Radiographic evidence of interstitial pulmonary edema after exercise at altitude

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Anholm, James D., Eric N. C. Milne, Paul Stark, Jonathan C. Bourne, and Paul Friedman. Radiographic evidence of interstitial pulmonary edema after exercise at altitude. J. Appl. Physiol. 86(2): 503–509, 1999.—Pulmonary function abnormalities after exercise are suggestive of pulmonary edema; however, radiographic evidence is lacking. Well-trained cyclists were studied to determine whether there is radiographic evidence of pulmonary edema after endurance exercise (cycling distance 5.3–131.5 km) at altitude. Chest radiographs obtained before exercise were coded for later interpretation. Films obtained after exercise were coded with a different number. A total of 74 sets of posteroanterior and lateral films were analyzed by three radiologists for signs of pulmonary edema. Radiographic changes were graded on a three-point scale. An edema score was calculated by summing the score for each individual radiographic finding for each radiologist and an overall edema score representing the mean scores from all three radiologists. The overall edema score increased from 0.8 ± 1.2 before exercise to 1.8 ± 1.6 after exercise (P < 0.01). These results suggest that, after prolonged high-intensity exercise at moderate altitude, there is radiographic evidence of early pulmonary edema in some cyclists.

Methods

Subjects. A total of 33 cyclists participated in these studies involving data collection on five occasions (Table 1). Subjects were recruited from local cycling clubs and recommendations of other cyclists and were included in these studies on the basis of their cycling ability, willingness to participate, and availability on the study dates. We attempted to recruit no more than 10–11 cyclists for each study, since additional subjects would result in unacceptable delays in obtaining radiographic studies. Cyclists were told that they would be asked to ride a long, difficult, hilly course as rapidly as possible. No one declined to participate because of the length or difficulty of the anticipated ride. All studies were approved by the Human Studies Committee at the Jerry L. Pettis Memorial Veterans Medical Center, and the subjects gave their written informed consent before participation in the studies.

All subjects were highly trained cyclists who routinely competed in local or national road (US Cycling Federation) or mountain biking (National Off-Road Bicycling Association) races. One subject participated in studies 1 and 3; another subject participated in studies 2 and 3; a third subject participated in studies 1–3. All other subjects were studied only once, giving a total of 37 pre- to postexercise comparisons.

Procedures. Each study shown in Table 1 was conducted in a similar manner; however, the cycling course varied, as did the duration of exercise. Subjects were transported from the altitude of their residence to 2,400 m, where they acclimated over the duration of exercise. Radiographic studies. Cyclists were told that they would be asked to ride a long, difficult, hilly course as rapidly as possible. No one declined to participate because of the length or difficulty of the anticipated ride. All studies were approved by the Human Studies Committee at the Jerry L. Pettis Memorial Veterans Medical Center, and the subjects gave their written informed consent before participation in the studies.

Table 1. Subject characteristics and cycling course description

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Race Type</th>
<th>Distance, km</th>
<th>Altitude Range, m</th>
<th>Total Altitude Climbed, m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilot</td>
<td>11</td>
<td>Mountain</td>
<td>5.3</td>
<td>2,713–3,369</td>
<td>656</td>
</tr>
<tr>
<td>Study 1</td>
<td>11</td>
<td>26 ± 8 Road</td>
<td>70.0</td>
<td>2,219–2,797</td>
<td>1,229</td>
</tr>
<tr>
<td>Study 2</td>
<td>4</td>
<td>17 ± 1 Road</td>
<td>95.0</td>
<td>2,219–2,797</td>
<td>1,650</td>
</tr>
<tr>
<td>Study 3</td>
<td>7</td>
<td>22 ± 4 Road</td>
<td>95.0</td>
<td>2,219–2,797</td>
<td>1,650</td>
</tr>
<tr>
<td>Study 4</td>
<td>4</td>
<td>30 ± 2 Road</td>
<td>131.5</td>
<td>2,097–3,121</td>
<td>2,405</td>
</tr>
</tbody>
</table>

Ages are means ± SD; n, no. of subjects.

http://www.jap.org
Table 2. Cycling intensity and delay before final imaging

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration, min</th>
<th>Peak HR, beats/min</th>
<th>%Peak HR During Ride</th>
<th>Elapsed Time, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilot</td>
<td>39 ± 11</td>
<td>NA</td>
<td>NA</td>
<td>63 ± 40</td>
</tr>
<tr>
<td>Study 1</td>
<td>146 ± 12</td>
<td>183 ± 8</td>
<td>89 ± 2</td>
<td>7 ± 4</td>
</tr>
<tr>
<td>Study 2</td>
<td>197 ± 19*</td>
<td>191 ± 6</td>
<td>86 ± 3</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>Study 3</td>
<td>206 ± 20</td>
<td>187 ± 8</td>
<td>87 ± 2</td>
<td>9 ± 2</td>
</tr>
<tr>
<td>Study 4</td>
<td>310 ± 12</td>
<td>183 ± 5</td>
<td>83 ± 4</td>
<td>NA†</td>
</tr>
</tbody>
</table>

Values are means ± SD. HR, heart rate; elapsed time, time after exercise before postexercise chest radiographs were obtained. Exercise duration for 1 subject in study 2 was not recorded accurately, and his data are not included. †Data not collected; however, elapsed time was similar to studies 1–3.

tilized for 12–48 h before testing. Before the start of exercise, posteroanterior (PA) and lateral chest radiographs were obtained for each subject. A second set of PA and lateral films was obtained immediately after completion of the cycling course.

The procedures varied somewhat among the various studies as follows: cyclists registered for a National Off-Road Bicycling Association-sponsored race at Mammoth Mountain, CA, were contacted before the race and comprised those who participated in our pilot study. Because of time constraints imposed by officially organized racing events, subsequent studies were conducted on separate dates acceptable to cyclists and investigators.

In study 1, 11 well-trained cyclists completed a course near Mammoth Lakes, CA. Four subjects recruited for study 1 lived at ~2,400-m altitude. The remaining subjects in this study lived at or near sea level. The course consisted of an initial 5-km uphill time trial followed by a 65-km time trial over a hilly course. Four subjects were US Cycling Federation category 1–2 riders. The others were well-trained, but not elite, cyclists.

Cyclists in study 2 completed the same 5-km uphill time trial used in study 1 and then rode an additional 85 km over difficult terrain (Table 1). All cyclists in this study lived at <600-m altitude.

Study 3 utilized the same course used for study 2. One cyclist in study 3 lived at ~1,800-m altitude; the others lived at <600 m.

In study 4 the cyclists competed over a longer and more difficult course than cyclists in the earlier studies. The cycling course involved ~2,400 m of climbing during the ~5 h of riding.1

Each study, except for the pilot study, incorporated a short, high-intensity time trial of 5–6 km at the beginning or very early in the race. Table 1 lists the total distance cycled.

Cyclists wore portable heart rate monitors (Polar Electro, Port Washington, NY) to record exercise intensity. Spirometry and arterial oxygen saturation data collected in some studies are incomplete and thus are not reported. Except for study 4, subjects were not allowed to draft one another. Because of the length and difficulty of the cycling course in study 4, it was believed that drafting would have only minimal effects on the results. Subjects were encouraged to maintain adequate hydration throughout the race and were given monetary rewards for maintaining their preexercise weight. Subjects additionally received monetary incentives to encourage peak performance. Additional details of the studies are shown in Tables 1 and 2.

Chest radiographs. All radiographic imaging was performed at the Mammoth Hospital. Chest radiographs in the

Table 3. Pre and postexercise spirometry data in study 1

<table>
<thead>
<tr>
<th></th>
<th>Preexercise</th>
<th>Postexercise</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, liters</td>
<td>4.93 ± 1.07</td>
<td>4.69 ± 0.86</td>
<td>t = 1.76</td>
</tr>
<tr>
<td>FEV₁, liters</td>
<td>3.85 ± 0.76</td>
<td>3.64 ± 0.74</td>
<td>t = 2.29</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>79 ± 13</td>
<td>78 ± 10</td>
<td>t &lt; 0.05</td>
</tr>
<tr>
<td>FEF 25–75% l/s</td>
<td>3.84 ± 1.89</td>
<td>3.34 ± 1.57</td>
<td>t = 1.77</td>
</tr>
</tbody>
</table>

Values are means ± SD. FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; FEF 25–75%, forced expiratory flow between 25 and 75% of FVC. *Not significant.

By comparison, even though the course for study 4 was more difficult that that for studies 1–3, it was shorter, although at higher altitude, than individual stages in the Tour de France race. The longest stage (stage 10) in the 1997 Tour de France was 242 km, and the highest altitude reached in the Tour de France was 2,407 m.

Fig. 1. Pre- and postexercise comparisons of chest radiographs in a subject from study 2. A: posteroanterior view of entire chest. White arrow, bronchus shown in coned-down views in B and C. B: normal bronchus before exercise. C: after exercise, same bronchus demonstrates peribronchial cuffing. Black arrow, area of chest enlarged in Fig. 2.
The PA and corresponding lateral chest radiographs were analyzed together as a set. Each set was coded with a different random number so that the radiologist did not know whether it was a pre- or a postexercise set of radiographs. A total of 74 sets of PA and lateral films from all the studies, including the pilot study, were analyzed in random order by three highly experienced chest radiologists. The interpretation for each set of films was completed before the radiologist proceeded with the next set. The radiologists knew the general study design; however, they did not know when the radiographs were obtained, nor did they know anything about the performance of the cyclist. While interpreting the radiographs the radiologist was unaware of the interpretation given by the other radiologists. Each radiologist who evaluated the films did so on a separate occasion, and each was given the same set of instructions for interpreting the films.

Films were analyzed by the radiologists for evidence of pulmonary edema with use of previously published criteria for the presence or absence of each of the following criteria: 1) loss of sharp definition of pulmonary vascular markings, 2) hilar blurring with or without perihilar haze, 3) Kerley A, B, or C lines, 4) peribronchial cuffing, 5) thickening of the fissures, 6) diffuse opacification, and 7) pleural effusion (22–24, 26, 27). Each of the above radiographic findings was graded on a three-point scale: 0 if the finding was absent, 1 if the finding was uncertain or only minimally present, and 2 if there was definite radiographic change. An edema score was calculated by summing the score for each of the individual radiographic findings. An overall edema score was calculated from the average scores of the three radiographic interpreters. Additionally, the radiographs were scored by each radiologist for recruitment of upper lung blood vessels (a marker of pulmonary blood volume).

Statistical analysis. Radiographic characteristics before and after exercise were compared using the Friedman analysis of variance test (a nonparametric analog of repeated-measures ANOVA). The Wilcoxon signed ranks test was used if more than one comparison was needed for a given pair of variables. The Wilcoxon signed ranks test was chosen for 1) films in the pilot study were obtained using a general X-ray film, whereas Kodak Ortho C X-ray film with Kodak Lanex medium intensification screens (Eastman Kodak, Rochester, NY) was used for the later studies. This combination of radiographic film and intensification screen is specially suited for chest radiography, allowing better visualization of the intrathoracic structures than more general-purpose film types. X-ray exposure times were automatically determined using a photo-timed system (GE MVP micro phototimer).
for comparisons of the edema scores before and after exercise. The level of significance was adjusted for multiple comparisons. Comparisons were performed using commercially available software (Systat, SPSS, Chicago, IL). Values are means ± SD. P < 0.05 was considered significant.

RESULTS

All subjects reported exhaustion at the end of the ride, but no cyclist had a productive cough. Except for two subjects, all cyclists completed the required course. One subject became fatigued, and another experienced bicycle mechanical problems. The course was shortened for these two subjects. Exercise intensity in all subjects remained high during the cycling events, with cyclists maintaining heart rates >80% of their peak heart rates throughout the events (Table 2).

The 11 subjects in study 1 performed spirometry before and after exercise. Forced expiratory volume in 1 s was reduced 5% after exercise compared with before exercise (P < 0.05 by paired t-test). Other spirometric values were unchanged by exercise (Table 3).

Radiographic findings. Chest radiographs were obtained as quickly as possible after completion of exercise. In the pilot study the cycling course ended a considerable distance from the hospital, resulting in an ~1-h delay before the radiographs could be taken (Table 2). In subsequent studies the course ended at the hospital and follow-up films were obtained 8 ± 3 min after exercise.

Table 4 shows data for each of the radiographic findings comprising the edema score for each of the interpreters as well as the overall edema score after the scores of all three radiologists were averaged. Subtle but clearly demonstrable radiographic changes were found by all three radiologists after exercise. Examples of these findings are shown in Figs. 1–4. Evidence of severe pulmonary edema (e.g., diffuse opacification) was not observed in any cyclist.

The edema scores (obtained by summing the various radiographic findings) were 0–6 of a total of 14 possible points. Each of the radiologists reported a higher edema score after exercise than before exercise (P < 0.05). Scoring varied slightly among the three radiologists interpreting the films; however, the change in the edema scores from before to after exercise was not statistically different among the radiologists.

Individual radiographic findings were averaged for all three radiographic interpreters. After correction for multiple statistical comparisons, only the loss of sharp definition of the pulmonary vascular markings was significant (P < 0.01). An overall edema score, representing the mean scores from all three radiologists, was calculated from the individual radiographic findings for the pre- and postexercise films. The overall edema score increased from 0.8 ± 1.2 before exercise to 1.8 ± 1.6 after exercise (P < 0.01).

After exercise the overall edema score was higher in 26 of the 37 cyclists (70%) and unchanged in 5 cyclists (14%); only 6 cyclists (16%) showed a decrease in the overall edema score. Nearly one-half of the cyclists (18 of 37) showed an increase in their overall edema score of ≥1 point, and nine cyclists (24%) had an increase of ≥2 points.

Altitude of residence of the cyclists had no effect on whether the subjects developed edema. Also, exercise performance in our cyclists did not correlate with the development of pulmonary edema.

Because of the small number of subjects in some of the studies, no attempt was made to analyze differences among the individual studies.

DISCUSSION

Summary of results. Prolonged, high-intensity exercise at altitude produced interstitial pulmonary edema, as detected by chest radiographic imaging. More than two-thirds of these cyclists demonstrated a worsening of the radiographic score after exercise, and 24% had an increased overall edema score of ≥2. In our study, exercise performance was not correlated with the devel-
Development of pulmonary edema. The spirometric changes we observed in a subgroup of our cyclists are consistent with the variable responses reported by others (14, 17, 19–21).

Sensitivity of chest imaging. Many techniques exist for assessing the presence of pulmonary edema, but these often require invasive procedures. Chest roentgenography is highly sensitive for the detection of pulmonary edema (8, 32). Several studies suggest that radiographic techniques, used by trained observers, are more sensitive for the detection of edema than currently available alternatives (4, 26, 31). In the present study the “blinded” interpretation of the chest films in random order eliminated the possibility of observer bias and strengthens the importance of these findings.

Other evidence for pulmonary edema after exercise. Considerable evidence for and against pulmonary edema formation after exercise has been reported. Anecdotal reports of hemoptysis in a soccer player (33) and pulmonary edema after a marathon (35) indicate that, at least under certain circumstances, edema may occur. Recently, Schaffartzik et al. (30) used a multiple inert gas technique for measuring ventilation-perfusion inequality in subjects during and after hypoxic exercise. They found persistent changes in ventilation-perfusion inequality up to 0.5 h into recovery and interpreted these changes as consistent with pulmonary edema formation. Other investigators, however, reported evidence against pulmonary edema formation after exercise. Studies by Miles et al. (19, 20) suggested that the postexercise decrease in DLCO are appropriate for the changes in cardiac output observed. Likewise, Hanel et al. (10, 11) reported that changes in DLCO after exercise reflect alterations in central blood volume, not pulmonary edema.

Gallagher et al. (7) were unable to document radiographic evidence of pulmonary edema after a short-duration maximal exercise bout (7); however, Caillaud et al. (2) found that athletes completing a triathlon demonstrated increased lung density on computed tomography.

Using bronchoalveolar lavage techniques, Hopkins et al. (12) found that intense exercise altered the blood-gas barrier in the lungs, resulting in higher concentrations of protein and red blood cells in the lavage fluid.

Edema is known to occur in other animals, such as the horse, in which pulmonary hemorrhage after strenuous exertion is common (25). Pulmonary edema has also been described in greyhound dogs (13) and in pigs (29).

Relationship of exercise-induced pulmonary edema to other types of edema. Younes and Bshouty (34) studied the effects of high pulmonary vascular blood flow on lung fluid filtration. At high flow rates, such as might be seen during exercise, lung weight progressively increased, even with a normal left atrial pressure. These results suggest that high cardiac output, when accompanied by hypoxic vasoconstriction as used in their model, results in edema formation.

None of the cyclists we studied manifested the characteristic radiologic findings of HAPE, which usually produces regional nongravitationally distributed edema, often described as patchy radiographic opacifications. HAPE is believed to occur in those parts of the lung that have not been affected by hypoxic vasoconstriction. That is, in HAPE, the edema is seen radiographically to occur where there is very high flow (distributed from the vasoconstricted areas) and appears therefore to have the same mechanism as the high-pressure (“stress failure”) edema described by West et al. (33), the pulmonary hemorrhage common in racehorses (25), greyhounds (13), and pigs (29) after strenuous exercise, and the high-flow states shown by Younes and Bshouty (34). The lung lavage study by Hopkins et al. (12)
suggests a mechanical disruption of the blood-gas barrier in humans after exercise at low altitude as well. The one factor integral to all these findings is very high blood flow through the pulmonary capillary bed. When complete recruitment of this capillary bed is achieved, the pressure in the precapillary vessels must rise, causing the transudation of fluid. It would appear that our radiologic findings of edema represent the effect of very high cardiac output, with increased recruitment of capillaries causing an increased capillary surface area for filtration and, therefore, increase in extravascular lung water, beyond the ability of the pulmonary lymphatics to clear.

Acclimatization to altitude is usually protective against the development of HAPE. In the present study, however, acclimatization did not provide protection from the ensuing exercise-induced edema formation, inasmuch as our cyclists living at moderate altitude were as likely as the others to develop edema.

In conclusion, we observed radiographic evidence of interstitial pulmonary edema after prolonged, high-intensity exercise at moderate altitude. The effect of this edema on exercise performance is unknown, but given the frequency of competitive events at moderate altitude, interstitial pulmonary edema is likely to be common.

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REFERENCES


