every 2 min, with the subjects pedaling at 50–60 rpm, until the imposed load could no longer be sustained.

At rest, three reproducible sets of maneuvers, consisting of four to six regular tidal breaths immediately followed by a forced expiration from end-tidal inspiration to near RV (partial forced expiration), a forced inspiration to TLC, and finally a forced expiration from TLC to RV, were performed. Flow was measured at 30% of forced vital capacity (FVC) from partial (Vpart 30) and maximal (Vmax 30) expirations and at 50% of FVC from forced inspiration. The same maneuvers (with the exception of the final forced expiration from TLC to RV) were repeated as a single set over the last 20 s of each load step up to maximum exercise. In the present study, Vpart 30 was used to detect the changes in airway caliber, for it is not affected by the flow during exercise. Changes in FRC and end-inspiratory lung volume (EILV) were estimated from changes in end-tidal expiratory and inspiratory volumes relative to TLC, assuming the latter remains unchanged during exercise. Expiratory flow reserve (EFR) was determined at each load step from the difference between partial and tidal expiratory flows 100 ml above FRC (33). If FRC was increased at some level of ventilation, then EFR was estimated as the difference between the tidal expiratory

**Fig. 1.** Diagrammatic representation of computation of expiratory flow limitation by comparing tidal flow ~100 ml above functional residual capacity (FRC) (ET) with partial forced expiratory flows (Pt). Examples are given for rest (A) and mid- (B) and maximum exercise (C). In each panel, the loop is the flow-volume curve recorded during tidal breathing, and diagonal line is Pt: A: expiratory flow reserve (EFR) is the difference in flow between Pt and ET, as indicated by the 2 arrows. B: with exercise, tidal loop is accommodated to lower lung volumes than at rest, as indicated by horizontal arrow. Pt and ET are the same at the end of expiration, so that EFR is now 0. C: tidal flow-volume loop is accommodated to a higher lung volume (horizontal arrow) to allow greater ventilation than in B. Tidal expiratory flow still equals partial flow near end expiration, yet EFR is now considered <0, as tidal expiratory flow is greater than partial flow at the lowest lung volume ever attained during exercise, were not FRC forced to increase.
to 6:00 PM either at control or LAR for all subjects. Before dismissal, 200 µg inhaled salbutamol were administered.

Group 2. Lung function and maximum exercise tests were performed on two different occasions. The first study day was when the subjects attended the clinic because of deterioration of NA. At this visit, subjects were physically examined, underwent an electrocardiogram, and had resting lung function assessed. If they agreed to participate in the study, they were coached to perform partial forced expiratory maneuvers and underwent a maximum exercise test. At the end of the study, the patients were given 200 µg salbutamol and then dismissed with appropriate therapy (800–1,600 µg budesonide twice daily, and salbutamol on demand) (29). In the next 4–6 wk before the next study, the patients attended the clinic at weekly intervals for monitoring of lung function and symptoms. The second study day was performed 4–6 wk later (control), when lung function had returned near to the individual’s best value, when rescue medications had to be taken less than twice a week, and when daily symptoms and nighttime awakenings due to asthma disappeared. The study was conducted at the same time as on the previous study day. Before dismissal, 200 µg inhaled salbutamol were administered.

Data Analysis

Analysis of breathing pattern at rest and during exercise was conducted by taking only regular breaths recorded before partial forced expiratory maneuvers. VT and inspiratory (Ti) and expiratory times were calculated breath by breath (29). In the next 4–6 wk before the next study, the patients attended the clinic at weekly intervals for monitoring of lung function and symptoms. The second study day was performed 4–6 wk later (control), when lung function had returned near to the individual’s best value, when rescue medications had to be taken less than twice a week, and when daily symptoms and nighttime awakenings due to asthma disappeared. The study was conducted at the same time as on the previous study day. Before dismissal, 200 µg inhaled salbutamol were administered.

Statistics

Student’s unpaired and paired t-tests were used to analyze differences between groups and conditions. P < 0.05 was considered statistically significant. All values are expressed as means ± SD.

RESULTS

Group 1

At control, resting lung function was, on average, close to the predicted normal values (Table 1). At maximum exercise (Table 2), workload and VO₂ were near the lower limits of the predicted normal values, whereas HR and VO₂-to-HR ratio (VO₂/HR) were within the normal range. \( V_{\text{p30}} \) increased by almost twofold, so that average EFR was still above zero, thus suggesting that some ventilatory reserve remained at the end of exercise. \( V_{\text{p30}} \) at end exercise was significantly greater than \( V_{\text{max}} \) at rest. Both \( V_{\text{max}} \) was decreased by 59 ± 34%, and \( V_{\text{p30}} \) was decreased by 63 ± 26%, which corresponded to an average 25% decrease in FEV₁. Neither TLC nor DLCO changed compared with control (Table 1). At maximum exercise (Table 2), there was a small, although significant (P < 0.02), decrease in power output, whereas VO₂, VE, and the classical descriptors of breathing pattern were not significantly different from control. This was associated with a remarkable reversal of bronchoconstriction, as suggested by the increase in \( V_{\text{p30}} \) nearly to threefold. \( V_{\text{p30}} \) at end exercise was significantly greater than \( V_{\text{max}} \) at rest. Average EFR at end exercise was close to zero. Although VT was essentially unchanged throughout exercise, both FRC and EILV were accommodated to slightly higher volumes than at control (Fig. 2).

Table 2. Main variables at maximum exercise

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>LAR</th>
<th>Control</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work rate, W</td>
<td>181 ± 34</td>
<td>171 ± 33*</td>
<td>159 ± 33</td>
<td>144 ± 42*</td>
</tr>
<tr>
<td>%Predicted</td>
<td>81 ± 16</td>
<td></td>
<td>80 ± 13</td>
<td></td>
</tr>
<tr>
<td>VO₂, l/min</td>
<td>2.34 ± 0.54</td>
<td>2.32 ± 0.48</td>
<td>2.01 ± 0.41</td>
<td>2.00 ± 0.64</td>
</tr>
<tr>
<td>%Predicted</td>
<td>78 ± 17</td>
<td></td>
<td>73 ± 14</td>
<td></td>
</tr>
<tr>
<td>VO₂/HR, ml/min</td>
<td>13.2 ± 3.5</td>
<td>13.6 ± 3.3</td>
<td>12.2 ± 3.0</td>
<td>13.1 ± 3.5</td>
</tr>
<tr>
<td>%Predicted</td>
<td>88 ± 13</td>
<td></td>
<td>88 ± 24</td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>176 ± 10</td>
<td>170 ± 13</td>
<td>166 ± 11</td>
<td>161 ± 25</td>
</tr>
<tr>
<td>%Predicted</td>
<td>95 ± 6</td>
<td></td>
<td>94 ± 6</td>
<td></td>
</tr>
<tr>
<td>VE, l/min</td>
<td>79.9 ± 18.1</td>
<td>78.1 ± 15.7</td>
<td>71.7 ± 13.9</td>
<td>72.4 ± 24.8</td>
</tr>
<tr>
<td>VT, liters</td>
<td>2.50 ± 0.68</td>
<td>2.43 ± 0.61</td>
<td>2.15 ± 0.18</td>
<td>1.83 ± 0.37*</td>
</tr>
<tr>
<td>BF, breaths/min</td>
<td>32 ± 4</td>
<td>33 ± 5</td>
<td>34 ± 7</td>
<td>39 ± 8‡</td>
</tr>
<tr>
<td>( V_{\text{p30}} ), Vs</td>
<td>3.08 ± 1.22</td>
<td>2.22 ± 0.83‡</td>
<td>2.45 ± 0.93</td>
<td>1.33 ± 0.72*</td>
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<tr>
<td>EFR, Vs</td>
<td>0.35 ± 1.42</td>
<td>0.09 ± 0.95</td>
<td>-0.70 ± 0.84</td>
<td>-1.20 ± 1.12</td>
</tr>
<tr>
<td>VE/VO₂</td>
<td>29.7 ± 2.8</td>
<td>29.7 ± 2.9</td>
<td>31.6 ± 3.8</td>
<td>34.0 ± 2.9*</td>
</tr>
<tr>
<td>FRC, % of TLC</td>
<td>43 ± 3</td>
<td>48 ± 7†</td>
<td>43 ± 15</td>
<td>54 ± 13*</td>
</tr>
<tr>
<td>EILV, % of TLC</td>
<td>78 ± 5</td>
<td>83 ± 5*</td>
<td>77 ± 9</td>
<td>81 ± 7</td>
</tr>
<tr>
<td>PETCO₂, Torr</td>
<td>39.0 ± 3.5</td>
<td>38.8 ± 3.3</td>
<td>37.7 ± 4.8</td>
<td>37.0 ± 4.4</td>
</tr>
</tbody>
</table>

Values are means ± SD. VO₂, oxygen consumption; HR, heart rate; VO₂/HR, oxygen pulse; VE, minute ventilation; VT, tidal volume; BF, breathing frequency; EFR, expiratory flow reserve; VO₂CO₂, carbon dioxide production; VE/VO₂, ratio of VE to VO₂; FRC, functional residual capacity; EILV, end-inspiratory lung volume; PETCO₂, end-tidal CO₂ pressure. Significant difference vs. control: *P < 0.05, †P < 0.01, and ‡P < 0.001.
Box Group 2

At NA, resting lung function showed a moderate obstructive defect (Table 1). At maximum exercise (Table 2), power output and $\dot{V}O_2$ were below the lower limits of predicted normal. HR and $\dot{V}O_2$/HR were within the normal range. Although $\dot{V}E_{part \ 30}$ remarkably increased with exercise by more than twofold compared with $\dot{V}max_{30}$ (Fig. 3), EFR remained well below zero ($P < 0.05$), thus strongly suggesting that the low respiratory reserve contributed to limit exercise. $\dot{V}E_{part \ 30}$ at end exercise was significantly greater than $\dot{V}max_{30}$ at rest ($P < 0.01$).

At control after appropriate therapy, resting lung function significantly improved, even though airflow obstruction was not fully reversed (Table 1). TLC and $DLCO$ remained unmodified compared with NA conditions. At maximum exercise (Table 2), there was a slight increase in power output ($P < 0.05$) compared with NA, but not in $\dot{V}O_2$, which still remained below the lower predicted normal limits. HR and $\dot{V}O_2$/HR were similar to NA conditions but was achieved with a significantly lower BF ($P < 0.001$) and larger $\dot{V}T$ ($P < 0.05$). The latter was made possible by a greater reduction in FRC than at NA ($P < 0.01$). Also, the $\dot{V}E$-to-$\dot{V}CO_2$ ratio significantly decreased compared with NA conditions ($P < 0.05$). The increase in $\dot{V}E_{part \ 30}$ at maximum load was significantly greater than at NA ($P < 0.02$). Nevertheless, EFR remained still below zero and not different from NA conditions. $\dot{V}E_{part \ 30}$ at end exercise was significantly greater than $\dot{V}max_{30}$ at rest ($P < 0.02$).

Partial Forced Expiratory Maneuvers

The average volume at which the partial forced expiratory maneuvers initiated relative to EILV at rest

Fig. 2. Tidal and partial flow-volume curves recorded in a representative subject of group 1 at control (A) and late asthmatic reaction (LAR) to allergen (B). Total lung capacity is at the intersection of y- and x-axes. Thin lines, rest; dashed lines, 100 W; thick lines, 200 W. At LAR, the increase in $Pt$ is so remarkable that tidal loop at maximum exercise can be accommodated within the outer loop without substantial differences in tidal volume ($\dot{V}r$) and breathing frequency, compared with control. $\dot{V}r$ is, however, accommodated to slightly higher lung volumes than at control.

Fig. 3. Tidal and partial flow-volume curves recorded in a representative subject of group 2 after appropriate therapy (A) and at natural asthma (NA) deterioration (B). Thin lines, rest; dashed lines, 100 W; thick lines, 200 W. Even though at NA the increase in partial flow is considerable, it is not sufficient to let $\dot{V}r$ expand as much as at control conditions, because FRC remains high. As a result, breathing frequency increases to maintain adequate ventilation similar to control.
and at maximum exercise is presented in Table 3. There was a tendency for the maneuvers to initiate from slightly but significantly higher volumes than EILV, although this was not consistent in all circumstances.

**DISCUSSION**

The most important finding of the present study is that an incremental exercise performed during either LAR or NA was associated with a remarkable reversal of airway narrowing, which allowed maximum $V_e$ and $V_{O_2}$ to be fully preserved. Nevertheless, breathing pattern adjustments, such as an increase of the operational lung volumes variably associated with rapid, shallow breathing, were necessary to compensate for incomplete bronchodilator responses during NA.

**Bronchodilator Response to Exercise**

That bronchodilatation occurs during exercise has already been reported by others by using pharmaco logically induced bronchoconstriction (3, 4, 17, 20, 36). What is new in this study is that, in both LAR and NA, in which the inflammatory component of the airway wall is expected to be greater than during pharmaco logically induced bronchoconstriction (13, 15), thus possibly making airway narrowing more resistant to bronchodilators (9), reversal of airway narrowing during exercise was impressive and similar in magnitude to that previously reported with chemical agents prevalently acting on the airway smooth muscle (ASM) (17, 36).

Exercise may affect airway caliber in various ways. Increased blood levels of adrenaline with strenuous exercise (6) may stimulate the $\beta_2$-adrenoceptors, thus resulting in ASM relaxation. Although this hypothesis could explain, at least in part, our findings, data from the literature would suggest that this might not be the case, as release in adrenaline is remarkably less in asthmatic than in healthy subjects and isocapnic hyperpnea without exercise is associated with similar bronchodilatation without modifying the plasma levels of catecholamines (6). High alveolar $CO_2$ concentrations are known to decrease bronchial tone in vitro (14). Whether this may contribute to the explanation of our results seems to be unlikely, as end-tidal $CO_2$ tension remained stable within the normal range for most of the time in all of our subjects of both groups and decreased just toward the end of exercise similarly to what generally happens in normal subjects. In addition, no differences in end-tidal $CO_2$ tension were observed within groups at maximum load. A decrease of vagal tone could also contribute to bronchodilatation during exercise. However, as LAR and NA are not primarily vagal reactions, it may be hard to believe that this mechanism played a dominant role in our study. Release of bronchodilator agents, such as NO, has been postulated as one of the mechanisms sustaining bronchodilatation during exercise in normal humans (8). However, recent data suggest rather that NO may contribute to exercise-induced bronchoconstriction (12, 26).

In the present study, changes in airway caliber during exercise were assessed by the use of partial forced expiratory flows measured at absolute lung volume. Compared with the more conventional lung function parameters, such as $FEV_1$, $FVC$, and instantaneous maximal flows at absolute lung volume, $V_{part\ 30}$ is more sensitive to changes in airway caliber, for it is not affected by the volume history effects of the deep breath preceding the maximum forced expiratory maneuver (32). In addition, its measurement is highly reproducible (31), as long as the volume at which partial forced expiratory maneuver is initiated is standardized and as long as TLC is actually achieved with the following inspiratory maneuver. For the purpose of the study, we asked our subjects to start the maneuver as close as possible from end-tidal expiration. The reported differences in Table 3 between the volume at which the maneuvers were initiated relative to EILV at maximum exercise would suggest some slight over estimation of bronchodilatation with maximum exercise, with the exception of group 2 at NA, yet not certainly sufficient to invalidate our interpretation of the remarkable increase in $V_{part\ 30}$. We do not have data proving that TLC was really always achieved with the inspiratory maneuver performed immediately after the forced expiration. However, the fact that all of the subjects were well cooperative and well instructed to perform reproducible maneuvers makes us confident that alignment of the partial flow-volume curves at TLC was sufficiently correct.

The effects of deep breaths on airway mechanics in vivo are well known (18, 27, 32). If the airway-to- parenchymal forces of interdependence are intact, the force generated with the deep inspiration is applied to the outer surface of the airway wall and from this to the underlying ASM. This would decrease the bronchial tone by two basic mechanisms: detachment of rapid-cycling cross bridges (16) or change in the configuration of the contractile elements inside the myocytes (21). Therefore, the increased depth of tidal breathing may be regarded as a mechanism leading to bronchodilatation during exercise. Although appealing, this explanation is apparently not sufficient to explain our results for two main reasons. First, if this were the case, then $V_{part\ 30}$ at maximum exercise should have been similar to or even less than $V_{max\ 30}$ before exercise. Second, our data are apparently in contrast to the notion that deep breaths to TLC are

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Table 3. Average difference between tidal EILV and volume from which partial expiratory maneuver initiated

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rest</th>
<th>Maximum Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.04 ± 0.21</td>
<td>0.35 ± 0.36‡</td>
</tr>
<tr>
<td>LAR</td>
<td>0.01 ± 0.02</td>
<td>0.29 ± 0.36§</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.13 ± 0.12*</td>
<td>0.31 ± 0.11§</td>
</tr>
<tr>
<td>NA</td>
<td>0.12 ± 0.25</td>
<td>0.06 ± 0.27</td>
</tr>
</tbody>
</table>

Values are means ± SD in liters. Significant difference vs. EILV; *$P < 0.02$, ‡$P < 0.01$, §$P < 0.001$. 

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ineffective in distending constricted airways in asthma (32, 34), which has been interpreted as the result of loss of airway-to-parenchymal interdependence or exaggerated stiffness of the contractile or noncontractile elements of the airways (27, 34). Can the hypothesis that the remarkable bronchodilatation observed with exercise in our asthmatic subjects was the result of the large breaths be reconciled with the notion that the deep breaths in asthma little affect airway mechanics? It is tempting to speculate that multiple tidal breaths of increasing magnitude are more effective in reducing airway tone than a single or a short series of deep breaths to TLC.

**Ventilatory Adaptation**

We observed two types of breathing adaptation to maximum exercise with LAR and NA. The first one was typical of LAR and was characterized by a selective increase in the operational lung volumes, i.e., FRC and EILV, without changes in VT and BF. The second one mostly occurred with NA and was characterized by more profound breathing adaptations, i.e., selective increase in FRC with constant EILV, decrease in VT, and increase in BF.

Increase in FRC has been repeatedly reported in chronic airflow obstruction during exercise (5, 22, 24, 25, 28, 30, 33) when the increase in tidal expiratory flow is such to equal or encroach on maximal flow. This condition is called expiratory flow limitation (EFL). Although difficult to prove, an appealing hypothesis linking EFL and increase in FRC during exercise is that, with the dynamic compression of the airways, neural stimuli arising from the triggered mechanoreceptors of the large intrathoracic airways could prematurely activate the inspiratory muscles, thus shifting the entire breath to a higher lung volume far from the EFL condition (5, 30, 33). The results of the present study are in line with this reasoning. All of the subjects with no or little EFR at rest could decrease FRC as soon as partial flow started increasing. Without reversal of airway narrowing, FRC would have increased instead, as generally observed in severe and fixed chronic obstructive pulmonary disease.

More complex is the interpretation of the rapid and shallow breathing occurring during NA at maximum exercise. One possibility is that the increase in FRC without a proportional increase in EILV would have constrained VT to remain low, thus requiring an increase in BF to achieve the required increase in VE. If this were the case, the increase in BF should have appeared only at high workloads. Analysis of individual responses to exercise showed that BF started to increase from the beginning of exercise during NA but not at control or during LAR (Fig. 4). This suggests that rapid, shallow breathing was caused by a primary increase in either FRC or BF. There are several stimuli (such as histamine, allergens, capsaicin, vascular congestion, dynamic compression of the airways) that may cause premature termination of the expiratory phase and tachypnea by acting on rapidly adapting receptors (10). We speculate that a larger amount of inflammatory mediators, airway wall edema, and intraluminal secretions during NA than LAR could lead to more severe airway narrowing and more airway dynamic collapse during tidal expiration.

**Effects on Exercise Performance**

Rapid, shallow breathing may be expected to impact on VE. With a small VT and high BF, indeed, dead space ventilation becomes relatively greater than alveolar
ventilation. Thus for a given $\dot{V}_{\text{CO}_2}$, $\dot{V}_E$ has to increase to maintain a constant arterial $\text{CO}_2$ tension. In this sense, the observed increase in the $\dot{V}_E$-to-$\dot{V}_{\text{CO}_2}$ ratio at maximum exercise would indicate that at least part of the $\dot{V}_E$ was inefficient for gas exchange.

Despite the preservation of $\dot{V}_E$ and $\dot{V}_{\text{CO}_2}$, maximum exercise capacity was slightly but significantly less during either LAR or NA compared with the respective control conditions. Although not specifically investigated in this study, we feel that this difference may represent an increased cost of breathing.

Conclusions

In conclusion, maximum $\dot{V}_E$ and $\dot{V}_{\text{CO}_2}$ during exercise are generally well preserved during LAR and NA, thanks to an impressive reversal of airway obstruction. This is likely due to the mechanical stretching of the tidal breaths on the airway walls. Breathing pattern adjustments, such as increase in operational lung volumes and rapid, shallow breathing, may be required to compensate for incomplete bronchodilator responses.

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REFERENCES


