Early onset of pulmonary gas exchange disturbance during progressive exercise in healthy active men

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Aguilaniu, B., P. Flore, J. Maitre, J. Ochier, J. R. Lacour, and H. Perrault. Early onset of pulmonary gas exchange disturbance during progressive exercise in healthy active men. J Appl Physiol 92: 1879–1884, 2002; 10.1152/japplphysiol.00630.1999.—Some recent studies of competitive athletes have shown exercise-induced hypoxemia to begin in submaximal exercise. We examined the role of ventilatory factors in the submaximal exercise gas exchange disturbance (GED) of healthy men involved in regular work-related exercise but not in competitive activities. From the 38 national mountain rescue workers evaluated (36 ± 1 yr), 14 were classified as GED and were compared with 14 subjects matched for age, height, weight, and maximal oxygen uptake (V˙O2 max; 3.61 ± 0.12 l/min) and showing a normal response (N). Mean arterial PO2 was already lower than N (P = 0.05) at 40% V˙O2 max and continued to fall until V˙O2 max (GED: 80.2 ± 1.6 vs. N: 91.7 ± 1.3 Torr). A parallel upward shift in the alveolar-arterial oxygen difference vs. %V˙O2 max relationship was observed in GED compared with N from the onset throughout the incremental protocol. At submaximal intensities, ideal alveolar Po2, tidal volume, respiratory frequency, and dead space-to-tidal volume ratio were identical between groups. As per the higher arterial Pco2 of GED at V˙O2 max, subjects with an exaggerated submaximal alveolar-arterial oxygen difference also showed a relative maximal hyperventilation. Results thus suggest the existence of a common denominator that contributes to the GED of submaximal exercise and affects the maximal ventilatory response.

alveolar-arterial oxygen difference; exercise ventilation; arterial hypoxemia

EXERCISE-INDUCED ARTERIAL hypoxemia (EIH) has been a common finding in endurance-trained young (3, 5) and master athletes (1, 2, 9, 15) that has also been described in regularly exercising young women (7, 11, 19, 20). The phenomenon defined as a decrease in arterial Po2 (Pao2) >10 Torr (5) has been related to a number of factors including venoarterial shunt, ventilation, and/or diffusion limitations (5, 18). A lower ventilation (VE)-to-maximal oxygen uptake (V˙O2 max) ratio is generally reported in athletic subjects exhibiting EIH compared with those who did not, suggesting that a relative hypventilation is a contributing factor to EIH occurrence (12, 14). Similarly, a diffusion limitation has been proposed, which could result from an incomplete equilibration of oxygen between alveolar gas and pulmonary capillary blood after a markedly shortened mean pulmonary capillary transit time or from a potential alteration in the integrity of the alveolar-capillary membrane or a combination of both (5, 6, 8, 18). Considering the systemic constraints imposed by maximal exercise intensity, it seems likely that, independent of the extent of their contribution, several concurrent mechanisms may act to express a disturbance in gas exchange.

In some subjects, maximal EIH has been observed to begin even in submaximal exercise and to worsen as work rate is increased (3, 7, 15–17). A common denominator in these studies may be the high aerobic capacity of subjects. In the studies by Dempsey et al. (3) and Rice et al. (16, 17), subjects were highly trained competitive endurance athletes with V˙O2 max ranging between 58 and 82 ml·kg−1·min−1. Similarly, Harms et al. (7) and more recently Wetter et al. (20) studied women endurance runners and found submaximal EIH in subjects showing levels of V˙O2 max 43–70 ml·kg−1·min−1. This observation may suggest that submaximal gas exchange disturbance (GED) is essentially related to the endurance athletic status or to smaller relative lung size, such as seen in women, and predisposing to ventilatory maldistribution and/or an imbalance between pulmonary capacity and demand for pulmonary oxygen transport.

In the present study, we examined arterial gases and ventilatory adaptations from rest to maximal exercise in healthy men of normal stature who were involved in regular work-related endurance exercise and training but who did not engage in specific athletic competitive activities. Similar to previous observations in athletes, our findings indicate an early onset of excessive alveolar-arterial oxygen difference (A-aDo2) in healthy nonathletic subjects exhibiting a progressively decreasing PaO2. We observed submaximal GED not to be accounted for by ventilatory responses or by athletic status or body stature. An interesting additional finding was that subjects showing an early onset of gas...

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exchange alteration were also those showing a relative hypoventilation at maximal exercise.

**METHODS**

**Subjects**

Thirty-eight healthy nonsmoking male professional national mountain rescue workers (age 36 ± 1 yr; weight 71.9 ± 1 kg; height 176 ± 1 cm) volunteered to take part in the study. In addition to their occupational physical activity, subjects took part in 13–16 h weekly of regular programmed outdoor physical activities such as mountain climbing and skiing to maintain and optimize their fitness level and specific working skills. All participants signed an informed consent form, and ethics approval was obtained from the institution’s ethics review board.

**Evaluation Procedures and Protocols**

Subjects were tested in the morning under standard laboratory environmental conditions (barometric pressure 749–752 Torr; temperature 19–22°C; relative humidity 50–55%), 3 h after a standard breakfast.

**Resting pulmonary function tests.** Before completing the incremental maximal exercise test, all participants were subjected to standard resting pulmonary function tests using a Masterlab spirometric system (Jaeger, Wurzburg, Germany) and including maximal expiratory flow volume curves generated from forced vital capacity and forced expiratory volume in 1 s (liters) and the expired flow rates at 25 and 75% of vital capacity (l/s) by use of criteria from the American Thoracic Society.

**Maximal exercise protocol.** All subjects then completed an incremental maximal exercise test on an electromagnetic braked cycle ergometer (Ergoline 800) using successive increases of 30 W every 90 s until voluntary exhaustion. Electrocardiograph recordings, oxygen uptake (V\textsubscript{O\textsubscript{2}}), expired CO\textsubscript{2} (V\textsubscript{CO\textsubscript{2}}), and V\textsubscript{T} as well as tidal volume (V\textsubscript{T}), breathing frequency, and respiratory exchange ratio were obtained continuously throughout the exercise protocol by using a breath-by-breath automated exercise metabolic system (CPX, Medical Graphics, St. Paul, MN). Values were averaged over the last 30 s of each workload to coincide with the simultaneous arterial blood sampling. Arterial blood samples were drawn from an indwelling brachial arterial catheter at rest as well as during the last 30 s of each workload of the incremental maximal exercise and at the third and fifth minute of exercise recovery.

**Treatment of data and blood sample analyses.** Arterial gas sample data obtained throughout the maximal exercise test were examined for evidence of mild exercise-induced hypoxemia defined as a fall in P\textsubscript{AO\textsubscript{2}} from baseline rest >10 Torr on non-temperature-corrected P\textsubscript{AO\textsubscript{2}}. Fourteen of the 38 subjects met this criteria and were classified as GED subjects. The data from these 14 GED subjects were compared with those from 14 of the 24 subjects with no GED (N) matched for age, height, weight, and maximal aerobic power. P\textsubscript{AO\textsubscript{2}} values corresponding to given relative exercise intensities between 30 and 100% of V\textsubscript{O\textsubscript{2 max}} were determined for each subject by using an interpolation procedure from the mathematical model of best fit from P\textsubscript{AO\textsubscript{2}} values at each workload.

**Determination of blood gases and blood lactate.** On sampling, blood was quickly analyzed for P\textsubscript{AO\textsubscript{2}}, P\textsubscript{ACO\textsubscript{2}}, and pH at 37° by using the standard electrodes (Radiometer ABL 330, Radiometer, Copenhagen, Denmark). The instrument was calibrated before and several times during the course of blood analysis by using precision buffers and gases. Oxygen hemoglobin saturation was calculated by using blood P\textsubscript{AO\textsubscript{2}} and arterial pH determinations.

To correct P\textsubscript{AO\textsubscript{2}} values for blood temperature during exercise, a subgroup of 16 subjects (8 of each of the 14 subjects of the GED and the N group) were asked to return to the laboratory to repeat the same exercise protocol while equipped with an esophageal temperature probe. Workload, V\textsubscript{O\textsubscript{2}}, and heart rate responses were identical to those of the initial test. Esophageal temperature was monitored throughout the exercise. Results indicated similar esophageal temperature kinetics in both GED and N with an average 1.8 ± 0.2°C increase from rest to maximal exercise as previously reported by others (7). A temperature correction factor based on the average esophageal temperature recording was then applied to all exercise P\textsubscript{AO\textsubscript{2}} and P\textsubscript{ACO\textsubscript{2}} values by using the following equations, where T is the temperature:

\[
\text{P}_{\text{AO2}}(c) = \text{antilog} [0.023 \times (T \ - \ 37)] + \log(\text{P}_{\text{AO2}})
\]

\[
\text{P}_{\text{ACO2}}(c) = \text{P}_{\text{ACO2}} \times \text{antilog} [0.021 \times (T \ - \ 37)]
\]

A-a\textsubscript{DO\textsubscript{2}} in PO\textsubscript{2} was calculated from the alveolar gas equation by using temperature-corrected (c) values for P\textsubscript{AO\textsubscript{2}} and P\textsubscript{ACO\textsubscript{2}} and correcting for saturation vapor pressure of water by using the equation \text{P}_{\text{H2O}} = 5.556 \times \exp(0.058T). Dead space-to-tidal volume ratio (V\textsubscript{D}/V\textsubscript{T}) was calculated by using the classic Bohr equation corrected by the valve box dead space.

Samples for blood lactate determination were drawn 2 min after the end of maximal exercise and were analyzed by use of a standard lactate analyzer (Microzym, SG1, Toulouse, France).

**Statistical Analyses**

Values are reported as means ± SE. Mean comparisons between GED and N subjects were achieved by using Student’s t-test for unpaired data. Mean comparisons at various relative exercise intensities were achieved by using a two-way ANOVA for repeated measures on the last factor. On finding of a significant F ratio (P < 0.05), post hoc data comparisons were achieved by using a Tukey’s test to locate group differences. Statistical significance was set at P < 0.05.

**RESULTS**

**Anthropometric and Resting Pulmonary Function Parameters**

Anthropometric and resting pulmonary function parameters are shown in Table 1. All participants exhibited normal pulmonary function tests. No differences in age, height, weight, or ventilatory parameters were found between subjects of groups GED and N.

**Maximal Exercise Data**

Maximal exercise data from GED and N subjects appear in Table 2. Results indicate similar maximal heart rate, V\textsubscript{O\textsubscript{2}}, \text{V\textsubscript{T}}, \text{V\textsubscript{E}/V\textsubscript{O\textsubscript{2}}, respiratory exchange ratio, and plasma lactate between GED and N. GED exhibited significantly lower P\textsubscript{AO\textsubscript{2}} and higher A-a\textsubscript{DO\textsubscript{2}} than N with a significantly higher value of P\textsubscript{ACO\textsubscript{2}} and a lower pH. Maximal values of V\textsubscript{T}, breathing frequency, calculated alveolar \text{V\textsubscript{E}}, and estimated V\textsubscript{t}/V\textsubscript{T} were not significantly different between GED and N.
Exercise Ventilatory and Pulmonary Gas Exchange Patterns

Figure 1 illustrates individual and group mean $PaO_2$ (Fig. 1A) as well as the calculated A-aDO$_2$ (Fig. 1B) at rest as well as for submaximal and maximal exercise in both GED and N. Resting values of $PaO_2$ and A-aDO$_2$ were not significantly different between groups. As expected in the N group, exercise-induced hyperventilation resulted in a gradual increase in mean $PaO_2$, at higher exercise intensities. In contrast, subjects of the GED group showed a gradual decline in $PaO_2$ with increasing exercise intensity. A significantly lower mean $PaO_2$ was observed in GED compared with N for all exercise intensities equal to or exceeding 40% $V_{O_2\text{max}}$. Post hoc contrasts revealed successive mean $PaO_2$ exercise values in GED to be significantly different from maximal exercise. An increase of the A-aDO$_2$ curve in GED compared with N such that values were significantly higher in GED for all exercise intensities. The extent of between-group difference remained relatively constant throughout the incremental exercise protocol widening only at near-maximal exercise. Recovery $PaO_2$ and A-aDO$_2$, 3 and 5 min after maximal exercise, were not found to be significantly different between groups.

Table 1. Anthropometric and resting pulmonary function data in subjects with or without exercise-induced gas exchange disturbance

<table>
<thead>
<tr>
<th></th>
<th>GED ($n=14$)</th>
<th>N ($n=14$)</th>
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</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>36 ± 2</td>
<td>36 ± 2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175 ± 1</td>
<td>176 ± 1</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>71.4 ± 1.5</td>
<td>72 ± 1.9</td>
</tr>
<tr>
<td>FVC, L</td>
<td>5.7 ± 0.2</td>
<td>5.7 ± 0.2</td>
</tr>
<tr>
<td>FEV$_1$, L/s</td>
<td>4.7 ± 0.2</td>
<td>4.7 ± 0.2</td>
</tr>
<tr>
<td>FEV$_{25-75}$, L/s</td>
<td>82.6 ± 2</td>
<td>82.1 ± 2</td>
</tr>
<tr>
<td>FEF$_{25-75}$, L/s</td>
<td>4.6 ± 0.3</td>
<td>4.7 ± 0.3</td>
</tr>
</tbody>
</table>

Values are means ± SE. GED, subjects with gas exchange disturbance; N, subjects with normal response; FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1 s; FEF$_{25-75}$, expired flowrates at 25 and 75% of vital capacity.

Table 2. Maximal exercise data with temperature correction in subjects with or without exercise-induced gas exchange disturbance

<table>
<thead>
<tr>
<th></th>
<th>GED ($n=14$)</th>
<th>N ($n=14$)</th>
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</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>182 ± 2</td>
<td>181 ± 2</td>
</tr>
<tr>
<td>Workload, W</td>
<td>325 ± 9</td>
<td>317 ± 10</td>
</tr>
<tr>
<td>$V_{O_2}$, L/min</td>
<td>3.61 ± 0.12</td>
<td>3.56 ± 0.09</td>
</tr>
<tr>
<td>$V_{O_2}$, ml·kg$^{-1}$·min$^{-1}$</td>
<td>50.5 ± 2.1</td>
<td>50.6 ± 1.2</td>
</tr>
<tr>
<td>$V_e$, L/min</td>
<td>127 ± 4.7</td>
<td>133 ± 4.9</td>
</tr>
<tr>
<td>$V_e$/V$O_2$</td>
<td>35.2 ± 1.2</td>
<td>37.4 ± 1.3</td>
</tr>
<tr>
<td>$PaO_2$, Torr</td>
<td>80.2 ± 1.6</td>
<td>91.7 ± 1.3</td>
</tr>
<tr>
<td>$PaCO_2$, Torr</td>
<td>38.1 ± 0.9</td>
<td>34.7 ± 0.9</td>
</tr>
<tr>
<td>A-aDO$_2$, Torr</td>
<td>33.2 ± 1.3</td>
<td>24.1 ± 1.6</td>
</tr>
<tr>
<td>RER</td>
<td>1.25 ± 0.02</td>
<td>1.25 ± 0.02</td>
</tr>
<tr>
<td>Plasma lactate, mmol/l</td>
<td>12.8 ± 0.7</td>
<td>12.1 ± 0.6</td>
</tr>
<tr>
<td>pH</td>
<td>7.28 ± 0.009</td>
<td>7.32 ± 0.01</td>
</tr>
<tr>
<td>Esophageal temperature, °C</td>
<td>38.3 ± 0.1</td>
<td>38.3 ± 0.1</td>
</tr>
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</table>

Values are means ± SE. $V_{O_2}$, oxygen uptake; $V_e$, ventilation; $PaO_2$, arterial $PO_2$; $PaCO_2$, arterial $PCO_2$; A-aDO$_2$, alveolar-arterial oxygen difference; RER, respiratory exchange ratio. *$P < 0.05$ between groups.
were found between groups for submaximal exercise intensities, except for near-maximal intensities (90 and 100% $V_{O2 \text{ max}}$), at which GED showed slightly but significantly higher values than N with mean differences corresponding to 2.3 and 2.8 Torr, respectively. Recovery mean $P_{ACO_2}$ values remained lower than baseline 3 and 5 min after maximal exercise but were not found to be significantly different between groups.

As expected, ideal $P_{AO_2}$ increased progressively with incremental exercise intensity in both groups; the relative increases corresponding to $\sim$12 and 17% in GED and N respectively (Fig. 3B). No significant between-group difference was observed for mean ideal $P_{AO_2}$ at any point including recovery. Figure 4 shows mean exercise ventilatory parameters in GED and N. Results show similar $\nu_T$ and breathing frequency responses with exercise and recovery in both groups. Similarly, $V_d/\nu_T$ was not different between groups at any observation point of exercise or recovery.

**DISCUSSION**

Previous studies have shown an alteration of submaximal pulmonary gas exchange in athletic groups of young and older men and highly trained women show-
ing a significant EIH at maximal exercise (15–17, 19, 20). In this study, a GED at the early onset of progressive maximal exercise was found in 37% of healthy active men showing similarities in body stature and physical fitness status on account of the professional demands of their occupation as mountain rescue workers. This prevalence is not far behind the ~50% prevalence of EIH estimated at sea level in highly trained athletes (5). This observation raises the question as to whether there exist predisposing factors in healthy individuals for exercise-induced GED that might become magnified as a result of endurance training. As previously suggested (3), endurance training may lead to an imbalance between pulmonary oxygen transport demands and oxygen delivery capacity on account of the cardiac output adaptation unmatched by pulmonary structural and functional adaptations. In addition, the pattern of repeated stress of intensive exercise inherent to endurance training could act to enhance inflammatory processes and secretory characteristics of pulmonary airways and parenchyma (2, 13, 15), predisposing to an exaggerated ventilation and/or perfusion maldistribution during exercise.

In the present study, a significantly higher A-aD O2 was observed in GED subjects as early as the first submaximal exercise determination (30% VO2 max) and increased thereafter throughout the exercise protocol. The exaggerated A-aD O2 could not be accounted for by any difference between groups in ideal PaO2, indicating that external ventilation was not a factor during mild or moderate exercise intensities. The observed GED in the early phase of exercise must therefore reflect an alteration of pulmonary oxygen conductance per se linked to either a circulatory or a peripheral air con- ductance component or a combination of both. A shortened pulmonary transit time as a result of an enhanced cardiac output in well-trained individuals as well as a putative interstitial pulmonary edema have been suggested as potential mechanisms for the reported hypoxemia of maximal or near-maximal exercise (8, 10, 18). In the present study, a difference in cardiac output and ensuing pulmonary transit time is unlikely because both VO2 and heart rate responses are the same in both groups and thus, also, presumably cardiac output. It may also be argued that the level of metabolic and circulatory demands for mild and moderate exercise are too low to account for substantial shear stress failure on the pulmonary vasculature. In agreement with this argument, our recovery data indicate similar arterial gases and A-aD O2 between groups with and without exercise pulmonary gas disturbances, decreasing the probability of a contribution by pulmonary edema.

Ventilation-perfusion mismatch currently appears as the most likely explanation for the maximal EIH in healthy endurance-trained subjects (5). Our data indicate subjects from both groups to have identical dead space ventilation throughout the exercise protocol. This result does not, however, exclude the possibility of an alteration in peripheral airway ventilation leading to an exaggerated ventilation-perfusion mismatch to explain the observed submaximal GED. Recently, Wetter et al. (20) examined the link between pulmonary gas exchange and airway function during prolonged exercise in healthy fit women. Their results show 8 of 17 runners to exhibit low PaO2 during steady-state exercise at 75% VO2 max but not at the previous steady-state level of 50% VO2 max. Their results revealed significant correlations between increased pulmonary closing volume and exercise SaO2 and A-aD O2 and showed several subjects to exhibit some abnormalities of airway resistance and/or reactivity, although this was not related to the degree of exercise-induced gas exchange impairment. Specific functional characteristics of small and large airway function were not obtained in the present study such that this relationship cannot be verified. On the other hand, in our study, as in other previous reports of submaximal exercise GED (1, 2, 15–17), the maximal exercise challenge consisted of a ramp protocol in which workload is increased every 1–2 min. In such rapid incremental protocols, the time at each exercise stage may be insufficient to allow for stability of ventilatory parameters. This time factor might be especially important in the presence of predisposing peripheral airway dysfunction, which could emphasize the inhomogeneity of pulmonary mechanical time constants and lead to maldistribution of ventilation and reduced alveolar oxygen clearance.

Finally, an interesting observation of the present study is the fact that, as shown by PaCO2 data, subjects exhibiting an early exercise widening of A-aD O2 also exhibited a lesser hyperventilation during near-maximal exercise. In highly trained athletes, the extent of maximal EIH has been clearly related to the degree of hyperventilation (12, 14). Why subjects showing impairment in gas exchange in the early phases of a progressive maximal exercise would also be those demonstrating a lesser hyperventilation remains to be clarified. A common denominator for these concurrent events could be peripheral airway constraints contributing to maldistribution of pulmonary flow in the early phases of exercise and potentially affecting the maximal exercise ventilatory response through mechanical or reflex influences. It may thus be of interest for future investigations to confirm the occurrence of submaximal GED by using steady-state rather than rapid incremental exercise protocols and to examine its relationship with peripheral pulmonary airway characteristics and/or maximal exercise ventilation.

In conclusion, the present observations indicate that the GED-susceptible healthy individuals exhibit an early onset of alveolar-arterial oxygen widening throughout the incremental exercise protocol, which appears independent of the ventilatory response. The early phenomenon appears, however, to be compounded by a relative hypoventilation as subjects exhibiting an early exaggerated alveolar-arterial widening also exhibit a relative hypoventilation at maximal exercise. The present observations of GED in 37% of subjects matched for age, body stature, and physical fitness status suggest that factors unrelated to an exaggerated systemic demand for pulmonary capaci-
ties appear to be involved in the GED. The fact that alveolar ventilation and ventilatory efficiency were similar in subjects exhibiting a GED or not suggests the involvement of an exaggerated ventilatory maldistribution as the main responsible factor. The extent to which a cumulative effect of successive non-steady-state exercise loads contributes to the present observations also needs to be considered.

REFERENCES


