

## Case Report

# Excessive Gas Exchange Impairment During Exercise in a Subject with a History of Bronchopulmonary Dysplasia and High Altitude Pulmonary Edema

ANDREW T. LOVERING,<sup>1</sup> LEE M. ROMER,<sup>1</sup> HANS C. HAVERKAMP,<sup>1</sup>  
JOHN S. HOKANSON,<sup>2</sup> and MARLOWE W. ELDRIDGE<sup>1,3</sup>

### ABSTRACT

Lovering, Andrew T., Lee M. Romer, Hans C. Haverkamp, John S. Hokanson, and Marlowe W. Eldridge. Excessive gas exchange impairment during exercise in a subject with a history of bronchopulmonary dysplasia and high altitude pulmonary edema. *High Alt. Med. Biol.* 8:62–67, 2007.—A 27-year-old male subject ( $\dot{V}O_{2\max}$ , 92% predicted) with a history of bronchopulmonary dysplasia (BPD) and a clinically documented case of high altitude pulmonary edema (HAPE) was examined at rest and during exercise. Pulmonary function testing revealed a normal forced vital capacity (FVC, 98.1% predicted) and diffusion capacity for carbon monoxide ( $D_{LCO}$ , 91.2% predicted), but significant airway obstruction at rest [forced expiratory volume in 1 sec (FEV<sub>1</sub>), 66.5% predicted; forced expiratory flow at 50% of vital capacity (FEF<sub>50</sub>), 34.3% predicted; and FEV<sub>1</sub>/FVC = 56.5%] that was not reversible with an inhaled bronchodilator. Gas exchange worsened from rest to exercise, with the alveolar to arterial P<sub>O<sub>2</sub></sub> difference (AaD<sub>O<sub>2</sub></sub>) increasing from 0 at rest to 41 mmHg at maximal normoxic exercise ( $\dot{V}O_2 = 41.4$  mL/kg/min) and from 11 to 31 mmHg at maximal hypoxic exercise ( $\dot{V}O_2 = 21.9$  mL/kg/min). Arterial P<sub>O<sub>2</sub></sub> decreased to 67.8 and 29.9 mmHg at maximal normoxic and hypoxic exercise, respectively. These data indicate that our subject with a history of BPD is prone to a greater degree of exercise-induced arterial hypoxemia for a given  $\dot{V}O_2$  and F<sub>I<sub>O<sub>2</sub></sub></sub> than healthy age-matched controls, which may increase the subject's susceptibility to high altitude illness.

**Key Words:** alveolar-to-arterial P<sub>O<sub>2</sub></sub> difference; pulmonary function; bronchopulmonary dysplasia; hypoxia; intrapulmonary shunt

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<sup>1</sup>University of Wisconsin School of Medicine and Public Health, Department of Population Health Sciences, John Rankin Laboratory of Pulmonary Medicine, Madison, Wisconsin.

<sup>2</sup>University of Wisconsin School of Medicine and Public Health, Department of Pediatrics, Cardiology, Madison, Wisconsin.

<sup>3</sup>University of Wisconsin School of Medicine and Public Health, Department of Pediatrics, Critical Care Medicine and Biomedical Engineering, Madison, Wisconsin.

## INTRODUCTION

**H**IGH ALTITUDE PULMONARY EDEMA (HAPE) is a noncardiogenic, permeability edema that occurs with rapid ascent to high altitudes (Schoene, 2004; Bartsch et al., 2005). Pulmonary function at sea level in subjects susceptible to HAPE (HAPE-s) is normal (Eldridge et al., 1996), and gas exchange as determined by the alveolar to arterial  $P_{O_2}$  difference ( $AaD_{O_2}$ ) is not different from control subjects at rest or during near maximal exercise (85%  $\dot{V}_{O_{2max}}$ ) in normoxia or hypoxia (Podolsky et al., 1996). Furthermore, HAPE-s subjects may have augmented flow-dependent pulmonary vascular reactivity (Eldridge et al., 1996).

We present data demonstrating excessive gas exchange impairment during normoxic and hypoxic exercise in an otherwise asymptomatic male subject with a history of bronchopulmonary dysplasia (BPD) and a physician-documented incidence of HAPE at a moderate altitude (2927 m). Bronchopulmonary dysplasia is a chronic lung disease that typically develops in preterm infants who require prolonged mechanical ventilation and/or high inspired oxygen concentrations (Bhandari and Bhandari, 2003; Hjalmarson and Sandberg, 2005). Individuals with BPD have poor pulmonary function at term (Hjalmarson and Sandberg, 2005) resulting from abnormal alveolarization (Margraf et al., 1991) and abnormal pulmonary vascularization (Bhatt et al., 2001; Parker and Abman, 2003). Furthermore, many BPD patients have mild pulmonary hypertension and brisk pulmonary vascular reactions to hypoxia (Stenmark and Abman, 2005). These pulmonary characteristics should predispose individuals with BPD to gas exchange abnormalities during hyperdynamic conditions such as exercise and therefore may increase their risk for developing HAPE or other altitude illnesses.

## CASE REPORT

A normally fit (92% predicted  $\dot{V}_{O_{2max}}$ ) 27-year-old male subject, with a clinically documented case of HAPE at 2927 m at age 13 yr, was brought to the laboratory to be evaluated

for exercise-induced intrapulmonary arteriovenous shunting. Based on our previous studies (Eldridge et al., 2004), approximately 90% of subjects tested have intrapulmonary shunting during exercise. We have hypothesized that intrapulmonary arteriovenous shunts may act as pressure relief valves during periods of high pulmonary pressures and blood flows. Because subjects with HAPE have an accentuated pulmonary vascular response to hypoxic exercise (Eldridge et al., 1996), we hypothesized that HAPE-susceptible subjects may in fact not have exercise-inducible intrapulmonary shunts. Subsequently, we found that the subject was born premature at an estimated gestational age of 32 to 33 weeks and a birth weight of 1588 g. He developed respiratory distress at 5 h of age, requiring oxygen therapy (25%–30%  $O_2$ ) for 54 days. He did not receive surfactant and never required intubation or mechanical ventilation. He was discharged home with a diagnosis of BPD.

Anthropometric, pulmonary function and lung diffusion capacity for carbon monoxide ( $D_{LCO}$ ) are shown in Table 1. Pulmonary function was determined according to ATS standards (1995). Forced vital capacity (FVC) and  $D_{LCO}$  were normal. However, the subject showed significant airway obstruction with reductions in (1) forced expiratory volume in 1 sec ( $FEV_1$ ), (2) forced expiratory flow at 50% of vital capacity ( $FEF_{50}$ ), and (3)  $FEV_1/FVC$  (Table 1). On a separate day, pulmonary function was assessed before and after inhalation of a  $\beta$ -agonist (albuterol<sup>®</sup> aerosol, 180  $\mu$ g).  $\beta$ -agonist administration resulted in very minor improvements in pulmonary function (Table 1).

The subject completed two incremental cycle ergometer exercise tests to exhaustion while breathing normoxic ( $F_{I_{O_2}} = 0.209$ ) and hypoxic ( $F_{I_{O_2}} = 0.12$ ) gas, respectively. The order of the tests was randomized, with the subject performing the hypoxic exercise first. The tests were separated by 1 h. The initial work rate was set at 65 W, with the work rate increased by 30 W every 2 min until volitional exhaustion. Apical four-chamber saline contrast echocardiograms with harmonic imaging were performed at rest (Cypress Ultrasound Systems, Acuson/Semins, Mountain View, CA) during the

TABLE 1. ANTHROPOMETRIC METABOLIC RATE, DIFFUSION CAPACITY, AND PULMONARY FUNCTION DATA

Age, yr	27	
Height, cm	187	
Weight, kg	86.5	
$D_{L_{CO}}$ , mL/min/mmHg	36.2 (91.2)	
$\dot{V}_{O_{2max}}$ , mL/kg/min, normoxia	41.4 (92.2)	
$\dot{V}_{O_{2max}}$ , mL/kg/min, hypoxia	21.9	
<i>Pulmonary function</i>	<i>Pre-albuterol</i>	<i>Post-albuterol</i>
FVC, L	6.13 (98.1)	6.47 (103.5)
FEV <sub>1</sub> , L	3.46 (66.5)	3.83 (73.7)
FEV <sub>1</sub> /FVC	0.56 (66.9)	0.59 (70.7)
FEF <sub>50</sub> , L/s	2.16 (34.3)	2.34 (37.2)

Values in parentheses are percent predicted. FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s; FEF<sub>50</sub>, forced expiratory flow at 50% of vital capacity;  $D_{L_{CO}}$ , diffusion capacity for carbon monoxide.

Calculations used for determination of percent predicted values were from Knudson et al. (1983), Knudson et al. (1987), and Bruce et al. (1973).

last minute of each 2-min exercise stage and 3 min after the final exercise load, as described previously (Eldridge et al., 2004). The subject demonstrated intrapulmonary shunting at rest in hypoxia and during submaximal exercise in both normoxia and hypoxia (Fig. 1). Arterial blood samples were drawn anaerobically over 10 to 20 sec during each exercise stage and analyzed for  $P_{O_2}$ ,  $P_{CO_2}$ , and pH with a blood-gas analyzer calibrated with tonometered blood (ABL300, Radiometer). The subject had normal resting gas exchange while breathing normoxic air, as indicated by an alveolar-to-arterial  $P_{O_2}$  difference (AaD<sub>O<sub>2</sub></sub>) of 0 mmHg; while breathing hypoxic gas, it widened to 11 mmHg (Fig.

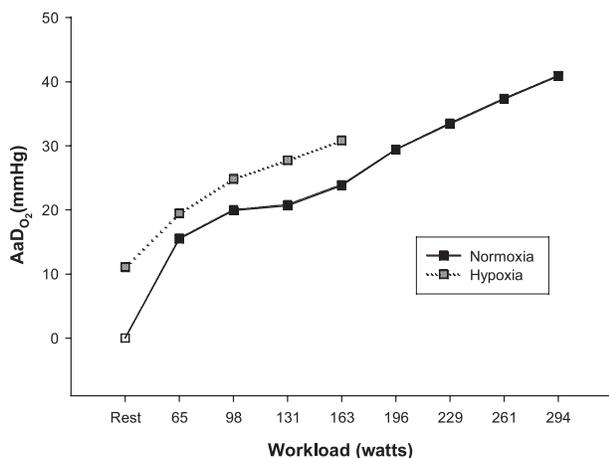


FIG. 1. Gas exchange efficiency at rest and during normoxic and hypoxic exercise. Open symbol indicates no intrapulmonary shunting. Filled symbols indicate intrapulmonary shunting of contrast microbubbles.

1). With both normoxic and hypoxic exercise, the AaD<sub>O<sub>2</sub></sub> widened significantly to 41 and 31 mmHg, respectively, contributing to significant decreases in arterial oxygenation, even during normoxic exercise (Fig. 2). Arterial  $P_{CO_2}$  remained relatively constant throughout normoxic exercise and was 38.7 mmHg at maximal exercise (Fig. 2). We were surprised that the subject did not demonstrate a more marked hyperventilation, particularly since there was a reduction in pH from 7.45 at rest to 7.24 at maximal exercise and an increase in arterial lactate from 0.53 to 9.98 mM (Table 2). The combined effect of hypoxia and exercise elicited a more robust ventilatory response, as indicated by the reduction in  $P_{aCO_2}$  to 30.1 mmHg. However, the maximal workload was also reduced substantially in hypoxia (Fig. 2).

## DISCUSSION

We found that a young subject with a history of BPD and a documented case of HAPE developed an excessively widened AaD<sub>O<sub>2</sub></sub> and arterial hypoxemia at  $\dot{V}_{O_2}$ 's of 41.4 mL/kg/min and 21.9 mL/kg/min during normoxic and hypoxic exercise, respectively. These degrees of EIAH are typically not seen at these metabolic rates (Dempsey and Wagner, 1999). In healthy humans, the AaD<sub>O<sub>2</sub></sub> at rest is typically 5 to 10 mmHg, which increases to 20 to 25 mmHg at maximal exercise (Dempsey and

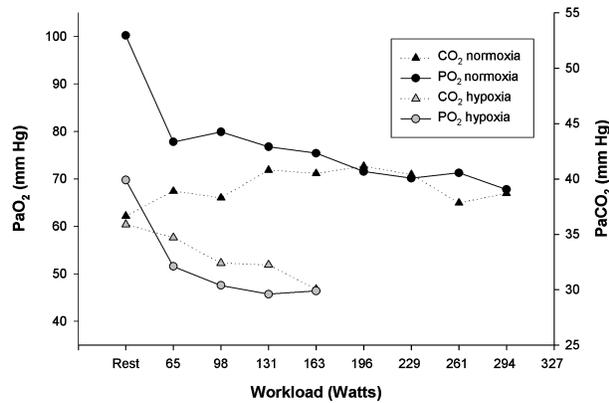


FIG. 2. Arterial blood gases at rest and during normoxic and hypoxic exercise.

Wagner, 1999). The causes for the increased  $AaD_{O_2}$  during exercise include ventilation to perfusion ( $\dot{V}_A/\dot{Q}$ ) heterogeneity, diffusion limitation, extrapulmonary shunt (Dempsey and Wagner, 1999) and, although controversial, intrapulmonary shunt (Eldridge et al., 2004; Stickland et al., 2004). Typically, HAPE-s subjects have neither abnormal resting pulmonary function (Selland et al., 1993; Eldridge et al., 1996) nor gas exchange disturbance at rest in normoxia (Podolsky et al., 1996). Although  $\dot{V}_A/\dot{Q}$  heterogeneity is increased slightly during normoxic and hypoxic exercise (85% of  $\dot{V}_{O_{2max}}$ ) in HAPE-s individuals compared to controls (Podolsky et al., 1996),  $AaD_{O_2}$  at maximal exercise is not significantly different.

Our subject with a history of BPD had abnormal resting pulmonary function and excessive gas exchange impairment during normoxic and hypoxic exercise, which is atypical for HAPE-s subjects. In normoxic exercise, our

subject demonstrated a surprisingly weak hyperventilatory response to exercise ( $Pa_{CO_2}$  of 38.7 mmHg), despite a significant increase in lactate and a significant decrease in pH. We did not measure flow volume loops during exercise, so we do not know if the subject was flow limited during exercise. However, in normoxia the  $V_E/V_{CO_2}$  slope was 24.6 and the value at the lactate threshold was 27.1, suggesting that the hyperventilation was adequate (Wasserman et al., 1999), despite the reduction in  $Pa_{O_2}$ . Furthermore, with hypoxic exercise, the subject clearly demonstrated an increase in ventilation compared to normoxic exercise, as evidenced by a reduction in  $Pa_{CO_2}$  to 30.1 mmHg. The further increase in ventilation with hypoxic exercise was likely caused by the combined hypoxic and exercise stimuli, which would result in greater hyperventilation in hypoxic exercise compared to normoxic exercise (Pugh et al., 1964). These data suggest that our subject may have altered chemoreflexes. Indeed, it is known that patients with BPD have blunted and abnormal chemoreflex responses (Garg et al., 1988; Calder et al., 1994).

Patients who survive BPD have poor resting pulmonary function (Hjalmarson and Sandberg, 2005) and abnormal alveolar and pulmonary vascular development (Stenmark and Abman, 2005). These characteristic features of BPD would likely have an effect on  $\dot{V}_A/\dot{Q}$  matching and equilibration of oxygen between the alveoli and pulmonary capillaries that would impair gas exchange efficiency and exacerbate arterial hypoxemia during hyperdynamic states such as exercise. Indeed, Wagner et al. (1996) demonstrated an increase in  $\dot{V}_A/\dot{Q}$

TABLE 2. METABOLIC RATE DATA AND BLOOD GAS

	<i>Normoxia</i>		<i>Hypoxia</i>	
	<i>Rest</i>	<i>Max</i>	<i>Rest</i>	<i>Max</i>
$V_{O_2}$ (mL/kg/min)	4.8	41.4	6.0	21.9
$Pa_{CO_2}$ (mmHg)	36.7	38.7	35.9	30.1
$Pa_{O_2}$ (mmHg)	100.2	67.8	39.9	29.9
$Sa_{O_2}$ (%)	100	89	81	64
$HCO_3^-$ (mmol/L)	26.25	16.73	26.85	20.25
pH	7.447	7.240	7.464	7.425
Lactate (mmol/L)	0.53	9.98	0.66	5.41
Temperature ( $^{\circ}C$ )	37.3	37.9	36.9	37

heterogeneity at rest in asthmatic subjects with a similar degree of mid-expiratory flow limitation as that in our subject. Furthermore, Mitchell and Teague (1998) reported a reduction in  $D_{LCO}$  during exercise in adolescent children with a history of BPD compared to adolescents with prematurity, but without a history of BPD. In combination, these findings suggest that a history of BPD may predispose individuals to excessive gas exchange inefficiency during exercise.

Contrary to our hypothesis, the subject demonstrated intrapulmonary arteriovenous shunting during normoxic exercise. Interestingly, with hypoxia, intrapulmonary arteriovenous shunting was present at rest and persisted throughout exercise. Previously, we and others have reported that transpulmonary passage of microbubbles does not typically occur at rest in healthy human subjects in normoxia (Eldridge et al., 2004; Stickland et al., 2004). The opening of these intrapulmonary arteriovenous pathways at rest while breathing 12%  $O_2$  suggests that  $O_2$  tension may be important in the regulation of these unique vascular pathways. Intrapulmonary shunting is a likely contributor to the gas exchange inefficiency that occurred in our subject.

We did not assess the pulmonary vascular responses to hypoxia and exercise in our subject. However, patients with BPD are known to have abnormalities of the pulmonary circulation, including elevated pulmonary vascular resistance and abnormal vasoreactivity (Mourani et al., 2004). Furthermore, decreased angiogenesis may limit pulmonary vascular surface area, resulting in further elevations in pulmonary resistance and impaired gas exchange. However, the  $V_E/V_{CO_2}$  slope data obtained in our subject were within the normal range of healthy human subjects, whereas an individual with pulmonary vascular disease would be expected to have a significantly steeper  $V_E/V_{CO_2}$  slope (Wasserman et al., 1999).

We present a subject with a history of BPD who rapidly developed HAPE at a modest altitude. The subject was found to have significant airway obstruction at rest, exercise-induced intrapulmonary shunting, and excessive gas exchange impairment during both normoxic and

hypoxic exercise. Other abnormalities associated with BPD that may increase the risk for significant altitude illness include blunted chemoreflexes, pulmonary hypertension, a brisk hypoxic pulmonary pressor response, and an augmented flow-dependent pulmonary vascular reactivity. In summary, individuals with BPD should be advised accordingly before going to moderate or high altitudes.

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Address reprint requests to:

*Andrew T. Lovering*

*John Rankin Laboratory of Pulmonary Medicine*

*University of Wisconsin Medical School*

*Department of Population Health Sciences*

*Room 4245 MSC, 1300 University*

*Madison, WI 53706-1532*

*E-mail: atlovering@wisc.edu*

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