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

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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 6 wk before the study. They were known to be sensitized to house dust mites and to develop a late asthmatic reaction (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.

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 exposure to allergen and 2) whether this effect, if present, is sufficient to preserve maximum ventilation and exercise capacity.

METHODS

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 exposure to allergen and 2) whether this effect, if present, is sufficient to preserve maximum ventilation and exercise capacity.

IN HEALTHY SUBJECTS, FORCED expiratory flows slightly increase during exercise, which suggests bronchodilatation (19, 24, 25, 33). In asthma, bronchodilatation with exercise has been inconsistently reported (3, 4, 7, 8) 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 closed and the four preceding end-tidal expirations. Residual volume (RV) was obtained by subtracting tidal volume decreased and breathing frequency increased. In conclusion, remarkable exercise bronchodilatation occurs during either LAR or NA and allows VE,max and VO2,max to be preserved with small changes in breathing pattern and a slight reduction in Wmax.

incremental exercise; natural asthma; late asthmatic reaction; deep inhalation; breathing pattern

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five to six regular tidal breaths immediately followed by a
maximal (Vmax, SensorMedics) expirations and
finally a forced expiration from TLC to RV, were performed.
Flow was measured at 30% of forced vital capacity (FVC)
respectively; Vmax 30/Vpart 30, ratio of Vmax 30 to Vpart 30; TLC, total
lung capacity; DlCO, single-breath carbon monoxide diffusion
capacity. Significant difference vs. control: ‡P < 0.05, †P < 0.01, and
§P < 0.001.

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, measured
at the level of the lowest FRC ever recorded during
exercise, FRC is now 0. Pt and ET are the same at the end of expiration, so that EFR
indicated by the 2 arrows. A: expiratory
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 a higher lung volume 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.

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 a higher lung volume than at rest, as indicated by horizontal arrow. Pt and ET are the same at the end of expiration, so that EFR
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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.

Experimental Protocols

Group 1. Subjects attended the laboratory on a prestudy
day for clinical history, physical examination, electrocardio-
gram, 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 condi-
tions (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 expira-
tory 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 mani-
fested with a decrease in Vpart 30 of the same extent as above.
Lung function and exercise studies were performed from 3.00
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 in-
creased 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.

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 inte-
grated 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 sus-
tained.

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 (par-
tial forced expiration), a forced inspiration to TLC, and
partially a maximal forced expiratory flow of 30% of FVC,
respectively; Vmax 30/Vpart 30, measured 15 min after dosing, was decreased by at
least 36% and 0.16 l/s of control. At each step, forced expira-
tory 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 mani-
fested with a decrease in Vpart 30 of the same extent as above.
Lung function and exercise studies were performed from 3.00

Table 1. Anthropometric and functional characteristics of the subjects

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>10/4</td>
<td>6/2</td>
</tr>
<tr>
<td>Age, yr</td>
<td>25 ± 4</td>
<td>34 ± 15</td>
</tr>
<tr>
<td>Height, cm</td>
<td>176 ± 7</td>
<td>172 ± 7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23 ± 2</td>
<td>25 ± 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>LAR</th>
<th>Control</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, liters</td>
<td>3.93 ± 0.85</td>
<td>2.96 ± 0.83</td>
<td>2.98 ± 0.79</td>
<td>2.08 ± 0.55</td>
</tr>
<tr>
<td>% Predicted</td>
<td>95 ± 14</td>
<td>79 ± 17</td>
<td>97 ± 10</td>
<td></td>
</tr>
<tr>
<td>FVC, liters</td>
<td>4.99 ± 1.18</td>
<td>4.41 ± 1.22</td>
<td>4.36 ± 0.89</td>
<td>3.57 ± 0.67</td>
</tr>
<tr>
<td>% Predicted</td>
<td>103 ± 14</td>
<td>97 ± 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vmax 30, l/s</td>
<td>2.17 ± 0.85</td>
<td>0.86 ± 0.70</td>
<td>1.23 ± 0.63</td>
<td>0.55 ± 0.48</td>
</tr>
<tr>
<td>Vpart 30, l/s</td>
<td>1.81 ± 0.85</td>
<td>0.62 ± 0.46</td>
<td>1.31 ± 0.49</td>
<td>0.42 ± 1.26</td>
</tr>
<tr>
<td>Vmax 30/Vpart 30</td>
<td>1.29 ± 0.42</td>
<td>1.62 ± 0.59</td>
<td>0.81 ± 0.48</td>
<td>1.61 ± 1.21</td>
</tr>
<tr>
<td>TLC, liters</td>
<td>7.08 ± 1.34</td>
<td>7.01 ± 1.40</td>
<td>6.63 ± 1.01</td>
<td>6.98 ± 1.16</td>
</tr>
<tr>
<td>% Predicted</td>
<td>107 ± 8</td>
<td>103 ± 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DlCO, ml•min⁻¹•l⁻¹</td>
<td>35.2 ± 6.0</td>
<td>33.7 ± 5.9</td>
<td>32.4 ± 5.1</td>
<td>34.5 ± 5.8</td>
</tr>
<tr>
<td>Torr⁻¹</td>
<td>102 ± 10</td>
<td>105 ± 9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Anthropometric and functional characteristics of the subjects

![Flow-volume loop](image_url)
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 wk after the first study day (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 dismissed, 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 time (TI) and expiratory times were calculated breath by breath and averaged over several breaths. This allowed minute ventilation (VT), breathing frequency (BF), mean inspiratory (ratio of VT to TI) and expiratory flows (ratio of VT to expiratory time), and ratio of TI to total respiratory cycle duration to be computed. Partial forced expiratory flow at rest and during exercise was measured at 30% of the largest FVC at control of either test (V_{part 30}). Thus, assuming TLC is constant between and within study days, V_{part 30} was always taken at the same absolute lung volume.

**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 VO_{2} were near the lower limits of the predicted normal values, whereas HR and VO_{2}-to-HR ratio (VO_{2}/HR) were within the normal range. V_{part 30} 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_{part 30} at end exercise was significantly greater than V_{max 30} at rest (P < 0.001).

At LAR, V_{max 30} was decreased by 59 ± 34%, and V_{part 30} was decreased by 63 ± 26%, which corresponded to an average 25% decrease in FEV_{1}. Neither TLC nor DL_{CO} 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 VO_{2}, 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_{part 30} nearly to threefold. V_{part 30} at end exercise was significantly greater than V_{max 30} at rest (P < 0.001). 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>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>LAR</td>
</tr>
<tr>
<td>Work rate, W</td>
<td>181 ± 34</td>
<td>171 ± 33*</td>
</tr>
<tr>
<td>%Predicted</td>
<td>81 ± 16</td>
<td>81 ± 16</td>
</tr>
<tr>
<td>VO_{2}, l/min</td>
<td>2.34 ± 0.54</td>
<td>2.32 ± 0.48</td>
</tr>
<tr>
<td>%Predicted</td>
<td>78 ± 17</td>
<td>78 ± 17</td>
</tr>
<tr>
<td>VO_{2}/HR, ml/beat</td>
<td>13.2 ± 3.5</td>
<td>13.6 ± 3.3</td>
</tr>
<tr>
<td>%Predicted</td>
<td>88 ± 13</td>
<td>88 ± 13</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>176 ± 10</td>
<td>170 ± 13</td>
</tr>
<tr>
<td>%Predicted</td>
<td>95 ± 6</td>
<td>95 ± 6</td>
</tr>
<tr>
<td>VE, l/min</td>
<td>79.9 ± 18.1</td>
<td>78.1 ± 15.7</td>
</tr>
<tr>
<td>V_{part 30}, l/min</td>
<td>2.50 ± 0.68</td>
<td>2.43 ± 0.61</td>
</tr>
<tr>
<td>BF, breaths/min</td>
<td>32 ± 4</td>
<td>33 ± 5</td>
</tr>
<tr>
<td>VO_{2}/V_{CO_{2}}</td>
<td>3.98 ± 1.22</td>
<td>2.22 ± 0.83*</td>
</tr>
<tr>
<td>EFR, l/s</td>
<td>0.35 ± 1.42</td>
<td>0.09 ± 0.95</td>
</tr>
<tr>
<td>VE/V_{CO_{2}}</td>
<td>29.7 ± 2.8</td>
<td>29.7 ± 2.9</td>
</tr>
<tr>
<td>FRC, % of TLC</td>
<td>43 ± 3</td>
<td>48 ± 7†</td>
</tr>
<tr>
<td>EILV, % of TLC</td>
<td>78 ± 5</td>
<td>83 ± 5*</td>
</tr>
<tr>
<td>PET_{CO_{2}}, Torr</td>
<td>39.0 ± 3.5</td>
<td>38.8 ± 3.3</td>
</tr>
</tbody>
</table>

Values are means ± SD. VO_{2}, oxygen consumption; HR, heart rate; VO_{2}/HR, oxygen pulse; VE, minute ventilation; VT, tidal volume; BF, breathing frequency; EFR, expiratory flow reserve; VO_{2}/V_{CO_{2}}, carbon dioxide production; VE/V_{CO_{2}}, ratio of VE to V_{CO_{2}}; FRC, functional residual capacity; EILV, end-inspiratory lung volume; PET_{CO_{2}}, end-tidal CO_{2} pressure. Significant difference vs. control: *P < 0.05, †P < 0.01, and ‡P < 0.001.
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 $V_{part\ 30}$ remarkably increased with exercise by more than twofold compared with $V_{max\ 30}$ (Fig. 3), $EFR$ remained well below zero ($P < 0.05$), thus strongly suggesting that the low respiratory reserve contributed to limit exercise. $V_{part\ 30}$ at end exercise was significantly greater than $V_{max\ 30}$ at rest ($P < 0.01$).

At control after appropriate therapy, resting lung function significantly improved, even though air flow 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 $VT$ ($P < 0.05$). The latter was made possible by a greater reduction in $FRC$ than at NA ($P < 0.01$). Also, the $VE$-to-$\dot{V}CO_2$ ratio significantly decreased compared with NA conditions ($P < 0.05$). The increase in $V_{part\ 30}$ at maximum load was significantly greater than at NA ($P < 0.02$). Nevertheless, EFR remained still below zero and not different from NA conditions. $V_{part\ 30}$ at end exercise was significantly greater than $V_{max\ 30}$ 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...
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>Group 1</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>Group 2</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 ± 0.23</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.

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\textsubscript{E} and V\textsubscript{O\textsubscript{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 pharmacologically induced bronchconstriction (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 pharmacologically induced bronchconstriction (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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{1}, FVC, and instantaneous maximal flows at absolute lung volume, \(\dot{V}_{\text{part 30}}\) 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 overestimation 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 \(V_{\text{part 30}}\). 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 \(V_{\text{part 30}}\) at maximum exercise should have been similar to or even less than \(V_{\text{max 30}}\) before exercise. Second, our data are apparently in contrast to the notion that deep breaths to TLC are...
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 $\dot{V}CO_2$, $\dot{V}e$ has to increase to maintain a constant arterial CO$_2$ tension. In this sense, the observed increase in the $\dot{V}e$-to-$\dot{V}CO_2$ 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 $\dot{V}O_2$, 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 $\dot{V}O_2$ 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


