Gas exchange during exercise in habitually active asthmatic subjects

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Gas exchange during exercise in habitually active asthmatic subjects


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Few studies have evaluated gas exchange during exercise in asthmatic subjects (5, 12, 19, 20, 24, 35). Collectively, these studies lack generalizability and are difficult to interpret for a variety of reasons. First, characterization of the subjects’ airway disease was incomplete and lacking in detail. Small subject numbers and the use of children as participants further confound the generalizability of previous studies to asthmatic subjects as a population. Importantly, the exercise protocols were either discontinuous or of relatively short duration (5–10 min), and the exercise was generally performed at low metabolic rates (<2.0 l/min O2 uptake [V̇O2]), which were not sufficient to stress the pulmonary system’s capabilities for ventilation and gas exchange.

There are several reasons to suspect greater gas exchange disturbance during exercise in asthmatic than in healthy non-asthmatic subjects. It has been shown using the multiple inert gas elimination technique that alveolar ventilation-to-perfusion (VA/Q) nonuniformity at rest is greater in even mildly to moderately asthmatic subjects than in healthy subjects; this often results in a considerably widened alveolar-to-arterial PO2 difference (A–aDO2) and, although less often, arterial hypoxemia (54). This gas exchange disturbance is thought to be primarily caused by an uneven distribution of alveolar ventilation (VA) due to narrowed and obstructed airways (54). The airway narrowing is caused by a variety of factors that arise as a consequence of airway inflammatory mediator release, including bronchial smooth muscle contraction, mucosal edema and thickening of the airway wall, peribronchial fluid accumulation and “cuffing” of the small airways, and luminal mucus and liquid accumulation (9). Additionally, the increased airflow during exercise is thought to stimulate the release of inflammatory mediators (e.g., histamine and leukotrienes) from airway cells during or shortly after exercise in asthmatic subjects (6). Because the bronchial smooth muscle and the vascular effects of these mediators are responsible for the peripheral airway changes that likely contribute to gas exchange disturbance in asthmatic subjects, exercise may cause or exacerbate any impairment in gas exchange. Thus gas exchange during exercise in asthmatic subjects might be impaired because of airway dysfunction at rest or an airway inflammatory response caused by the exercise.

Airway resistance, which is often high in asthmatic subjects, increases the propensity for expiratory flow limitation (EFL) and dynamic hyperinflation during exercise in asthmatic compared with nonasthmatic subjects (14, 34, 52). In healthy subjects, EFL and dynamic hyperinflation have been shown to blunt the very important compensatory hyperventilation of heavy exercise (33, 40, 41), and presumably the same should hold true for asthmatic subjects. Thus high-resistance airways might predispose many asthmatic subjects to a less robust ventilatory response and arterial hypoxemia during exercise. However, bronchodilation, which is known to occur during exercise in asthmatic subjects (14, 39, 52), might help protect against excessive EFL in asthmatic subjects with airflow limitation at rest. The extent of exercise ventilatory constraint will consequently depend on the extent of baseline airflow limitation, the magnitude of exercise-induced bronchodilation, and the requirement for ventilation as dictated by the exercise workload.

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The aim of this study was to characterize the gas exchange and breathing mechanics responses to submaximal and high-intensity exercise to exhaustion in habitually active asthmatic subjects. We also sought to determine the relations among airway inflammation, breathing mechanics, and gas exchange during the exercise and hypothesized that significant relations would exist among them.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board and the Human Subjects Committee of the University of Wisconsin-Madison. Subjects were recruited by poster and newspaper advertisement, and by contact with university, community, and regional running, triathlon, and cycling clubs. Potential subjects were provided a detailed description of all study procedures and risks and agreed to participate after signing an informed consent form for human research.

Subject Selection

Habitually active men and women (aged 18–45 yr) with a known history of asthma or suspected asthma underwent several screening sessions to determine eligibility for participation (see Screening Studies). Potential subjects taking oral or inhaled steroids were excluded from study participation. A total of 94 individuals completed at least one screening study: 27 met the inclusion criteria for participation, and 21 of these subjects completed the entire protocol. The subjects consisted of five recreational triathletes, three recreational endurance runners, one cyclist, one collegiate ultimate Frisbee player, one collegiate football player, one competitive gymnast, one collegiate club hockey player, one equestrian athlete, and seven subjects who exercised for general health.

Palmonary Function Testing

Lung volumes and forced expiratory flow rates were determined according to American Thoracic Society recommendations (3) with a commercially available system (Jaeger). Functional residual capacity (FRC) was measured in a body plethysmograph, and total lung capacity (TLC) was calculated as the sum of FRC and the inspiratory capacity (IC). Forced oscillation (IOS; model MS-IOS, Jaeger) was performed at a fixed breathing frequency and duty cycle (12 breaths/min, duty cycle = 0.35) and was used to determine total respiratory resistance (Rrs, 5 Hz) and frequency dependence of resistance (Rrs, 5–25 Hz). Exhaled nitric oxide (eNO) was measured as described previously (2).

Methacholine Challenge

Airway reactivity was determined using a five-breath dosimeter protocol with methacholine chloride (Provocholine, Methapharm, Coral Springs, FL) according to American Thoracic Society recommendations (4). After diluent inhalation, doubling doses of methacholine (0.031–16 mg/ml) diluted in saline were inhaled. After each dose, IOS and two forced vital capacity (FVC) maneuvers were performed (in that order), and the testing was concluded when FEV1 decreased by ≥20% from the postdiluent value or after the maximum dose of 16 mg/ml was achieved.

Arterial Blood Measurements

Samples of arterial blood were drawn anaerobically over 10–20 s at rest and during exercise for measurement of arterial PO2 (PaO2), arterial PCO2 (PaCO2), and pH via a blood-gas analyzer (modelABL505, Radiometer, Copenhagen, Denmark), and oxyhemoglobin saturation (SaO2) was measured with a CO-oximeter (model OSM-3, Radiometer). Arterial blood lactate concentration was measured using an electrochemical analyzer (model 1500 Sport, Yellow Springs Instrument, Yellow Springs, OH).

Exercise Study Apparatus

The apparatus used for the exercise studies has been described previously (57). Room air (laboratory temperature = 24 ± 1.2°C, relative humidity = 47.6 ± 12.4%) was used as the inspirate for the first eight subjects enrolled in the study (Table 1). Compressed dry air from a gas cylinder (0.21 inspired O2 fraction, laboratory temperature = 24 ± 1.3°C) was used as the inspirate for the remaining 13 subjects. For each individual subject, the same inspirate was breathed at all exercise workloads during the screening and arterial blood exercise studies.

Breathing Mechanics Measurements During Exercise

Before exercise, subjects performed several maximum volitional flow-volume loops (MFVLs) while standing on the treadmill and breathing on the same apparatus used during exercise. EFL was estimated as described previously (41), and end-expiratory lung volume (EELV) during exercise was determined by subtracting the exercise IC volume from TLC. Ventilatory capacity during exercise was estimated using the preexercise MFVL and the spontaneous exercise tidal flow-volume loops as described previously (34). Ventilatory capacity was thus calculated on the basis of the maximal expiratory flow rates achievable (as defined by the MFVL) at the actual operating lung and tidal volumes measured during the exercise. A nasopharyngeal 10-cm latex balloon-tipped catheter (Ackrad Laboratories, Cranford, NJ) connected by polyethylene tubing to a differential pressure transducer (Validyne) was used to measure esophageal pressure. Inspiratory pulmonary resistance (RLi) was calculated at peak inspiratory flow according to the technique of Mead and Whittenberger (21, 42).

Medications

Subjects were instructed to refrain from using short-acting β-agonists within 12 h and any long-acting β-agonists, antihistamines, leukotriene modifiers, and sodium cromoglycate within 48 h of each study. Table 2 includes a list of medications for each subject enrolled in the study. Additionally, subjects were instructed to refrain from ingesting any food, beverages, or other products containing caffeine for ≥8 h before all studies.

Screening Studies

Up to three separate screening studies were completed to determine eligibility for participation. Eligible subjects were required to demonstrate at least one of four inclusion criteria: 1) ≥12% increase in...
### Table 1. Inclusion criteria results

<table>
<thead>
<tr>
<th>Subj No.</th>
<th>FEV1.0 Reversibility, %change after β2-agonist inhalation</th>
<th>EIB, %change FEV1.0</th>
<th>Sputum Eosinophils, %WBCs</th>
<th>PC_{20}, mg/ml</th>
<th>No. of Inclusion Criteria Achieved</th>
<th>Group†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>16.5                                                     -14.9               4.0                        1.06          4 Hi-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>13.5                                                     -14.5               7.0                        3.38          4 Hi-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>19.9                                                     -36.1               15.1                       0.57          4 Lo-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>11.1                                                     -18.7               21.0                       0.40          4 Lo-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5*</td>
<td>12.1                                                     -14.4               0.2                        1.82          3 Hi-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>12.0                                                     -28.4               47.9                       &gt;16           3 Hi-SaO2</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>20.1                                                     -22.8               0.3                        0.17          3 Hi-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>14.3                                                     -20.9               0                           0.29          3 Lo-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>31.9                                                     -20.3               1.8                        0.61          3 Hi-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>32.2                                                     -17.6               0                           0.75          3 Hi-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>13.9                                                     -32.4               1.8                        0.69          3 Hi-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12*</td>
<td>16.2                                                     -15.3               3.6                        ND            3 Hi-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>7.7                                                      -21.7               10.0                       0.29          3 Lo-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>20.2                                                     -29.3               0                           0.17          3 Lo-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>2.3                                                      -18.5               3                           2.81          3 Lo-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16*</td>
<td>7.7                                                      -14.4               3                           4.57          2 Hi-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17*</td>
<td>9.0                                                      -11.7               3.7                        &gt;16           2 Hi-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18*</td>
<td>3.8                                                      -14.4               2.5                        1.10          2 Lo-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19*</td>
<td>15.5                                                     -3.5                0.3                        ND            1 Hi-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20*</td>
<td>4.3                                                      -0.1                0.3                        0.30          1 Lo-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>3.1                                                      -28.1               0.5                        &gt;16           1 Lo-SaO2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SD 13.7 ± 8.2 -18.6 ± 9.2 6.0 ± 11.0 0.72 ± 2.8 ± 0.9
No. of subjs meeting criteria 14 18 11 15 13 (Lo-SaO2) 8 (Hi-SaO2)

Subjects were ordered from 1 to 21 according to number of inclusion criteria met during the screening studies, beginning with subjects who met requirements of all 4 inclusion criteria. FEV1.0, forced expiratory volume in 1.0 s; PC_{20}, methacholine concentration causing a 20% fall in FEV1.0; Hi-SaO2, subjects with oxyhemoglobin saturation >94.5% during prolonged bout; Lo-SaO2, subjects with oxyhemoglobin saturation ≤94% during prolonged bout; ND, no data available; EIB, exercise-induced bronchospasm. *Subjects who breathed ambient air during exercise studies. †Allocation into Hi- or Lo-SaO2 group was not among inclusion criteria and was determined retrospectively on completion of the exercise study. ‡Geometric mean.

### Table 2. Gender, VO_{2max} pulmonary function, medications, and atopy status

<table>
<thead>
<tr>
<th>Subj No.</th>
<th>Gender</th>
<th>VO_{2max}, ml/kg·min(^{-1})</th>
<th>FEV1.0, liters</th>
<th>FEV1.0/FVC</th>
<th>FEF25-75, l/s</th>
<th>Res 5 Hz, cmH_{2}O·l·s(^{-1})</th>
<th>Medications</th>
<th>Atopy, +/-</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>49.8 (101)</td>
<td>3.58 (83)</td>
<td>77.5</td>
<td>2.72 (57)</td>
<td>4.22</td>
<td>SAB</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>45.3 (94)</td>
<td>4.74 (103)</td>
<td>69.4</td>
<td>2.88 (56)</td>
<td>8.14</td>
<td>SAB, AH, NCS</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>39.2 (122)</td>
<td>3.06 (99)</td>
<td>60.4</td>
<td>1.59 (44)</td>
<td>6.2</td>
<td>SAB, AH</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>61.8 (146)</td>
<td>4.61 (105)</td>
<td>73.8</td>
<td>3.37 (74)</td>
<td>3.69</td>
<td>SAB, AL</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>52.4 (107)</td>
<td>3.98 (93)</td>
<td>64.4</td>
<td>2.56 (53)</td>
<td>5.34</td>
<td>SAB, AH</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>41.0 (126)</td>
<td>3.68 (120)</td>
<td>69.4</td>
<td>2.43 (71)</td>
<td>3.82</td>
<td>SAB</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>44.9 (131)</td>
<td>3.69 (107)</td>
<td>76.7</td>
<td>2.94 (74)</td>
<td>4.59</td>
<td>SAB</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>45.0 (129)</td>
<td>3.15 (97)</td>
<td>72.6</td>
<td>2.46 (59)</td>
<td>5.34</td>
<td>SAB, AH</td>
<td>ND</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>50.8 (103)</td>
<td>3.36 (78)</td>
<td>66.1</td>
<td>2.26 (47)</td>
<td>5.87</td>
<td>SAB</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>46.1 (96)</td>
<td>3.42 (68)</td>
<td>54.6</td>
<td>1.63 (29)</td>
<td>10.37</td>
<td>SAB, AH, AL</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>38.7 (120)</td>
<td>2.87 (95)</td>
<td>75.7</td>
<td>2.18 (61)</td>
<td>6.47</td>
<td>LAB, AH, NCS</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>52.5 (109)</td>
<td>3.77 (92)</td>
<td>80.2</td>
<td>3.35 (72)</td>
<td>5.93</td>
<td>SAB</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>56.7 (124)</td>
<td>3.27 (83)</td>
<td>72.5</td>
<td>2.25 (53)</td>
<td>3.03</td>
<td>SAB</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>40.6 (87)</td>
<td>3.47 (76)</td>
<td>73.7</td>
<td>2.42 (50)</td>
<td>4.81</td>
<td>SAB, NCS</td>
<td>+</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>39.9 (97)</td>
<td>3.54 (84)</td>
<td>65.4</td>
<td>2.05 (46)</td>
<td>7.89</td>
<td>SAB</td>
<td>+</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>51.4 (160)</td>
<td>3.49 (117)</td>
<td>82.9</td>
<td>3.38 (96)</td>
<td>4.81</td>
<td>SAB, AH, NCS</td>
<td>+</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>49.0 (147)</td>
<td>3.87 (113)</td>
<td>79.1</td>
<td>3.36 (86)</td>
<td>1.78</td>
<td>SAB</td>
<td>+</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>41.6 (129)</td>
<td>2.91 (89)</td>
<td>79.7</td>
<td>2.47 (66)</td>
<td>5.35</td>
<td>SAB, LAB</td>
<td>+</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>57.6 (120)</td>
<td>3.94 (93)</td>
<td>71.9</td>
<td>2.65 (56)</td>
<td>4.91</td>
<td>SAB</td>
<td>ND</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>54.6 (116)</td>
<td>4.17 (91)</td>
<td>77.4</td>
<td>3.28 (64)</td>
<td>4.05</td>
<td>SAB</td>
<td>+</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>54.0 (129)</td>
<td>4.48 (94)</td>
<td>74.7</td>
<td>3.36 (68)</td>
<td>3.5</td>
<td>SAB, AL</td>
<td>+</td>
</tr>
</tbody>
</table>

VO_{2max}, maximum O2 uptake; FVC, forced vital capacity; FEF25-75, mean forced expiratory flow during middle 50% of FVC; Rs, total respiratory resistance at a frequency of 5 Hz; SAB and LAB, short and long-acting β-agonist; AH, antihistamine; AL, antileukotriene; NCS, nasal corticosteroid; ND, no data available. Prediction equations for VO_{2max} for male (M) and female (F) subjects are from Refs. 11 and 16 respectively; prediction equations for FEV1.0 and FEF25-75 are from Ref. 36. *Percent predicted values (in parentheses) are significantly different from predicted values (P < 0.05).
FEV<sub>1.0</sub>, from the baseline value, after inhalation of two actuations of albuterol, 2) demonstration of exercise-induced bronchospasm (EIB), defined as ≥10% decrease in FEV<sub>1.0</sub> after an incremental exercise test to exhaustion, 3) ≥2% eosinophils (as percentage of white blood cells) in the cellular phase of the induced sputum, and 4) ≤4.0 mg/ml methacholine causing a 20% decrease in FEV<sub>1.0</sub> (PC<sub>20</sub>). Eligible subjects completed an exercise study designed to evaluate breathing mechanics and gas exchange during submaximal and high-intensity exercise to exhaustion.

**Exercise Study Protocol**

Subjects voided their bladder immediately on arrival at the laboratory. Fluid ingestion was standardized and included a total of 800 ml of water distributed in four servings (150–250 ml per serving) throughout the study. Preexercise lung function tests, including spirometry, IOS, FRC and TLC, and eNO, were completed. A 20-gauge arterial catheter was inserted percutaneously into a radial artery under local 1% lidocaine anesthesia, and a nasopharyngeal temperature probe (Mallinckrodt Medical, St. Louis, MO) and balloon-tipped catheter were placed intranasally into the lower one-third of the esophagus. After the resting lung function tests and catheter placement, a baseline urine sample was collected. Immediately before the exercise, three MFVL and repeated IC maneuvers were performed while the subjects stood on the treadmill.

Subjects initially exercised at two submaximal workloads for 3 min each (sub-1 and sub-2), and blood samples were collected and IC maneuvers were performed during the final 30 s of each workload. After a brief (≈3–5 min) rest, exercise was resumed and performed to exhaustion at a constant speed and grade (hereafter referred to as the prolonged exercise bout) that elicited a metabolic rate of exhaustion at a constant speed and grade (hereafter referred to as the prolonged exercise bout). Notably, in sub-3, 5, and 10, FEV<sub>1.0</sub>/FVC was <65% and FEF<sub>25–75</sub> was 29–53% of predicted. TLC (6.58 ± 1.02 liters) and FRC (3.08 ± 0.49 liters) were 102 and 100% of predicted normal (3), respectively, and diffusing capacity of the lung for carbon monoxide (33.4 ± 7.1 ml·min<sup>−1</sup>·Tor<sup>−1</sup>) averaged 88% of the predicted value [<P < 0.05 vs. predicted (38)]. Mean phase III slope from the single-breath N<sub>2</sub> washout averaged 1.19 ± 0.50% N<sub>2</sub>/l (range 0.61–2.35% N<sub>2</sub>/l), and slopes were >2.0 SD above the normal range (1.97 ± 0.26% N<sub>2</sub>/l) in 4 of 21 subjects (49). eNO was elevated (52.4 ± 35.6 ppb) compared with previous data in normal subjects, in which eNO measured using the same methodology was ~25–35 ppb (50, 57).

**Exercise Responses**

**Exercise-induced oxyhemoglobin desaturation.** Subjects were divided into two groups on the basis of nadir Sa<sub>O2</sub>, during the prolonged bout (15): those that maintained >94% Sa<sub>O2</sub>, [mean ± SD, 95.6 ± 1.0% (Hi-Sa<sub>O2</sub>), n = 13] and those in which Sa<sub>O2</sub> decreased to ≤94% [mean ± SD, 92.4 ± 1.2%, range 90.1–94.0% (Lo-Sa<sub>O2</sub>), n = 8; Fig. 1A]. The Lo-Sa<sub>O2</sub> group exhibited significant and sustained decreases in Pa<sub>O2</sub>, beginning at sub-2 and at all times during the prolonged bout (Fig. 1B). In the Hi-Sa<sub>O2</sub> group, Pa<sub>O2</sub> initially decreased 6.6 Torr at minute 1 of the prolonged bout, but thereafter it rose progressively so that it was slightly greater than the resting value by the end of the exercise. Both groups exhibited a variable but progressive metabolic acidosis, and arterial blood lactate rose similarly in both groups during the exercise (Fig. 2).

In the Lo-Sa<sub>O2</sub> group, the rapid drop in Pa<sub>O2</sub>, accounted for the majority of the initial fall in Sa<sub>O2</sub>, (69 ± 14% of the total decrease in Sa<sub>O2</sub> at minute 1) during the prolonged bout. Thereafter, further decreases in Sa<sub>O2</sub> were due solely to the effects of progressive decreases in pH and increases in body temperature on the position of the oxyhemoglobin dissociation curve. Thus, at the end of prolonged exercise, the decreased Pa<sub>O2</sub>, accounted for 17% and the combined effects of pH and temperature for the remaining 83% of the total decrease in Sa<sub>O2</sub>.

**Metabolic rate and ventilation.** There were no significant differences in V<sub>O2</sub> between the groups during the exercise bouts (Table 3). During prolonged exercise, there was a progressive ~34% rise in minute ventilation (Ve) from minute 1 to after end exercise, and this increase was mediated solely by an
increased breathing frequency in both groups. The dead space-to-tidal volume ratio decreased from rest during exercise but rose significantly over the final half of prolonged exercise. The ventilatory equivalent for CO2 production (VE/VCO2) also rose over time during prolonged exercise and was significantly lower in the Lo- than in the Hi-SaO2 group from minute 5 to the end of exercise.

Contributors to decreased PaO2. There were clear differences between groups in the A-aD O2 and PaCO2 (Fig. 3): A-aDO2 was wider and PaCO2 was higher during exercise at all times in the Lo-SaO2 group. A-aDO2 was on average 7.4 ± 1.9 Torr wider in the Lo- than in the Hi-SaO2 group during the prolonged bout (P > 0.05). In the Hi-SaO2 group, PaCO2 decreased from rest to 34.0 ± 2.7 Torr by the end of the exercise (P < 0.0001). In contrast, in the Lo-SaO2 group, after a slight decrease from rest at minute 1 during the prolonged bout, PaCO2 rose progressively, increasing to 39.8 ± 4.0 Torr at exhaustion. VE/VCO2 was significantly correlated with PaCO2 during prolonged exercise (Fig. 4), indicating that the primary determinant of PaCO2 was the magnitude of the total ventilatory response. Additionally, the magnitudes of the A-aDO2 and PaCO2 were significantly correlated to PaO2 (Fig. 5). Five subjects showed no hyperventilatory response to prolonged heavy-intensity exercise, i.e., PaCO2 of ~40 Torr or greater at exercise termination.

PaO2 can be viewed as a function of two variables: 1) the adequacy of the ventilatory response, as defined by the alveolar PO2, and 2) the efficiency of gas exchange, quantitated as A-aDO2. The A-aDO2 accounted for 62 and 75% of the decrease in PaO2 during submaximal exercise and early during the prolonged bout, respectively. The contribution of insufficient alveolar hyperventilation to the decreased PaO2 increased progressively from 25% during minute 1 of prolonged exercise to 46% at exercise termination.

Breathing mechanics. Pulmonary resistance was similar in the two groups before the exercise (Fig. 6), and although group means for Rli increased slightly from baseline during all three workloads, there were no major group mean time-dependent changes during the prolonged bout. During the prolonged bout, in six subjects Rli was decreased at minute...
Table 3. Resting and exercise metabolic rate and ventilation for the Hi- and Lo-SaO2 groups

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Sub-1</th>
<th>Sub-2</th>
<th>Minute 1</th>
<th>Minute 3</th>
<th>Minute 5</th>
<th>End (11.2 ± 0.15 min)</th>
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</thead>
<tbody>
<tr>
<td>%VO2max</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hi-SaO2</td>
<td>8.8±1.1</td>
<td>58.5±9.2</td>
<td>72.7±9.7</td>
<td>84.9±4.8</td>
<td>90.5±5.3*</td>
<td>90.9±5.7*</td>
<td>89.8±5.1*</td>
</tr>
<tr>
<td>Lo-SaO2</td>
<td>8.7±1.9</td>
<td>60.2±3.7</td>
<td>74.0±7.2</td>
<td>79.5±6.8†</td>
<td>85.8±6.2*</td>
<td>89.7±5.5*</td>
<td>90.3±6.0*</td>
</tr>
<tr>
<td>VO2, ml·kg⁻¹·min⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hi-SaO2</td>
<td>4.15±1.1</td>
<td>27.7±4.1</td>
<td>34.6±5.5</td>
<td>40.7±6.1*</td>
<td>43.1±5.3*</td>
<td>44.0±5.1*</td>
<td>42.8±4.8*</td>
</tr>
<tr>
<td>Lo-SaO2</td>
<td>4.23±1.1</td>
<td>29.1±1.2</td>
<td>35.1±7.1</td>
<td>38.7±8.8*</td>
<td>41.8±9.5*</td>
<td>43.7±9.9*</td>
<td>43.8±8.8*</td>
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<tr>
<td>Ve, l/min</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hi-SaO2</td>
<td>11.2±2.6</td>
<td>58.0±9.0</td>
<td>73.0±9.8</td>
<td>82.7±16.1</td>
<td>97.4±16.4*</td>
<td>101.3±16.5*</td>
<td>112.2±20.3*</td>
</tr>
<tr>
<td>Lo-SaO2</td>
<td>11.1±4.1</td>
<td>57.0±13.5</td>
<td>71.5±17.3</td>
<td>79.1±25.7</td>
<td>91.9±27.4*</td>
<td>96.6±27.3*</td>
<td>105.3±30.7*</td>
</tr>
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<td>VT, l/breath</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hi-SaO2</td>
<td>0.76±0.18</td>
<td>1.8±3.7</td>
<td>2.0±4.0</td>
<td>2.1±4.4</td>
<td>2.2±4.7*</td>
<td>2.2±3.9*</td>
<td>2.0±3.4</td>
</tr>
<tr>
<td>Lo-SaO2</td>
<td>0.87±0.30</td>
<td>2.1±5.2</td>
<td>2.2±4.8</td>
<td>2.4±6.6</td>
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<td>f, breaths/min</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hi-SaO2</td>
<td>15.0±3.3</td>
<td>31.6±3.4</td>
<td>36.1±7.3</td>
<td>39.2±8.5</td>
<td>42.9±8.3*</td>
<td>44.1±7.1*</td>
<td>54.2±5.7*</td>
</tr>
<tr>
<td>Lo-SaO2</td>
<td>13.6±5.1</td>
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<td>32.9±8.6</td>
<td>33.5±8.5</td>
<td>36.5±9.1</td>
<td>39.2±10.2*</td>
<td>44.5±11.2†</td>
</tr>
<tr>
<td>Vt/Vt, r</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hi-SaO2</td>
<td>0.29±0.10</td>
<td>0.17±0.9</td>
<td>0.17±0.9</td>
<td>0.14±0.4</td>
<td>0.14±0.4</td>
<td>0.14±0.3</td>
<td>0.20±0.05</td>
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<tr>
<td>Lo-SaO2</td>
<td>0.26±0.06</td>
<td>0.14±0.05</td>
<td>0.13±0.06</td>
<td>0.13±0.05</td>
<td>0.12±0.05</td>
<td>0.14±0.05</td>
<td>0.19±0.03</td>
</tr>
<tr>
<td>Vt/VCO2, r</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hi-SaO2</td>
<td>42.5±9.9</td>
<td>31.4±4.2</td>
<td>30.3±3.7</td>
<td>30.5±3.0</td>
<td>29.7±2.7</td>
<td>29.8±1.6</td>
<td>33.8±2.5*</td>
</tr>
<tr>
<td>Lo-SaO2</td>
<td>37.8±5.7</td>
<td>28.0±3.1</td>
<td>27.3±3.6</td>
<td>28.5±3.5</td>
<td>27.1±3.4*</td>
<td>27.2±3.4†</td>
<td>28.6±3.7†</td>
</tr>
</tbody>
</table>

Values are means ± SD. SaO2, oxyhemoglobin saturation; sub-1 and sub-2, submaximal workloads; VO2, O2 uptake; Ve, minute ventilation; VT, tidal volume; f, breathing frequency; Vt/Vt, dead space-to-tidal volume ratio; Ve/VCO2; ventilatory equivalent for CO2 production. *Significantly different from minute 1 (P < 0.05). †Significantly different from Hi-SaO2 (P < 0.05).

I compared with baseline (−0.9 ± 0.7 cmH2O·l⁻¹·s⁻¹), whereas in most of the subjects (n = 14), Rli increased compared with baseline (+1.4 ± 1.2 cmH2O·l⁻¹·s⁻¹). After minute 1 of exercise, Rli remained unchanged or decreased in 19 subjects (average change from minute 1 = −0.3 ± 0.6 cmH2O·l⁻¹·s⁻¹) and increased by 2.0 cmH2O·l⁻¹·s⁻¹ at end exercise in 1 subject. There was a significant positive correlation between Rli and PaCO2 at the end of the prolonged bout (r = 0.45, P = 0.05).

Several measurements of breathing mechanics at rest and during exercise are summarized in Table 4. There were no significant differences between the Hi- and Lo-SaO2 groups for any of the reported variables. Overall, ventilation was mechanically constrained; EFL was evident during at least one measurement time in all eight subjects in the Lo-SaO2 group and in 11 of the 13 subjects in the Hi-SaO2 group during the exercise. Measured Ve expressed as a percentage of ventilatory capacity reached 84 and 97% during the prolonged bout in the Hi- and Lo-SaO2 subjects, respectively. EELV was similar in the Hi- and Lo-SaO2 groups throughout the exercise bouts, averaging ~51% of TLC at rest, decreasing slightly during sub-1, and then increasing to resting levels during sub-2. During the prolonged bout, EELV increased progressively to ~0.27 liter greater than resting FRC at the final measurement in both groups. There were no significant correlations between EFL or Ve expressed as a percentage of ventilatory capacity and EELV/TLC, Ve/VCO2, or PaCO2 during the exercise bouts.

Fig. 3. Individual and group mean data for primary determinants of arterial P2O2; alveolar-to-arterial P2O2 difference (A-dO2), which represents gas exchange efficiency, and arterial P2CO2 (PaCO2), which represents the magnitude of ventilatory response, in Hi- and Lo-SaO2 groups at rest, during submaximal exercise (sub-1 and sub-2), and during the prolonged exercise bout to exhaustion. Lines and symbols are described in Fig. 1 legend. Values are means ± SD. *Significantly different from baseline (P < 0.05). †Significant difference between Hi- and Lo-SaO2 groups (P < 0.05).
Relations Between Baseline Pulmonary Function and Exercise Gas Exchange

Baseline Rrs 5–25 Hz was higher in the Lo-SaO2 group before exercise (2.2 ± 1.7 and 0.8 ± 1.3 cmH2O·l−1·s for Lo- and Hi-SaO2 subjects, respectively, *P = 0.04), but there were no other significant differences in baseline lung function between the groups. There were no significant correlations between baseline FEV1.0, FEV1.0/FVC, FEF25–75, or Rs at 5 Hz and the four measures of gas exchange (i.e., PaO2, PaCO2, A-aDO2, and SaO2) during sub-1, sub-2, or the prolonged bout. However, baseline Rs at 5–25 Hz was significantly correlated with PaO2 (*r = −0.53, *P = 0.01), PaCO2 (*r = 0.53, *P = 0.01), and SaO2 (*r = −0.47, *P = 0.03) at the end of the prolonged bout.

Airway Inflammation

Eosinophils at baseline amounted to 6% of the white blood cells in the sputum and did not change after exercise (Table 5). After exercise, urinary 9α,11β-PGF2 was significantly increased by 117 ± 207% from the baseline value when all subjects were combined and analyzed as one group. Sputum histamine after exercise was increased above baseline in the Lo-SaO2 subjects (37.8 ± 27.1 vs. 61.4 ± 47.3 ng/ml, *P = 0.04), but not in the Hi-SaO2 group (34.3 ± 30.5 vs. 39.1 ± 26.6 ng/ml, *P = 0.75). When all subjects were analyzed as one group, postexercise sputum histamine was significantly correlated with PaO2 (*r = 0.60, *P = 0.007) and the A-aDO2 (*r = 0.54, *P = 0.02) measured at the end of the prolonged bout. Additionally, the change in histamine after exercise (i.e., the difference between postexercise and baseline) was significantly correlated with the changes in PaO2 (*r = −0.68, *P = 0.002).
and the A-aDo2 (r = 0.50, P = 0.03) between rest and the end of the prolonged bout.

**Individual Subject Examples**

Figures 7 and 8 contrast the exercise results for two subjects with similar VO2 max and MFVLs but with different ventilatory responses and arterial blood gases during the exercise. Figure 7 shows a subject with a high Rl at rest and a scooped expiratory limb of the MFVL (forced expiratory flow at 50% of vital capacity = 46% predicted). Consequently, EFL occurred at a very moderate increase in Ve, and substantial increases in EELV ensued. Pulmonary resistance decreased by ~1.5 cmH2O·l−1·s during sub-1 and early during the prolonged bout but increased to the resting value during sub-2 and across time during the prolonged bout. Presumably at least in part because of the high resistive and elastic work of breathing, Pao2 rose progressively during the exercise, and concomitant decreases in Pao2 and SaO2 ensued. Finally, the unchanged expiratory limb of the immediate-postexercise MFVL shows the lack of a significant exercise-induced bronchodilatory response.

Similarly, Fig. 8 shows data from a subject with a high resting Rl, a scooped expiratory limb of the MFVL (forced expiratory flow at 50% of vital capacity = 69% predicted), and EFL during exercise. In contrast to the example in Fig. 7, however, EELV was maintained below FRC throughout the exercise and Rl was decreased from rest at each exercise workload, remaining constant across time during the prolonged bout. Despite the ventilatory constraint, the exercise hyperventilation response was adequate in this subject, and Pao2 was maintained within the normal range.

**DISCUSSION**

**Summary of Findings**

Gas exchange and breathing mechanics were assessed in 21 habitually active asthmatic subjects during high-intensity, constant-work rate treadmill exercise to exhaustion. Significant decreases in SaO2 during the exercise were noted in 8 of the 21

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**Table 4. Expiratory flow limitation, ventilatory capacity, and operating lung volumes at rest and during exercise in Hi- and Lo-Sao2 groups**

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Sub-1</th>
<th>Sub-2</th>
<th>Minute 1</th>
<th>Final (9.4 ± 3.8 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFL, %Vn</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hi-Sao2</td>
<td>0.25 ± 0.08</td>
<td>0.52 ± 0.08</td>
<td>0.51 ± 0.06</td>
<td>0.50 ± 0.09</td>
<td>0.55 ± 0.06</td>
</tr>
<tr>
<td>Lo-Sao2</td>
<td>0.51 ± 0.04</td>
<td>0.48 ± 0.04</td>
<td>0.50 ± 0.06</td>
<td>0.48 ± 0.08</td>
<td>0.54 ± 0.06</td>
</tr>
<tr>
<td><strong>EELV/tLC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hi-Sao2</td>
<td>4.19 ± 0.63</td>
<td>5.17 ± 0.70*</td>
<td>5.46 ± 0.75*</td>
<td>5.33 ± 0.69*</td>
<td>5.70 ± 0.91*</td>
</tr>
<tr>
<td>Lo-Sao2</td>
<td>4.35 ± 0.79</td>
<td>5.34 ± 1.01*</td>
<td>5.61 ± 1.01*</td>
<td>5.61 ± 1.3*</td>
<td>5.93 ± 1.16*</td>
</tr>
<tr>
<td><strong>VL/IC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hi-Sao2</td>
<td>0.63 ± 0.08</td>
<td>0.77 ± 0.05*</td>
<td>0.81 ± 0.06*</td>
<td>0.82 ± 0.07†</td>
<td>0.86 ± 0.06†</td>
</tr>
<tr>
<td>Lo-Sao2</td>
<td>0.65 ± 0.06</td>
<td>0.79 ± 0.06*</td>
<td>0.83 ± 0.06*</td>
<td>0.84 ± 0.06*</td>
<td>0.88 ± 0.04†</td>
</tr>
<tr>
<td><strong>Vt/vve</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hi-Sao2</td>
<td>0.16 ± 0.05</td>
<td>0.37 ± 0.06*</td>
<td>0.41 ± 0.05*</td>
<td>0.42 ± 0.07†</td>
<td>0.40 ± 0.05*</td>
</tr>
<tr>
<td>Lo-Sao2</td>
<td>0.17 ± 0.05</td>
<td>0.41 ± 0.09*</td>
<td>0.43 ± 0.08*</td>
<td>0.48 ± 0.10*</td>
<td>0.47 ± 0.07*</td>
</tr>
<tr>
<td><strong>Vt/vvc</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hi-Sao2</td>
<td>0.25 ± 0.09</td>
<td>0.53 ± 0.10*</td>
<td>0.62 ± 0.09†</td>
<td>0.63 ± 0.09†</td>
<td>0.68 ± 0.09†</td>
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<tr>
<td>Lo-Sao2</td>
<td>0.27 ± 0.08</td>
<td>0.60 ± 0.10*</td>
<td>0.64 ± 0.09*</td>
<td>0.68 ± 0.10*</td>
<td>0.76 ± 0.08†</td>
</tr>
</tbody>
</table>

Values are means ± SD. EFL, expiratory flow limitation; Vu/VtCap, Vu as a fraction of calculated ventilatory capacity; EELV, end-expiratory lung volume; TLC, total lung capacity; EILV, end-inspiratory lung volume; VC, vital capacity; IC, inspiratory capacity. *Significantly different from rest; †significantly different from sub-1; ‡significantly different from sub-2; §significantly different from minute 1 (P < 0.05).

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**Table 5. Induced sputum cell counts and inflammatory mediators in sputum supernatant and urine**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Postexercise</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell counts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of WBCs counted</td>
<td>561 ± 139</td>
<td>516 ± 163</td>
</tr>
<tr>
<td>Total cells, WBCs/ml plug × 10^6</td>
<td>2.2 ± 2.6</td>
<td>1.5 ± 0.59</td>
</tr>
<tr>
<td>Squamous epithelial, %total cells</td>
<td>29.0 ± 15.0</td>
<td>30.0 ± 16.9</td>
</tr>
<tr>
<td>Macrophages, %WBCs</td>
<td>85.7 ± 12.5</td>
<td>87.0 ± 18.9</td>
</tr>
<tr>
<td>Neutrophils, %WBCs</td>
<td>8.1 ± 9.3</td>
<td>3.9 ± 1.6</td>
</tr>
<tr>
<td>Lymphocytes, %WBCs</td>
<td>0.82 ± 2.9</td>
<td>0.14 ± 0.26</td>
</tr>
<tr>
<td>Eosinophils, %WBCs</td>
<td>6.0 ± 11.0</td>
<td>9.2 ± 19.0</td>
</tr>
<tr>
<td>Macrophages × 10^6/ml plug</td>
<td>1.8 ± 2.0</td>
<td>1.3 ± 0.62</td>
</tr>
<tr>
<td>Neutrophils × 10^6/ml plug</td>
<td>2.6 ± 6.5</td>
<td>0.65 ± 0.88</td>
</tr>
<tr>
<td>Lymphocytes × 10^6/ml plug</td>
<td>9.0 ± 22.1</td>
<td>2.3 ± 5.3</td>
</tr>
<tr>
<td>Eosinophils × 10^6/ml plug</td>
<td>1.1 ± 2.7</td>
<td>1.4 ± 3.2</td>
</tr>
</tbody>
</table>

| **Inflammatory mediators** |          |              |
| Sputum histamine, ng/ml  | 40.1 ± 29.4 | 64.0 ± 78.3  |
| Urinary 9α,11β-PGF2α, ng/mmol creatinine | 96.5 ± 67.4 | 142.3 ± 78.8* |

Values are means ± SD. WBC, white blood cells; PGF2α, prostaglandin F2α. *Significantly different from baseline (P < 0.05).
subjects due in part to a decreased \( \text{PaO}_2 \), which in turn was caused by a widened \( \text{A-aDO}_2 \) and an insufficient ventilatory response. Ventilation was constrained during the exercise, as suggested by extensive EFL, a high fractional utilization of the maximum ventilatory capacity, pronounced dynamic hyperinflation, and a variable but high pulmonary resistance. These mechanical constraints likely contributed to the highly heterogeneous exercise ventilatory response, with several subjects exhibiting a rising \( \text{PaCO}_2 \) or frank \( \text{CO}_2 \) retention (40 Torr \( \text{PaCO}_2 \)) during exercise. Sputum histamine and urinary \( \text{9PGF}_2 \) were increased after exercise, providing evidence for an airway inflammatory response to the exercise stimulus. Furthermore, the postexercise sputum histamine levels were significantly correlated with several measures of gas exchange during exercise.

Phenotypic Diversity Among Subjects

We used four different tests of airway function to evaluate our subjects for airway pathology consistent with the diagnosis of asthma. Our subjects showed variable degrees of airway hyperresponsiveness, airflow limitation, and airway inflammation (Table 1). Thus the results from the inclusion criteria studies highlight the heterogeneity of bronchial asthma and the lack of association between different tests of airway function in asthmatic subjects.

Also, subjects 6, 17, and 21 had a \( \text{PC}_{20} \) >16 mg/ml. This is important given the notion that airway hyperresponsiveness to direct-acting stimuli is necessary for the diagnosis of asthma. The alternative view is that asthma is more akin to a syndrome with multiple phenotypes and indicators of airway pathology (55). Asthma is a complex and heterogeneous condition, and in our view it is overly simplistic to ascribe the diagnosis of asthma on the basis of one outcome measure. Furthermore, we sought to study a group of subjects with a diverse range of airway characteristics consistent with the diagnosis of bronchial asthma.

Exercise-Induced Arterial Hypoxemia

In the present study, the decreased \( \text{SaO}_2 \) during prolonged heavy-intensity exercise was due almost equally to a decreased \( \text{PaO}_2 \) and a temperature- and pH-induced shift in the oxyhemoglobin dissociation curve. Similar to previous findings in healthy young adults, the exercise \( \text{PaO}_2 \) was highly related to the efficiency of gas exchange, as measured with the \( \text{A-aDO}_2 \), and to the magnitude of the ventilatory response during the exercise, as revealed by the \( \text{PaCO}_2 \) (Fig. 5).

An important difference between the present study and previous studies on gas exchange during exercise in asthmatic subjects (see the introduction) is that our subjects were active and, therefore, capable of working at moderately high work...
rates and at a high percentage of their \( V_{O2\ max} \) for several minutes. Thus the exercise was at a sufficiently high metabolic requirement to stress the capacity of the cardiopulmonary system for gas exchange and \( O_2 \) transport. Previous studies of asthmatic subjects exercising at lower exercise intensities have shown preservation of, or increased, \( PaO_2 \) during exercise (5, 12, 19, 20, 24, 35).

In the present group of subjects, the exercise-induced arterial hypoxemia (EIAH) occurred at lower exercise metabolic rates and in subjects with lower \( V_{O2\ max} \) than previously reported in healthy nonasthmatic individuals. In health, significant EIAH occurs only in a minority of subjects of moderate-to-high fitness who are able to achieve high metabolic rates for several minutes (15, 57); it is infrequent in men and women with a \( V_{O2\ max} \) of less than \(~60\) and 50 ml·kg\(^{-1}\)·min\(^{-1}\), respectively (30, 57). In contrast, 50\% of our asthmatic subjects (2 men and 2 women) in the Lo-Sao group had a \( V_{O2\ max} \) of \(<42\) ml·kg\(^{-1}\)·min\(^{-1}\) (range 39.2–41.6) and were exercising at a mean metabolic rate of only 36.1 ml·kg\(^{-1}\)·min\(^{-1}\) at the end of the prolonged bout. Furthermore, 10 of 21 subjects had a \(~10\)-Torr decrease in \( PaO_2 \) during the prolonged exercise bout, with this initial drop persisting to the end of the bout in 7 of the 10 subjects. In contrast, Wasserman et al. (56) found no reduction in \( PaO_2 \) in 10 healthy but untrained men who performed constant-load cycle exercise to exhaustion at an exercise intensity similar to that used in our prolonged bout.

Baseline Pulmonary Function and Arterial Blood Gas Status During Exercise

Because of the potential for narrowed airways to alter the ventilation distribution and minimize the hyperventilation of heavy exercise, it is reasonable to hypothesize that the level of baseline airflow limitation might provide some prediction of arterial blood gas status during exercise in asthmatic subjects. However, for a given level of baseline airflow limitation in our subjects, exercise \( PaO_2 \) and \( PaCO_2 \) spanned a wide range of values. For example, for eight subjects, baseline \( FEV_{1,0}/FVC \) was 77\%, mean forced expiratory flow from 25\% to 75\% of vital capacity was 2.94 l/s (74\% predicted), respiratory system resistance at 5 Hz was 4.59 cmH\(_2\)O·l·s\(^{-1}\), maximal voluntary ventilation was 113.0 liters (97.7\% predicted). Lower \( PaCO_2 \) in this subject than in the subject described in Fig. 7 legend was due to a higher \( Vu/VCO2 \) during exercise (31 vs. 26 during the prolonged exercise bout).
exercise causes progressive reductions in mixed venous \textit{O}_2 content, increases in cardiac output, and demands large increases in \textit{V}_A, all of which should compromise arterial blood gas status in subjects with already impaired airway and gas exchange function. On the other hand, exercise promotes bronchodilation, which should improve the capacity for ventilation and also improve \textit{V}_A/Q distribution. However, the magnitude of any exercise-induced bronchodilation is likely to be variable in asthmatic subjects, depending in part on the level of irreversible airflow limitation. For example, \textit{subjects} 15, 18, 20, and 21 showed some amount of baseline airflow limitation that was only minimally improved after \textit{β}-agonist inhalation (Tables 1 and 2).

\textbf{Breathing Mechanics During Exercise}

Pulmonary resistance showed large variability among subjects during exercise: \textit{R}_{L_1} was normal in several subjects (\textit{$<$2 cmH}_2O \cdot l^{-1} \cdot s^-1) but increased in others (\textit{$>$2–3 cmH}_2O \cdot l^{-1} \cdot s^-1) relative to values previously reported in healthy subjects (8, 21). The slight group mean increases in \textit{R}_{L_1} during exercise are largely explainable by the increased inspiratory flow rates (peak inspiratory flow = 0.7 ± 0.2 l/s at rest vs. 4.7 ± 1.0 l/s during prolonged exercise bout) and the nonlinearity of the pressure-flow relationship (8, 22). On the basis of previous studies that determined transpulmonary pressure at different pressure-flow relationship (8, 22). On the basis of previous studies that determined transpulmonary pressure at different pressure-flow relationship (8, 22).

In the present study, \textit{P}_{aCO_2} spanned a wide range of values at all exercise workloads. During submaximal exercise, the mean values for \textit{P}_{aCO_2}, were consistent with results from the literature that reported arterial blood gas values during treadmill exercise in asthmatic (5, 12) and nonasthmatic (29, 57) subjects. In contrast, during high-intensity exercise (i.e., prolonged bout), several subjects displayed a normal exercise hyperventilation (<35 Torr \textit{P}_{aCO_2}), whereas others showed a high or progressively rising \textit{P}_{aCO_2} across time. Furthermore, four subjects had frank \textit{CO}_2 retention (41.2–46.6 Torr \textit{P}_{aCO_2}) at end exercise. The high prevalence of an insufficient hyperventilatory response in our subjects contrasts with previous studies in asthmatic subjects who showed a normal or even greater hyperventilation during exercise than healthy control subjects (5, 12, 19, 24, 28, 35). The moderate exercise intensities used in these studies, however, required only modest increases in \textit{V}_A, which did not stress the capacity of the pulmonary system to generate airflow. However, one of five subjects in a previous study did retain \textit{CO}_2 (\textit{$<$45 Torr) during moderate-intensity treadmill exercise (5).

What are the causes of the heterogeneous ventilatory response during exercise in the present group of asthmatic subjects? First, it is clear that the failure to adequately reduce \textit{P}_{aCO_2} was due to an inadequate increase in \textit{V}_E, rather than an excessive dead space-to-tidal volume ratio (Fig. 4). Ventilation during high-intensity exercise is determined by the net effect of two competing influences: 1) the magnitude of and sensitivity to multiple feedforward and chemoreceptor- and locomotorlinked feedback inputs to the brain stem acting to stimulate ventilation out of proportion to \textit{CO}_2 production (45), and 2) the constraints on ventilation imposed by the mechanical characteristics of the extra- and intrathoracic airways and chest wall, in combination with the capacity for pressure development by the respiratory muscles. In this regard, many of the asthmatic subjects in this study had a high airway resistance with a compromised capacity for expiratory airflow (i.e., high flow- resistive work of breathing) and a high elastic work of breathing and shortened diaphragm as a consequence of dynamic hyperinflation during the exercise. EFL is also associated with an increased EELV and attenuates the exercise hyperventilation during high-intensity exercise in healthy, young highly fit men (33, 41) and women (40), in physically active older adults (31), and in subjects with chronic airflow limitation (44). Importantly, however, the extent of mechanical constraint and dynamic hyperinflation in our subjects was markedly greater than that seen in even highly fit athletes exercising at higher metabolic rates with far greater ventilatory requirements.
difference (26). In health, there is also variation in the physiological response to EFL, in terms of its effects on operating lung volumes and on the ventilatory response (33). We can only conclude that EFL and a high $VE$ expressed as a percentage of ventilatory capacity were present in all subjects who lacked a sufficient hyperventilation during the exercise; however, EFL, per se, did not always result in a blunted ventilatory response during exercise.

Airway Inflammation

There is good reason to postulate a relation between airway inflammation and gas exchange during exercise (see the introduction). Exercise caused an increase in urinary 9α,11β-PGF$_2$ when all subjects were analyzed as one group and an increase in sputum histamine in the Lo-SaO$_2$ group only, providing evidence for mast cell degranulation during or shortly after exercise in asthmatic subjects. Other investigators also showed an increase in urinary 9α,11β-PGF$_2$ after exercise in asthmatic subjects (43, 46). The osmotic hypothesis of EIB stipulates that inflammatory mediators be released into the airway wall during or shortly after exercise (6); however, previous studies are inconsistent regarding the airway inflammatory response to exercise in asthmatic subjects (10, 13, 23, 31, 36, 43, 46). Some of the discrepancy is probably due to the difficulty in accurately detecting changes in inflammatory mediators in the airway lumen or mucosal layer, differences in metabolism of the mediators and the time interval between exercise and collection of sputum or bronchoalveolar lavage, and differences in exercise work rate between the separate studies.

Does airway inflammatory mediator release in response to exercise in asthmatic subjects affect gas exchange during the provocative exercise bout? On the one hand, we found significant correlations between postexercise sputum histamine and A-aDO$_2$ and PaO$_2$ during exercise and also between the exercise-induced change in histamine and the differences in PaO$_2$ and A-aDO$_2$ between end exercise and rest. Thus exercise PaO$_2$ was lower and A-aDO$_2$ was wider in subjects with increased sputum histamine after exercise. If released during exercise, the effects of these mediators on the bronchial vasculature and smooth muscle may have caused a worsened ventilation distribution and perpetuated the development of arterial hypoxemia, even in the absence of reductions in large airway caliber during exercise. Indeed, inhalation of the inflammatory mediators histamine, leukotriene D$_4$, and platelet-activating factor causes an increase in resting A-aDO$_2$ and a decrease in PaO$_2$ in asthmatic subjects (1, 17, 18).

On the other hand, the lack of a time-dependent increase in A-aDO$_2$ or decrease in PaO$_2$ beyond minute 1 of exercise (Figs. 1 and 3) suggests that the inflammatory mediator release did not occur during but only after the exercise [the conventional but untested hypothesis (6)] or that any mediator release during exercise does not negatively impact pulmonary gas exchange. One of the principal effects of inflammatory mediator release is bronchial smooth muscle contraction, but the bronchoprotective effect of exercise in asthmatic subjects (51) might prevent this contraction. Other compensatory mechanisms that would help prevent deterioration in gas exchange in the face of inflammatory mediator release include regional hypoxic pulmonary vasoconstriction, collateral ventilation, and the increase in overall $VA/Q$ during exercise. Constant-load, high-intensity exercise in nonasthmatic subjects also does not result in any time-dependent decreases in PaO$_2$ or increases in A-aDO$_2$ beyond minute 1 of exercise (29, 57), and acute administration of a cocktail of anti-inflammatory agents before exercise in trained young nonasthmatic subjects had no effect on gas exchange during exercise (58). Future studies that acutely block or chronically treat the airway inflammation of asthma are a necessary next step to rigorously determine the effects of airway inflammation on exercise gas exchange.

Conclusions

Habitually active, mildly to moderately asthmatic subjects appear to develop exercise-induced arterial hypoxemia at lower metabolic rates than their nonasthmatic counterparts. This is related in large part to an insufficient exercise ventilatory response, likely as a consequence of substantial mechanical constraints for ventilation at only moderate levels of $VE$. Additionally, we found evidence supporting a role for airway inflammatory mediator release in the widened A-aDO$_2$ and decreased PaO$_2$ during exercise in asthmatic subjects.

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