Exercise-induced arterial hypoxaemia in healthy young women

Craig A. Harms, Steven R. McClaran, Glenn A. Nickele, David F. Pegelow, William B. Nelson and Jerome A. Dempsey

Department of Preventive Medicine, John Rankin Laboratory of Pulmonary Medicine, University of Wisconsin, Madison, WI 53705, USA

(Received 19 June 1997; accepted after revision 11 November 1997)

1. We questioned whether exercise-induced arterial hypoxaemia (EIAH) occurs in healthy active women, who have smaller lungs, reduced lung diffusion, and lower maximal O_2 consumption rate ($\dot{V}_{O_2,max}$) than age- and height-matched men.

2. Twenty-nine healthy young women with widely varying fitness levels ($\dot{V}_{O_2,max}$, 57 ± 6 ml kg^{-1} min^{-1}; range, 35–70 ml kg^{-1} min^{-1}; or 148 ± 5%; range, 93–188% predicted) and normal resting lung function underwent an incremental treadmill test to $\dot{V}_{O_2,max}$ during the follicular phase of their menstrual cycle. Arterial blood samples were taken at rest and near the end of each workload.

3. Arterial P_{O_2} (P_{a,O_2}) decreased > 10 mmHg below rest in twenty-two of twenty-nine subjects at $\dot{V}_{O_2,max}$ (P_{a,O_2}, $77{\cdot}5 \pm 0{\cdot}9$ mmHg; range, 67–88 mmHg; arterial O_2 saturation (S_{a,O_2}), $92{\cdot}3 \pm 0{\cdot}2$%; range, 87–94%). The remaining seven subjects maintained P_{a,O_2} within 10 mmHg of rest. P_{a,O_2} at $\dot{V}_{O_2,max}$ was inversely related to the alveolar to arterial O_2 difference (A-aDO_2) ($r = -0{\cdot}93$; 35–52 mmHg) and to arterial P_{CO_2} (P_{a,CO_2}) ($r = -0{\cdot}62$; 26–39 mmHg).

4. EIAH was inversely related to $\dot{V}_{O_2,max}$ ($r = -0{\cdot}49$); however, there were many exceptions. Almost half of the women with significant EIAH had $\dot{V}_{O_2,max}$ within 15% of predicted normal values ($\dot{V}_{O_2,max}$, 40–55 ml kg^{-1} min^{-1}); among subjects with very high $\dot{V}_{O_2,max}$ (55–70 ml kg^{-1} min^{-1}), the degree of excessive A-aDO_2 and EIAH varied markedly (e.g. A-aDO_2, 30–50 mmHg; P_{a,O_2}, 68–91 mmHg).

5. In the women with EIAH at $\dot{V}_{O_2,max}$, many began to experience an excessive widening of their A-aDO_2 during moderate intensity exercise, which when combined with a weak ventilatory response, led to a progressive hypoxaemia. Inactive, less fit subjects had no EIAH and narrower A-aDO_2 when compared with active, fitter subjects at the same $\dot{V}_{O_2}$ (40–50 ml kg^{-1} min^{-1}).

6. These data demonstrate that many active healthy young women experience significant EIAH, and at a $\dot{V}_{O_2,max}$ that is substantially less than those in their active male contemporaries. The onset of EIAH during submaximal exercise, and/or its occurrence at a relatively low $\dot{V}_{O_2,max}$, implies that lung structure/function subserving alveolar to arterial O_2 transport is abnormally compromised in many of these habitually active subjects.

The structural capacities of the lung are commonly viewed to be over-built with respect to demand for pulmonary O_2 transport in the healthy untrained human during maximal exercise near sea level. However, it has recently become clear that the capacities of the lung, airways and chest wall do not always exceed the demands imposed by maximal exercise. Most notably, many young adult male athletes with maximal O_2 consumption rate ($\dot{V}_{O_2,max}$) > 150% of normal, show significant exercise-induced arterial hypoxaemia (EIAH) and/or significant air flow limitation during maximal exercise (Rowell, Taylor, Wang & Carlson, 1964; Dempsey, Hanson & Henderson, 1984; Johnson, Saupe & Dempsey, 1992; Powers *et al.* 1992). Furthermore, when the EIAH is prevented by adding small amounts of O_2 to the inspirate, $\dot{V}_{O_2,max}$ increases in proportion to the amount of arterial O_2 desaturation experienced while breathing room air (Powers, Lawler, Dempsey, Dodd & Landry, 1989; Harms, McClaran, Nickele, Pegelow & Dempsey, 1997). Other examples of an under-built lung during exercise include: (1) many healthy elderly fit humans with a normal age-dependent deterioration in lung function who encounter expiratory air flow limitation and EIAH at much lower

$\dot{V}_{O_2,max}$ than in the younger athlete (Johnson & Dempsey, 1991; Prefaut, Anselme, Caillaud & Masse-Biron, 1994), and (2) exercising thoroughbred horses who show extreme hypoxaemia, CO_2 retention, and even pulmonary haemorrhage (Bayly, Hodgson, Schulz, Dempsey & Gollnick, 1989; West *et al.* 1993).

We questioned whether healthy young women might be especially vulnerable to exercise-induced pulmonary limitations, perhaps even at work rates that are substantially less than those required in young men. The basis for this hypothesis is found in the considerable literature which shows that the adult female lung has a smaller vital capacity, reduced airway diameter and a smaller diffusion surface, relative to males, even when gender comparisons are made at comparable stature, sitting height and body mass (Mead, 1980; Thurlbeck, 1982; Schwartz, Katz, Fegley & Tockman, 1988*a*, *b*).

METHODS

Subjects

Twenty-nine young adult women (non-smoking), aged 18–42 years, with resting pulmonary function within normal limits, were recruited to participate in this study. Twenty-four of the subjects were runners (including thirteen former collegiate runners and one former Olympian) and most competed regularly in middle and long distance races. These subjects ran at least three times per week and averaged 32·5 miles per week. Five subjects were sedentary. Informed consent was obtained in writing from each subject and all procedures were approved by the Institutional Review Board of the University of Wisconsin-Madison. Physical characteristics and resting pulmonary function of the subjects are shown in Table 1. All subjects were free of any history or symptoms of cardio-pulmonary disease, including exercise-induced asthma. In additional studies (McClaran, Harms, Pegelow & Dempsey, 1996), all subjects also showed a normal increase in their maximal flow : volume envelope immediately following maximal exercise. All tests were performed during the follicular phase of the menstrual cycle as determined by progesterone levels and self-reported basal temperature recordings over a 30 day period. None of our subjects reported abnormalities with their menstrual cycle in the 6 months prior to testing.

Measurements

During all tests, subjects breathed through a low-resistance (0·9–1·0 $cmH_2O\,l^{-1}\,s^{-1}$ at 5–6 $l\,s^{-1}$ flow rate) two-way valve (Hans Rudolph, Model 2400) with low dead space (< 150 ml), and expired gases were sampled continuously at the mouth via a Perkin-Elmer mass spectrometer (model 1100). Inspiratory and expiratory flow rates were measured separately by pneumotachographs (Johnson *et al.* 1992). All signals were displayed on a chart recorder, sent through an analog-to-digital board, and sampled on a computer at 75 Hz.

Arterial blood was obtained from a 20-gauge indwelling plastic catheter inserted in the brachial or radial artery under local 1% lidocaine anaesthesia. Multiple blood samples of 3–4 ml were drawn anaerobically (on and off the mouthpiece) over 20–30 s during a 15 min rest period in the sitting position and during the final minute at each grade during a progressive treadmill test to $\dot{V}_{O_2,max}$. Measurements of arterial P_{O_2} (P_{a,O_2}), P_{CO_2} (P_{a,CO_2}) and pH were made with a blood gas analyser calibrated with tonometered blood (Radiometer ABL300), and measurements of O_2 saturation (S_{a,O_2}) and haemoglobin were made with a co-oximeter (Radiometer OSM3). Calculated S_{a,O_2} (based on measured P_{a,O_2} and changes in body temperature and pH) were in close agreement with obtained S_{a,O_2} measurements ($r = 0{\cdot}94$; where S_{a,O_2} is expressed as a percentage, calculated $S_{a,O_2} = 1{\cdot}035$(obtained S_{a,O_2}) + 3·15). Blood gases were corrected for *in vivo* temperature changes during exercise as measured from a thermocouple placed intranasally in the lower third of the oesophagus (Mon-a-Therm 6500). Oesophageal temperature increased $1{\cdot}8 \pm 0{\cdot}6$ °C from rest to maximal exercise. The alveolar gas equation was used to calculate ideal alveolar oxygen tension (P_{A,O_2}) and the alveolar-arterial oxygen tension difference (A-aDO_2) (Otis, 1964). P_{A,O_2} was found to be significantly related to and slightly higher than the directly measured end-tidal P_{O_2} ($r = 0{\cdot}84$; $P_{A,O_2} = 0{\cdot}907\,(P_{ET,O_2}) + 11{\cdot}643$). Blood lactate concentration was analysed by means of a YSI Lactate Analyser (model 1500 Sport) and plasma potassium was analysed by ion-specific electrodes (AVL Electrolyte Analyser, series 9100). Progesterone was determined by radioimmunoassay (Endocrine Sciences, Tarzana, CA, USA).

Experimental protocols

Subjects completed two progressive incremental maximal O_2 uptake exercise tests ($\dot{V}_{O_2,max}$) with an identical protocol on a treadmill between 48 h and 1 week of each other. The first exercise test served to familiarize subjects with the protocol. A 5–10 min warm-up period at 4–6 mph with 0% gradient was followed by increasing the speed of the treadmill by 2 mph every 2·5 min until a comfortable speed of 6, 8 or 10 mph was reached. At this stage, the slope of the treadmill was increased 2% every 2·5 min until volitional fatigue. The mean length of time for the test was 12 ± 2 min. Between the final two workloads, the change in V_{O_2} with respect to increasing workload was reduced in slope, so that $\dot{V}_{O_2}$ increased 85 ± 5 $ml\,min^{-1}$ in twenty-four subjects and decreased 38 ± 3 $ml\,min^{-1}$ in five subjects between the final two workloads.

Defining EIAH

In this study, our goal was to determine the adequacy of pulmonary gas exchange during exercise among healthy female subjects. For this purpose, we reasoned that a reduction in P_{a,O_2} of > 10 mmHg below resting values, which occurred during strenuous and/or maximal intensity exercise, represented a clear, measurable inability to maintain P_{a,O_2} in the face of increasing demands for O_2 transport. Whether in a given subject this degree of arterial hypoxaemia also caused a significant measurable limitation to systemic O_2 delivery and to $\dot{V}_{O_2,max}$ requires further experimentation.

Statistical analysis

A split plot analysis of variance (time × group) with Tukey *post hoc* test was used to compare mean values across work rates. Groups were compared with weighted means. Pearson product moment coefficients were used to determine relationships. Significance for all tests was set at $P < 0{\cdot}05$.

RESULTS

Resting lung function

Mean, range and per cent predicted values for womens' and mens' resting lung functions are shown in Table 1. Our subjects' total lung capacity (TLC) and vital capacity (VC) were significantly higher while lung diffusion capacity (DLCO) was lower than predicted. TLC, VC, functional residual capacity (FRC), forced expiratory volume in 1 s

Table 1. Subject characteristics and resting pulmonary function ($n = 29$)

	Mean ± S.D.	Range	Percentage predicted	
			Women †	Men ‡
Age (years)	27 ± 7	18–42	—	—
Height (cm)	166 ± 7	155–179	—	—
Weight (kg)	59 ± 6	45–75	—	—
[Hb] (g dl^{-1})	13·8 ± 0·8	12·8–15·5	—	—
[Progesterone] (ng ml^{-1})§	0·8 ± 0·4	0·2–1·3	—	—
$\dot{V}_{O_2,max}$ (ml kg^{-1} min^{-1})	57 ± 6	35–70	148 ± 5*	133 ± 6*
TLC (l)	5·6 ± 0·7	4·5–7·8	106 ± 3*	94 ± 2*
VC (l)	4·1 ± 0·5	2·8–5·4	106 ± 3*	88 ± 2*
FRC (l)	2·9 ± 0·3	1·8–4·1	102 ± 4	107 ± 4*
$FEV_{1\cdot0}$ (l)	3·4 ± 0·5	2·6–4·7	106 ± 3	87 ± 3*
MEF_{50} (l s^{-1})	4·4 ± 0·5	3·5–5·3	103 ± 3	91 ± 2*
DLCO (ml min^{-1} $mmHg^{-1}$)‖	27·5 ± 4·5	19–39	88 ± 2*	78 ± 3*
DLCO/V_A (ml min^{-1} $mmHg^{-1}$ l^{-1})‖	6·72 ± 0·36	6·01–7·26	90 ± 2*	81 ± 3*

§ Standard progesterone range for follicular phase of menstrual cycle = 0·1–1·4 mg ml^{-1}. * Predicted value significantly different than obtained value, $P < 0·05$ (Student's unpaired t test). ‖ Measurement of DLCO obtained in only 23 of the 29 subjects. † Pulmonary function values in women as a percentage of normal values predicted for women of same age and height. ‡ Pulmonary function in women as a percentage of normal values predicted for men of same age and height. DLCO/V_A, ratio of DLCO to alveolar volume. Prediction equations from Crapo & Morris (1981) and Crapo, Morris & Gardner (1982).

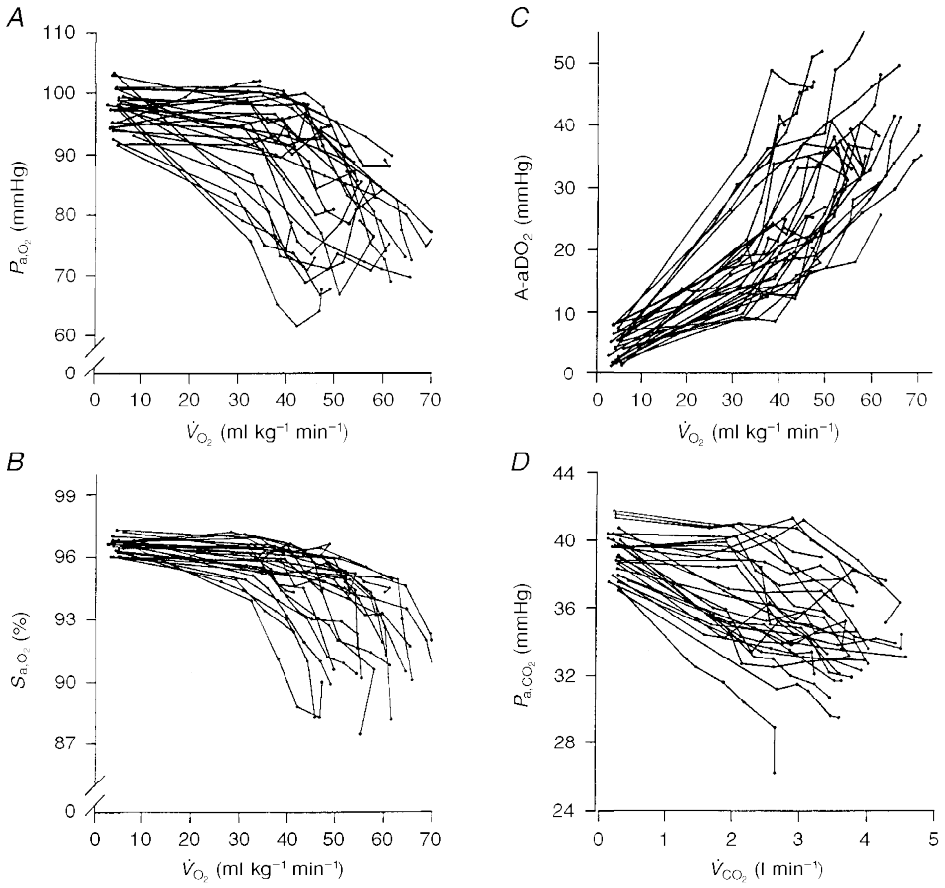

Figure 1. Arterial blood gases during rest and progressive exercise

A, individual arterial oxygen pressure (P_{a,O_2}); *B*, arterial oxygen saturation (S_{a,O_2}); *C*, alveolar to arterial oxygen pressure difference (A-aDO_2); *D*, carbon dioxide pressure (P_{a,CO_2}) during rest and each exercise workload to $\dot{V}_{O_2,max}$; $n = 29$. $\dot{V}_{CO_2}$, CO_2 consumption rate.

Table 2. Mean resting data and data at $\dot{V}_{O_2,max}$ for twenty-nine female subjects divided into three groups based on the fall in P_{a,O_2} at $\dot{V}_{O_2,max}$

Reduction in P_{a,O_2} (rest − $\dot{V}_{O_2,max}$)	Group 1 (no EIAH; $n = 7$) < 10 mmHg	Group 2 (mild EIAH; $n = 7$) 10–20 mmHg	Group 3 (severe EIAH; $n = 15$) > 20 mmHg
Resting data			
Height (cm)	169 ± 3	162 ± 4	165 ± 7
Weight (kg)	65·5 ± 6·1 *	56·3 ± 2·8	56·9 ± 6·4
DLCO (ml min^{-1} mmHg^{-1})	—	25·3 ± 3·3	27·1 ± 5·1
DLCO/V_A (ml min^{-1} mmHg^{-1} l^{-1})	—	6·63 ± 0·47	6·79 ± 0·71
TLC (l)	5·47 ± 0·33	5·26 ± 0·70	5·68 ± 0·08
VC (l)	4·18 ± 0·24	3·91 ± 0·61	4·07 ± 0·58
MEF_{50} (l s^{-1})	4·69 ± 0·20	4·18 ± 0·38	4·26 ± 0·47
[Hb] (g dl^{-1})	13·2 ± 1·4	14·2 ± 0·7	13·6 ± 0·6
Data at $\dot{V}_{O_2,max}$			
$\dot{V}_{O_2}$ (ml kg^{-1} min^{-1})	47·4 ± 3·4 *	57·0 ± 3·1	60·6 ± 2·3
(range)	31–55	50–62	43–70
(l min^{-1})	3·10 ± 0·63	3·21 ± 0·51	3·45 ± 0·23
$\dot{V}_E$ (l min^{-1})	103·9 ± 12· 4	110·7 ± 10·5	107·0 ± 12·8
V_T (l)	2·10 ± 0·29	2·12 ± 0·29	2·04 ± 0·41
Frequency (breaths min^{-1})	50 ± 7	53 ± 8	54 ± 9
$\dot{V}_E/\dot{V}_{CO_2}$	29·8 ± 3·1	29·4 ± 3·5	27·7 ± 2·0
V_D/V_T	0·16 ± 0·03	0·15 ± 0·02	0·15 ± 0·01
P_{A,O_2} (mmHg)	118·0 ± 3·2	119·3 ± 4·6	113·9 ± 2·9 †
P_{a,O_2} (mmHg)	93·3 ± 2·7 *	86·3 ± 0·5	73·2 ± 0·9 †
A-aDO_2 (mmHg)	25·0 ± 2·3 *	33·5 ± 2·1	40·4 ± 2·3 †
S_{a,O_2} (%)	95·3 ± 0·4 *	93·8 ± 0·3	90·4 ± 0·2 †
P_{a,CO_2} (mmHg)	31·7 ± 1·2	32·1 ± 1·1	35·4 ± 0·7 †
pH	7·293 ± 0·047	7·268 ± 0·060	7·290 ± 0·065
[Lactate] (mM)	10·0 ± 1·5	10·5 ± 2·7	10·2 ± 1·7
[K^+] (mM)	6·4 ± 0·3	6·3 ± 0·5	6·4 ± 0·7
Body temperature (°C)	38·3 ± 0·1	38·2 ± 0·1	38·2 ± 0·1

Values are means ± S.D.; * significantly different from groups 2 and 3, $P < 0·05$; † significantly different from groups 1 and 2, $P < 0·05$. $\dot{V}_E$, expiratory ventilation; V_T, tidal volume; V_D, dead space.

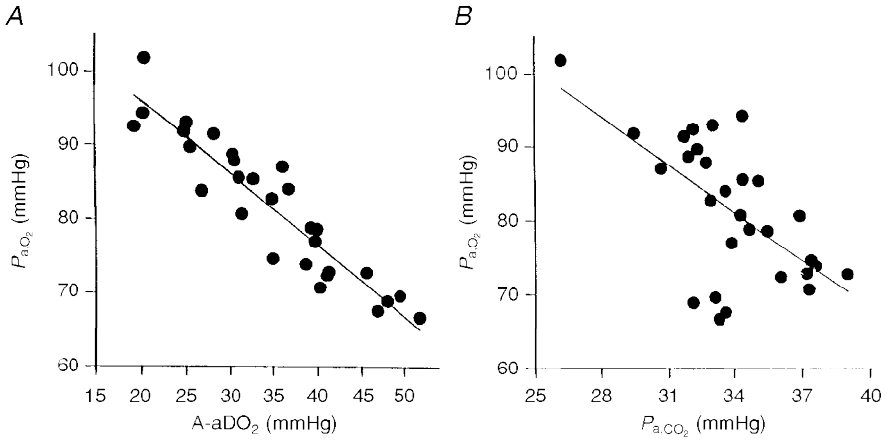

Figure 2. The relationship between P_{a,O_2} and A-aDO_2 and between P_{a,O_2} and P_{a,CO_2} at $\dot{V}_{O_2,max}$

A, P_{a,O_2} *vs.* A-aDO_2; $r = 0·93$ *, $y = -0·971x + 115·4$; *B*, P_{a,O_2} *vs.* P_{a,CO_2}; $r = 0·62$ *, $y = -2·15x + 154·4$; $n = 29$; * $P < 0·05$. A similar relationship ($r = 0·62$) was also observed between $\dot{V}_E/\dot{V}_{CO_2}$ and P_{a,O_2} at $\dot{V}_{O_2,max}$ (not shown).

($FEV_{1\cdot0}$), maximal expiratory flow at 50% of VC (MEF_{50}), and DLCO were all lower for our women subjects when compared with height- and weight-matched men based on prediction equations.

Individual subject responses

Individual data for arterial blood gases at each exercise stage to $\dot{V}_{O_2,max}$ are shown in Fig. 1*A–D*. At rest, blood gases in all subjects were well within the normal range. There was much variability in the responses to exercise. Seven of the twenty-nine subjects maintained P_{a,O_2} within 10 mmHg of resting values at $\dot{V}_{O_2,max}$ (P_{a,O_2}, 89–103 mmHg and S_{a,O_2}, 95–97%). The remaining twenty-two subjects reduced their $P_{a,O_2} > 10$ mmHg below their resting values at $\dot{V}_{O_2,max}$ (P_{a,O_2}, 67–88 mmHg). In these subjects, S_{a,O_2} at $\dot{V}_{O_2,max}$ was 87–94%, resulting from the combination of the reduced P_{a,O_2} along with acid shifts in pH_a (−0·06 to −0·25) and increases in temperature (1·1 to 3·0 °C) (see Table 2). This EIAH occurred at a $\dot{V}_{O_2,max}$ ranging from 43 to 70 ml kg^{-1} min^{-1}.

A-aDO_2 increased from rest for all subjects in a near-linear fashion with increasing $\dot{V}_{O_2}$. At $\dot{V}_{O_2,max}$, these changes ranged from 3–10 times rest or 18–51 mmHg (Fig. 1*C*). During exercise, P_{a,CO_2} decreased from rest with considerable variability between subjects. End exercise P_{a,CO_2} values ranged from 27 to 39 mmHg. Note that seventeen subjects reduced P_{a,CO_2} at the first workload (~40% $\dot{V}_{O_2,max}$) with further reductions occurring throughout submaximal exercise, while twelve subjects maintained P_{a,CO_2} near resting values until the exercise intensity approached $\dot{V}_{O_2,max}$.

Causes of arterial hypoxaemia at $\dot{V}_{O_2,max}$

The relationships between P_{a,O_2} *vs.* A-aDO_2 and P_{a,CO_2} at $\dot{V}_{O_2,max}$ are shown in Fig. 2*A* and *B*, respectively. P_{a,O_2} was inversely related to A-aDO_2 ($r = -0{\cdot}93$; $P < 0{\cdot}001$); i.e. with no exceptions, those subjects who exhibited the greatest widening in A-aDO_2 at $\dot{V}_{O_2,max}$ had the most hypoxaemia. P_{a,O_2} was also inversely related to the magnitude of the hyperventilatory response at $\dot{V}_{O_2,max}$ as depicted by P_{a,CO_2} ($r = -0{\cdot}62$; $P < 0{\cdot}001$). However, there were several exceptions to this relationship. For example, the four subjects with the greatest hypoxaemia (P_{a,O_2}, 65–70 mmHg) showed a substantial hyperventilatory response (P_{a,CO_2}, 31–34 mmHg), and these subjects also had the widest A-aDO_2 (46–52 mmHg).

Resting lung diffusion capacity (DLCO) or per cent predicted DLCO were not significantly related to A-aDO_2 at $\dot{V}_{O_2,max}$ (Fig. 3*A* and *B*). However, eleven of the twenty-three subjects in whom DLCO was measured showed values that were > 20% below predicted, and eight of these eleven subjects widened A-aDO_2 in excess of 35 mmHg at $\dot{V}_{O_2,max}$.

Figure 4*A* and *B* shows that $\dot{V}_{O_2,max}$ was inversely related to P_{a,O_2} ($r = -0{\cdot}49$; $P = 0{\cdot}007$) and directly to A-aDO_2 ($r = 0{\cdot}40$; $P = 0{\cdot}033$). Although these relationships with $\dot{V}_{O_2,max}$ were significant, there were several notable exceptions of arterial hypoxaemia and substantial widening of A-aDO_2 in subjects with $\dot{V}_{O_2,max} < 50$ ml kg^{-1} min^{-1} (see below).

Contrasting subject groups with varying levels of EIAH throughout exercise

We separated the twenty-nine subjects into three groups based on the degree of hypoxaemia at $\dot{V}_{O_2,max}$ and their respective $\dot{V}_{O_2,max}$ (Fig. 5; Table 2). Group 1, with no hypoxaemia, had significantly lower $\dot{V}_{O_2,max}$ than groups 2 (10–20 mmHg reduction in P_{a,O_2}) and 3 (severe EIAH; > 20 mmHg reduction in P_{a,O_2} from rest), whereas groups 2 and 3 had similar $\dot{V}_{O_2,max}$. There were no significant differences among the three groups in age, height, lung volumes, maximal flow rates, DLCO or haemoglobin concentration (Table 2).

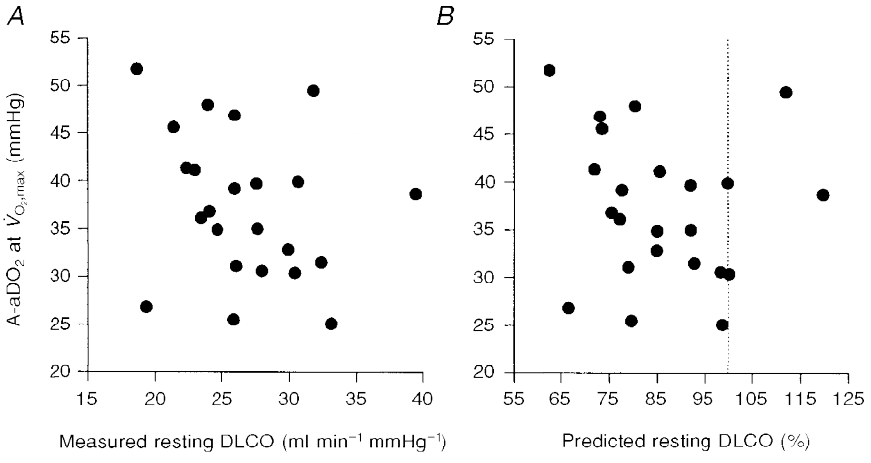

Figure 3. The relationship between A-aDO_2 at $\dot{V}_{O_2,max}$ and measured DLCO at rest, and between A-aDO_2 at $\dot{V}_{O_2,max}$ and per cent predicted DLCO

A, A-aDO_2 at $\dot{V}_{O_2,max}$ *vs.* DLCO at rest; *B*, A-aDO_2 at $\dot{V}_{O_2,max}$ *vs.* per cent predicted DLCO (see Crapo *et al.* 1982). The dotted line is 100% predicted. The relationships in both panels are not significant ($P > 0{\cdot}05$).

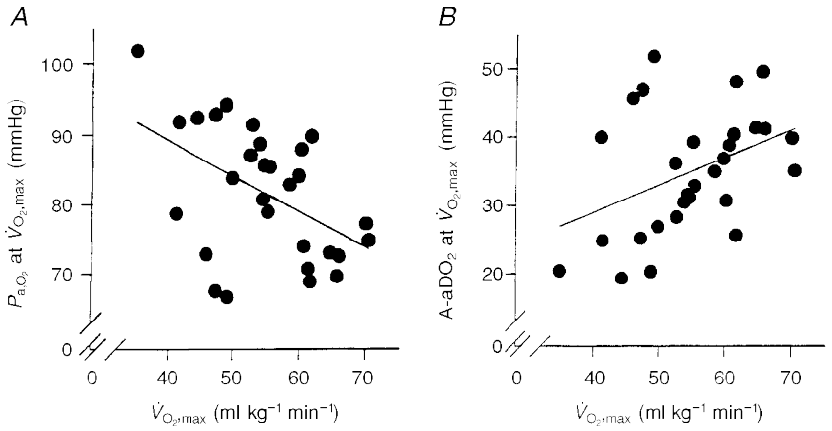

Figure 4. The relationship between $\dot{V}_{O_2,max}$ and P_{a,O_2} at $\dot{V}_{O_2,max}$, and between $\dot{V}_{O_2,max}$ and A-aDO$_2$ at $\dot{V}_{O_2,max}$

A, P_{a,O_2} *vs.* $\dot{V}_{O_2,max}$; $r = 0{\cdot}49$*; $y = -0{\cdot}515x + 109{\cdot}8$; *B*, A-aDO$_2$ *vs.* $\dot{V}_{O_2,max}$; $r = 0{\cdot}40$*; $y = 0{\cdot}400x + 12{\cdot}952$; $n = 29$; * $P < 0{\cdot}05$.

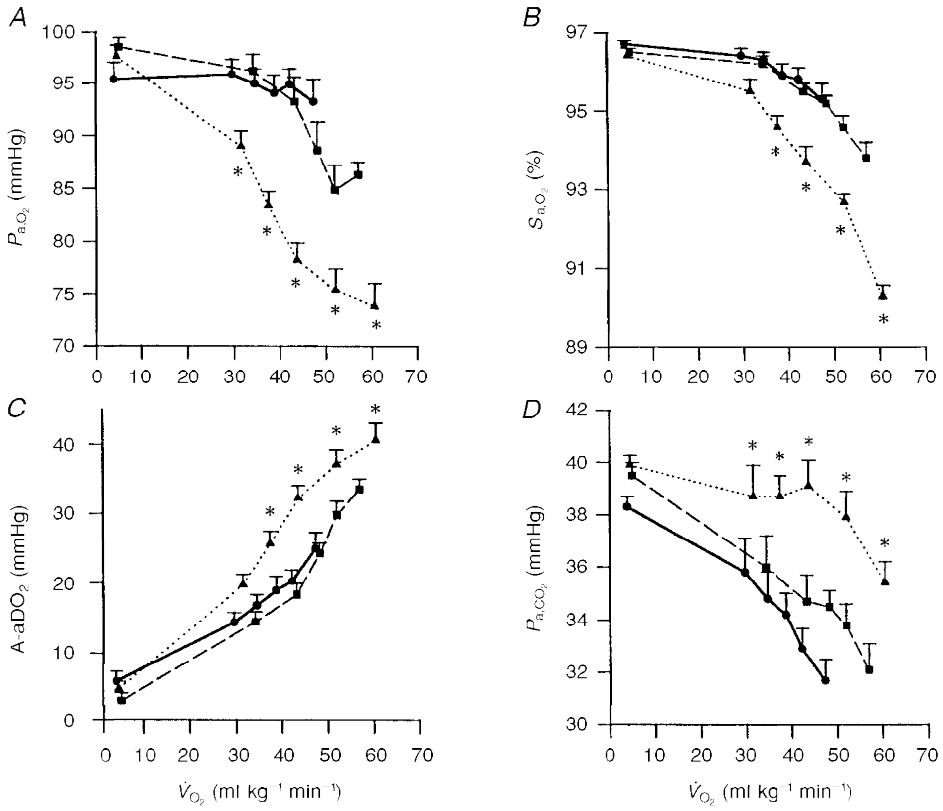

Figure 5. Mean changes in blood gases during progressive exercise to $\dot{V}_{O_2,max}$ in subjects divided into three groups based on the fall in P_{a,O_2} at $\dot{V}_{O_2,max}$ from resting values and their respective $\dot{V}_{O_2,max}$ values

Group 1 ($n = 7$), < 10 mmHg (●, continuous line); group 2 ($n = 7$), 11–20 mmHg (■, dashed line); group 3 ($n = 15$), > 20 mmHg (▲, dotted line). *A*, P_{a,O_2}; note that in the most hypoxaemic group 3, S_{a,O_2} fell from $96{\cdot}7 \pm 0{\cdot}1$ % at rest to $90{\cdot}4 \pm 0{\cdot}2$ % at maximal exercise; 42 % of the fall in S_{a,O_2} was due to the fall in P_{a,O_2} and 58 % of the desaturation was due to rightward shift of the HbO_2 dissociation curve because of increasing acidity and temperature (see Table 2). *B*, S_{a,O_2}. *C*, A-aDO$_2$. *D*, P_{a,CO_2}. Values are means ± S.E.M.; * denotes group 3 mean value significantly different from groups 1 and 2, $P < 0{\cdot}05$.

Groups 1 and 2 showed similar trends in P_{a,O_2}, P_{a,CO_2} and A-aDO_2 throughout submaximal exercise. Differences between these two groups occurred only at the higher workloads achieved by group 2 subjects during which they further widened their A-aDO_2 and decreased P_{a,O_2} to 86·3 ± 0·5 mmHg.

Groups 2 and 3 had similar $\dot{V}_{O_2,max}$ but differed markedly in their respective responses to exercise. In group 3, P_{a,O_2} began to fall significantly (−7 ± 2 mmHg from rest) at even the lightest workload ($\dot{V}_{O_2}$, 25–45 ml kg^{-1} min^{-1}; 44 ± 3% $\dot{V}_{O_2,max}$) as A-aDO_2 widened and no hyperventilation occurred. At moderate intensity exercise ($\dot{V}_{O_2}$, 45–60 ml kg^{-1} min^{-1} or 74 ± 2% $\dot{V}_{O_2,max}$), P_{a,O_2} for group 3 had fallen 20 mmHg below rest as A-aDO_2 continued to widen to 4–5 times resting levels and a significant hyperventilation had not yet occurred. This onset of EIAH at mild to moderate exercise intensities occurred in eleven of the fifteen group 3 subjects; the remaining four subjects did not show significant EIAH until exercise intensity exceeded 80% $\dot{V}_{O_2,max}$. In contrast, group 2 widened their A-aDO_2 substantially less than did group 3 subjects at all workloads and hyperventilated progressively throughout exercise. Accordingly, group 2 avoided significant EIAH until very strenuous exercise, and even then P_{a,O_2} fell < 20 mmHg below resting values. At similar levels of maximal exercise, the P_{a,O_2} in group 3 subjects (mean 73·2 ± 0·9 mmHg) was 13 mmHg lower than in group 2, and this difference was attributable to a 7 mmHg wider A-aDO_2 and a 6 mmHg lower alveolar P_{O_2} in group 3.

Finally, because of the onset of EIAH in group 3 subjects during submaximal exercise, it is of interest to contrast group 1 *vs.* group 3 at similar exercise $\dot{V}_{O_2}$, maximal for group 1 and submaximal for group 3. Note at similar $\dot{V}_{O_2}$ values of 40–50 ml kg^{-1} min^{-1}, the substantially wider A-aDO_2, higher P_{a,CO_2} and therefore substantially lower P_{a,O_2} in group 3 (78·2 ± 2·0 mmHg) *vs.* group 1 subjects (93·3 ± 2·7 mmHg).

Gender effects

Figure 6*A* and *B* shows P_{a,O_2} *vs.* $\dot{V}_{O_2,max}$ and A-aDO_2 *vs.* $\dot{V}_{O_2,max}$, respectively, for the twenty-nine individual female subjects in this study compared with the range of mean values in young adult males from fourteen studies taken from the literature (see Dempsey, Powers & Gledhill, 1990, for summary). Note that for the male subjects, P_{a,O_2} at $\dot{V}_{O_2,max}$ is maintained near resting levels until $\dot{V}_{O_2,max}$ exceeds 60–65 ml kg^{-1} min^{-1}; many, but not all, highly fit male subjects with higher $\dot{V}_{O_2,max}$ experience significant EIAH. Women in the present study demonstrated comparable levels of EIAH and widened A-aDO_2 to similarly aged, highly fit men. Furthermore, as with males, not all highly fit women showed EIAH. However, EIAH (Fig. 6*A*) and excessively widened A-aDO_2 (Fig. 6*B*) occurred in women at a lower $\dot{V}_{O_2,max}$ compared with similarly aged men.

DISCUSSION

We have demonstrated significant arterial hypoxaemia during strenuous exercise in the majority of a sample of twenty-nine healthy young women of widely varying fitness levels. In general, exercise-induced arterial hypoxaemia was most prevalent in women with higher $\dot{V}_{O_2,max}$, although there were several cases of severe hypoxaemia in habitually active women exhibiting near normal levels of $\dot{V}_{O_2,max}$. The exercise-

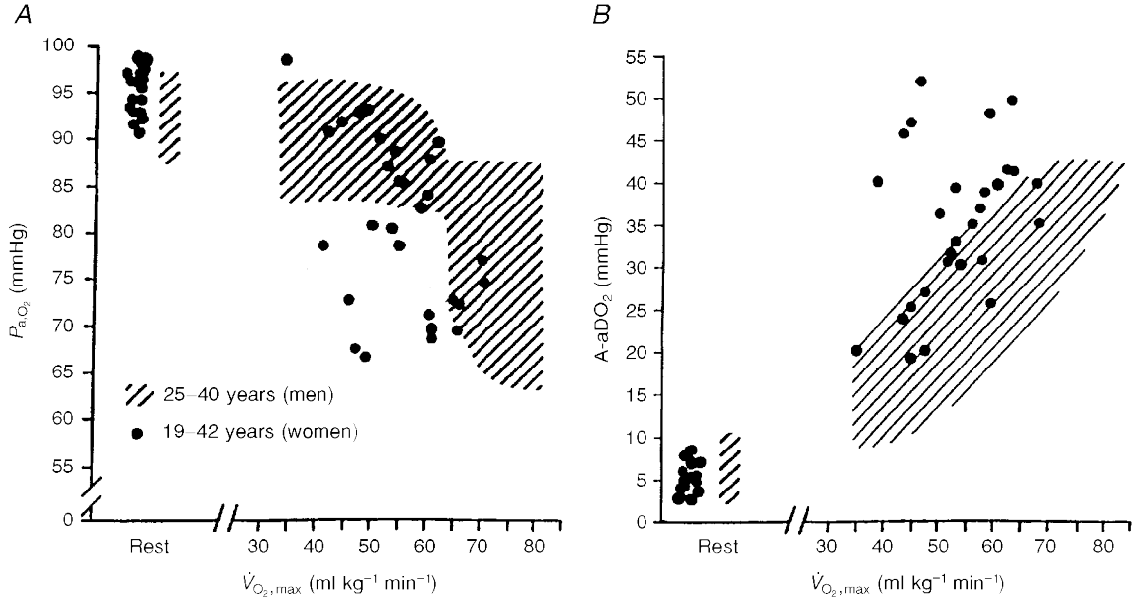

Figure 6. Comparison between young adult females ($n = 29$) and the mean range of values of young adult males in fourteen studies since 1960 which measured arterial blood gases at $\dot{V}_{O_2,max}$

The hatched area represents male data (see summary in Dempsey *et al.* 1990), and filled circles are individual values for female subjects. *A*, P_{a,O_2} *vs.* $\dot{V}_{O_2,max}$; *B*, A-aDO_2 *vs.* $\dot{V}_{O_2,max}$.

induced arterial hypoxaemia (EIAH) was primarily associated with an excessively widened alveolar to arterial P_{O_2} difference, which was not sufficiently compensated by the hyperventilatory response. Among those women who became hypoxaemic at $\dot{V}_{O_2,max}$, one-half began to experience an excessive widening of their A-aDO_2 and EIAH during moderate intensity exercise, and the hypoxaemia became progressively worse with further increases in workload.

Exercise-induced arterial hypoxaemia: gender effects

Both men and women demonstrate significant EIAH, which is most closely associated with an increasing A-aDO_2, but is also related to the absence of sufficient compensatory hyperventilation. The EIAH in women differed from that previously reported among young men in several ways. First, among female subjects, the minimum $\dot{V}_{O_2,max}$ at which EIAH occurred was substantially lower than in men. Furthermore, normally fit male subjects with $\dot{V}_{O_2,max}$ within 15% of predicted normal (i.e. in the 40–50 ml kg^{-1} min^{-1} range) have never been reported to demonstrate EIAH, which contrasts with our current study in which 40% of our female sample with $\dot{V}_{O_2,max}$ within 15% of normal ($\dot{V}_{O_2,max}$, 35–50 ml kg^{-1} min^{-1}) experienced EIAH. Finally, among both male and female subjects who demonstrated significant EIAH at maximal exercise, most subjects showed hypoxaemia beginning to develop during submaximal exercise of moderate intensity. Several highly fit young adult males also showed EIAH onset during submaximal exercise (Dempsey *et al.* 1984). Women appear to be especially prone to the onset of EIAH at submaximal exercise as shown in eleven of the fifteen most severe EIAH subjects (group 3) in the present sample.

We believe these gender comparisons allow us to propose that healthy young women are more susceptible to EIAH than are their male counterparts; however, we must also emphasize the need for more descriptive data in women. For example, sufficient studies in young adult men have been conducted to clearly document that the untrained normally widen their A-aDO_2 2- to 3-fold from rest to maximal exercise, and that they also hyperventilate, which raises alveolar P_{O_2} sufficiently during strenuous exercise to prevent P_{a,O_2} from falling below resting levels. However, we are aware of only one other study that measured arterial blood gases during exercise in women and these data were obtained only at maximal exercise in high $\dot{V}_{O_2,max}$ subjects (Gore *et al.* 1997). In both studies, subject samples are weighted towards the habitually active subject and usually with higher than normal $\dot{V}_{O_2,max}$. Our very surprising finding of significant EIAH in several of the active female subjects with near normal $\dot{V}_{O_2,max}$ clearly needs further testing in order to determine the prevalence of EIAH among the normal population of young women. In other words, we need to establish the 'reference' standard of response for these fundamental indices of lung function during exercise. Finally, we also wish to emphasize that all of our subjects were tested only in the follicular phase of the menstrual cycle in order to avoid any confounding effects of changes in ovarian hormones. Clearly these hormonal changes do affect a variety of ventilatory, cardiovascular, volume regulatory and haemotological functions, which may influence EIAH (Lebrun, 1993). These effects need to be studied.

Our findings also point to a greater susceptibility to EIAH in women in two other physiological circumstances. First, given the deterioration in lung elastic recoil, the increase in airway closing volume, and the reduced diffusion surface area coincident with the normal ageing process, we might also expect even greater gender effects on the prevalence of EIAH in older females across the entire fitness spectrum (Johnson & Dempsey, 1991; Prefaut *et al.* 1994). Secondly, even very modest reductions in inspired P_{O_2} (P_{I,O_2}) as experienced at only moderately high altitudes (P_{I,O_2}, ~125 mmHg; altitude, 1000–1500 m) have been shown to cause or to markedly exacerbate EIAH and to reduce $\dot{V}_{O_2,max}$ in highly fit males (Dempsey *et al.* 1984; Gore *et al.* 1997). Perhaps an even greater susceptibility to environmental hypoxia may be expected in fit females.

Mechanisms of EIAH

Exercise-induced hypoxaemia occurred in most of our subjects during both submaximal and maximal exercise as a result of two deficits; namely, an underlying excessive widening of the alveolar to arterial P_{O_2} difference, combined with a blunted ventilatory response that was insufficient to compensate for the underlying excessive A-aDO_2. Our study does not address the mechanisms causing the widened A-aDO_2. Previous studies in fit male subjects with no or modest EIAH have documented exercise-induced non-uniformity of ventilation to perfusion distribution (V_A/Q); by exclusion, these studies have also estimated a significant contribution to the widening of A-aDO_2 from diffusion disequilibrium (Torre-Bueno, Wagner, Saltzman, Gale & Moon, 1985) and/or from the normal small anatomical shunt (Gledhill, Froese & Dempsey, 1977). The smaller lung volumes and diffusion surface, narrowed airways, and even reduced levels of circulating haemoglobin in healthy women (see Introduction) provide a morphological basis for gender differences in both diffusion capacity and in the uniformity of intra-regional distribution of ventilation. Our female subjects as a group did show a significantly lower than normal DLCO at rest even if corrected for alveolar lung volume, but we were unable to distinguish between those subjects with and those without EIAH based solely on these resting measurements. Measurements of A-aDO_2 determinants are needed during exercise in these types of female subjects with varying degrees of EIAH. Our observations would suggest that the mechanism responsible is already often present during even submaximal exercise, a finding that favours significant contributions from V_A/Q maldistribution (see below).

Why did our most hypoxaemic subjects ventilate less at any given submaximal or maximal work rate? First, we emphasize that the higher P_{a,CO_2} throughout exercise in the

severe EIAH group was associated with an overall $\dot{V}_E$ (and $\dot{V}_E/\dot{V}_{CO_2}$), which were lower than those of group 2. Secondly, differences in the level of known circulating chemical stimuli and in mechanical constraints to ventilation can be ruled out by comparing the responses to exercise among the three groups shown in Fig. 5. Note (Table 2) that the known chemical stimuli in arterial blood were either similar (K^+, lactate, temperature) or even *greater* (i.e. lower P_{a,O_2} and pH_a) at all workloads in the group with the lower ventilatory responses. Significant expiratory flow limitation did occur during heavy and maximal exercise in our female subjects (see below) (McClaran *et al.* 1996). However, during mild and moderate exercise intensities, clear differences in ventilatory response were already present among the three groups, even though flow limitation was not present. Accordingly, by exclusion, we propose that the ventilatory control system in our most hypoxaemic group was less 'responsive' (or sensitive) to a given sensory stimulus throughout all exercise intensities. Whether or not these stimuli are the usual chemoreceptor feedback influences, the locomotor-linked stimuli responsible for 'exercise hyperpnoea', *per se*, or their combination is unknown.

During maximal exercise in our hypoxaemic female subjects (group 3), a clear role for mechanical limitation in preventing adequate compensatory hyperventilation does arise because of their underlying excessive A-aDO_2. For example, given the mean A-aDO_2 of 40 mmHg at maximal exercise, it can be shown (from the alveolar air equation) that these subjects must raise their $\dot{V}_E$ an additional 55 l min^{-1} (about a 50% increase) in order to raise alveolar P_{O_2} sufficiently to prevent significant EIAH (i.e. $P_{a,O_2} > 85$ mmHg). This $\dot{V}_E$ required for compensation of the widened A-aDO_2 is substantially in excess of these subjects' maximum flow : volume envelope (or maximum voluntary ventilation) and therefore not mechanically feasible (McClaran *et al.* 1996).

In summary, the data clearly show that in most subjects with EIAH, the A-aDO_2 is excessively widened and the ventilatory response reduced during both submaximal and maximal exercise. Our original hypothesis for this study focused on the reduced lung volume and diffusion surface in the female (see Introduction). However, it seems reasonable to suggest that these gender-dependent maximal dimensions of the lung and airways would only become critical determinants of pulmonary O_2 and CO_2 exchange at or near *maximal* exercise. The onset of EIAH during *submaximal* exercise in many of the subjects suggests that there may be additional important determinants of EIAH during less strenuous exercise.

Re-examination of the (high) demand *vs.* (normal) capacity concept of EIAH

A striking finding in our study was the onset of excessive A-aDO_2 and arterial hypoxaemia during *submaximal exercise* in many of the subjects who experienced EIAH during maximal exercise (see Fig. 5). The onset of significant hypoxaemia during submaximal exercise and its further progression with more strenuous exercise has only been observed in habitually active subjects, male and female. In our present study, this mainly included females with a high $\dot{V}_{O_2,max}$, but even occurred in *some active subjects with a near normal* $\dot{V}_{O_2,max}$.

These observations challenge the previously held concept that arterial hypoxaemia incurred at maximal exercise in many highly fit subjects represents the imbalance between the *normal capacity* of a healthy lung for diffusion and for V_A/Q distribution uniformity and the *extraordinarily high demands* for O_2 transport by a highly trained O_2 transport system (Dempsey, 1986). This concept was based on observations that the lung's diffusion capacity, lung volumes, and maximal flow : volume envelope usually remain relatively unaltered from normal in the highly fit or as a result of intense physical training, whereas other key determinants of maximal systemic O_2 transport and utilization such as left ventricular function, circulating blood volume, muscle capillary to mitochondrial diffusion capacity and muscle metabolic capacity are all enhanced in the trained state. However, the documentation of excessive A-aDO_2 during exercise at *equivalent* O_2 *uptakes* in many active (*vs.* inactive) subjects (see Fig. 5), implies that lung structure/function subserving alveolar to arterial O_2 transport is actually *abnormally* compromised in many of these active subjects. It remains to be determined if intense habitual physical training has the potential to actually compromise the normal morphology of the lung's alveolar-capillary interface.

Consequences

What are the consequences of EIAH in females? At any given *submaximal work rate*, $\dot{V}_{O_2}$ is not compromised, probably because an increased O_2 extraction by the working muscle is possible and this compensates for any hypoxaemia-induced deficiencies in O_2 transport. In fact, the reduced ventilatory response in those with EIAH is certainly more economical and may be beneficial under these circumstances. However, at maximal exercise, no room remains for compensation and the occurrence of EIAH means that the maximal (available) arterial-mixed venous oxygen difference will be compromised. Accordingly, preventing EIAH ($\leqslant 92\%$ S_{a,O_2}) via a mildly hyperoxic inspirate, which maintained S_{a,O_2} at resting levels, led to significantly higher $\dot{V}_{O_2,max}$ in men (Powers *et al.* 1989). Our preliminary findings also show a significant detrimental effect of EIAH on $\dot{V}_{O_2,max}$ in women (Harms *et al.* 1997).

Bayly, W. M., Hodgson, D. R., Schulz, D. A., Dempsey, J. A. & Gollnick, P. D. (1989). Exercise-induced hypercapnia in the horse. *Journal of Applied Physiology* **67**, 1958–1966.

Crapo, R. O. & Morris, A. H. (1981). Standardized single breath normal values for carbon monoxide diffusing capacity. *American Review of Respiratory Disease* **123**, 185–189.

Crapo, R. O., Morris, A. H. & Gardner, R. M. (1982). Reference values for pulmonary tissue volume, membrane diffusing capacity and pulmonary capillary blood volume. *Bulletin European Physiolpathologic Respiration* **18**, 893–899.

Dempsey, J. A. (1986). Is the lung built for exercise? *Medicine and Science in Sports and Exercise* **18**, 143–155.

Dempsey, J. A., Hanson, P. G. & Henderson, K. S. (1984). Exercise-induced arterial hypoxaemia in healthy human subjects at sea level. *Journal of Physiology* **355**, 161–175.

Dempsey, J. A., Powers, S. & Gledhill, N. (1990). Cardiovascular and pulmonary adaptations to physical activity: Discussion. In *Exercise, Fitness and Health*, ed. Bouchard, C., Shepard, R. J. & Stephens, T., pp. 205–216. Human Kinetics, Champaign, Illinois, USA.

Gledhill, N., Froese, A. B. & Dempsey, J. A. (1977). Ventilation to perfusion distribution during exercise in health. In *Muscular Exercise and the Lung*, ed. Dempsey, J. A. & Reed, C. E., pp. 325–344. University of Wisconsin Press, Madison, WI, USA.

Gore, C. J., Little, S. C., Hahn, A. G., Scroop, G. C., Norton, K. I., Bourdon, P. C., Woolford, S. M., Buckley, J. D., Stanef, T., Campbell, D. P., Watson, D. B. & Emonson, D. L. (1997). Reduced performance of male and female athletes at 580 m altitude. *European Journal of Applied Physiology* **75**, 136–143.

Harms, C. A., McClaran, S. R., Nickele, G., Pegelow, D. & Dempsey, J. A. (1997). High prevalence of exercise-induced arterial hypoxaemia and expiratory flow limitation in healthy young women. *Respiratory and Critical Care Medicine* (abstract) **144**, A910.

Johnson, B. D. & Dempsey, J. A. (1991). Demand *vs.* capacity in the aging pulmonary system. *Exercise and Sport Science Reviews* **19**, 171–210.

Johnson, B. D., Saupe, K. W. & Dempsey, J. A. (1992). Mechanical constraints on exercise hyperpnea in endurance athletes. *Journal of Applied Physiology* **73**, 874–886.

Lebrun, C. M. (1993). Effect of the different phases of the menstrual cycle and oral contraceptives on athletic performance. *Sports Medicine* **16**, 400–430.

McClaran, S. R., Harms, C. A., Pegelow, D. F. & Dempsey, J. A. (1996). Flow limitation affects control of breathing during heavy exercise in highly trained women. *Medicine and Science in Sports and Exercise* (abstract) **28**, S78.

Mead, J. (1980). Dysanapsis in normal lungs assessed by the relationship between maximal flow, static recoil, and vital capacity. *American Review of Respiratory Disease* **121**, 339–342.

Otis, A. B. (1964). The work of breathing. In *Handbook of Physiology*, section 3, *Respiration*, vol. II, chap. 17, ed. Fenn, W. O. & Rahn, H., pp. 463–476. Americal Physiological Society, Washington, DC, USA.

Powers, S. K., Lawler, J., Dempsey, J. A., Dodd, S. & Landry, G. (1989). Effects of incomplete pulmonary gas exchange on $V_{O_2,max}$. *Journal of Applied Physiology* **66**, 2491–2495.

Powers, S. K., Martin, D., Cicale, M., Collop, N., Huang, D., Mengelkoch, D. & Criswell, T. (1992). Exercise induced hypoxemia in athletes: role of inadequate hyperventilation. *European Journal of Applied Physiology* **65**, 37–42.

Prefaut, C. G., Anselme, F., Caillaud, C. & Masse-Biron, J. (1994). Exercise-induced hypoxemia in older athletes. *Journal of Applied Physiology* **76**, 120–126.

Rowell, L. B., Taylor, H. L., Wang, Y. & Carlson, W. S. (1964). Saturation of arterial blood with oxygen during maximal exercise. *Journal of Applied Physiology* **19**, 284–286.

Schwartz, J., Katz, S. A., Fegley, R. W. & Tockman, M. S. (1988*a*). Sex and race differences in the development of lung function. *American Review of Respiratory Disease* **138**, 1415–1421.

Schwartz, J. D., Katz, S. A., Fegley, R. W. & Tockman, M. S. (1988*b*). Analysis of spirometic data from a national sample of healthy 6- to 24-year-olds (NHANES II). *American Review of Respiratory Disease* **138**, 1405–1414.

Thurlbeck, W. M. (1982). Postnatal human lung growth. *Thorax* **37**, 564–571.

Torre-Bueno, J. R., Wagner, P. D., Saltzman, H. A., Gale, G. E. & Moon, R. E. (1985). Diffusion limitation in normal humans during exercise at sea level and simulated altitude. *Journal of Applied Physiology* **58**, 989–995.

West, J. B., Matthieu-Costello, O., Jones, J. H., Birks, E. K., Logeman, R. B., Pascoe, J. R. & Tyler, W. S. (1993). Stress failure of pulmonary capillaries in racehorses with exercise-induced pulmonary hemorrhage. *Journal of Applied Physiology* **75**, 1097–1109.

Acknowledgements

We wish to thank Dr Peter Hanson for technical assistance. Support for this project came from NHLBI (grant RO1 HL-15469). C. A. Harms and S. R. McClaran were supported by an NIH training grant (T32 HL-07654). C. A. Harms is the recipient of a Parker B. Francis Foundation Fellowship.

Corresponding author

C. A. Harms: Department of Kinesiology, 8 Natatorium, Kansas State University, Manhattan, KS 66506, USA.

Email: caharms@ksu.edu