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Exercise-induced interstitial pulmonary edema at sea-level in young and old healthy humans

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ABSTRACT

We asked whether aged adults are more susceptible to exercise-induced pulmonary edema relative to younger individuals. Lung diffusing capacity for carbon monoxide (DLCO), alveolar–capillary membrane conductance (D_m) and pulmonary–capillary blood volume (V_c) were measured before and after exhaustive discontinuous incremental exercise in 10 young (YNG; 27 ± 3 years) and 10 old (OLD; 69 ± 5 years) males. In YNG subjects, D_m increased (11 ± 7%, $P = 0.031$), V_c decreased (−10 ± 9%, $P = 0.01$) and DLCO was unchanged (30.5 ± 4.1 vs. 29.7 ± 2.9 mL/min/mm Hg, $P = 0.44$) pre- to post-exercise. In OLD subjects, DLCO and D_m increased (11 ± 14%, $P = 0.042$; 16 ± 14%, $P = 0.025$) but V_c was unchanged (58 ± 23 vs. 56 ± 23 mL, $P = 0.570$) pre- to post-exercise. Group-mean D_m/V_c was greater after vs. before exercise in the YNG and OLD subjects. However, D_m/V_c was lower post-exercise in 2 of the 10 YNG (−7 ± 4%) and 2 of the 10 OLD subjects (−10 ± 5%). These data suggest that exercise decreases interstitial lung fluid in most YNG and OLD subjects, with a small number exhibiting evidence for exercise-induced pulmonary edema.

1. Introduction

The volume of extravascular pulmonary fluid is a function of pulmonary capillary fluid extrusion relative to the rate of fluid removal from the pulmonary interstitium (Bates et al., 2011). While fluid flux across the pulmonary vasculature is determined by the balance between the hydrostatic pressure in the pulmonary capillaries and the hydrostatic pressure in the interstitial space as well as the permeability of the pulmonary capillaries to fluid, fluid clearance from the interstitial space is largely dependent on the activity of the pulmonary lymphatics. During heavy exercise, the increase in venous return along with an increase in pulmonary blood flow heterogeneity, which causes regional overperfusion in the pulmonary vasculature, results in a marked increase in pulmonary capillary pressure (Bates et al., 2011; Burnham et al., 2009; Eldridge et al., 2006; Kovacs et al., 2009; Reeves et al., 2005; Younes et al., 1987). Theoretically, such an increase in transcapillary fluid pressure should disturb lung fluid balance by promoting fluid movement from the pulmonary vasculature to the interstitial space via an increase in capillary leakage and, in extreme cases, degradation of the pulmonary microcirculation. However, whether interstitial pulmonary edema develops in response to exercise at sea-level in healthy humans remains controversial with some (Eldridge et al., 2006; McKenzie et al., 2005; Zavorsky et al., 2006; Caillaud et al., 1995) but not all (Brasileiro et al., 1997; Gallagher et al., 1988; Hodges et al., 2007; Manier et al., 1999; Marshall et al., 1971) previous studies reporting an increase in extravascular lung fluid following exercise. While the effects of hypoxia, sex and exercise intensity and duration have been explored, the influence of healthy aging on the incidence exercise-induced pulmonary edema remains unstudied.

Healthy aging is associated with remodeling of the pulmonary vasculature that is characterized by a reduction in capillary density (Butler and Kleinerman, 1970) and distensibility (Reeves et al., 2005), and an increase in pulmonary vascular stiffness and resistance (Ehrsam et al., 1983; Emirgil et al., 1967; Ghali et al., 1992; Gozna et al., 1974; Hosoda et al., 1984). This, along with an increase in the heterogeneity of pulmonary perfusion (Levin et al., 2007) and a reduction in left ventricular compliance (Arbab-Zadeh et al., 2004), serves to markedly increase pulmonary vascular pressures at rest and during exercise of a similar intensity in older relative to younger humans (Ehrsam et al., 1983; Emirgil et al., 1967; Kovacs et al., 2009; Lam et al., 2009; Reeves et al., 2005). In addition, with senescence there is atrophy of lymphatic muscle cells (Gashev and Zawieja, 2010) and a reduction in the phasic contraction amplitude and frequency of thoracic lymphatic ducts, resulting in diminished intrinsic lymphatic pump function and pump flow (Gasheva et al., 2007). In combination, it is possible that the aforementioned age-related changes in the pulmonary system increase fluid flux across the pulmonary vasculature while impairing fluid

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Table 1
Subject characteristics and resting pulmonary function.

	YNG	OLD
Age (years)	27 ± 3	69 ± 5**
Stature (cm)	177 ± 4	176 ± 4
Body mass (kg)	73.9 ± 7.0	75.3 ± 8.1
BMI (kg/m^2)	23.6 ± 2.6	24.3 ± 2.7
V_{O_2peak} (mL/kg/min)	54.3 ± 11.8	34.6 ± 9.0**
V_{O_2peak} (% age predicted)	130 ± 24	133 ± 27
TLC (% predicted)	115 ± 12	113 ± 17
FVC (% predicted)	110 ± 9	111 ± 21
FEV_1 (% predicted)	107 ± 11	114 ± 19
FEV_1/FVC (% predicted)	98 ± 5	103 ± 8
$FEF_{25–75}$ (% predicted)	108 ± 11	112 ± 23

Values are group means ± SD for 10 young (YNG) and 10 old (OLD) subjects. BMI, body mass index; V_{O_2peak}, peak oxygen consumption during maximal incremental exercise; TLC, total lung capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; FEF, forced expiratory flow.
** $P < 0.01$, values significantly different vs. YNG group.

clearance from the interstitial space, making older adults more susceptible to an exercise mediated accumulation of interstitial pulmonary fluid compared to younger individuals. Despite these important considerations, we are unaware of any previous study that has examined the role of healthy aging in the development of exercise-induced pulmonary edema. Accordingly, the aim of the present study was to determine whether non-sedentary healthy older adults are more susceptible to exercise-induced interstitial pulmonary edema relative to their younger counterparts. We hypothesized that exhaustive exercise would increase interstitial lung fluid to a greater extent in older compared to younger subjects, as evidenced by a greater pre- to post-exercise reduction in the alveolar–capillary membrane conductance (D_m) component of lung diffusing capacity (DLCO).

2. Materials and methods

2.1. Subjects

Ten young (YNG; 27 ± 3 years) and 10 old (OLD; 69 ± 5 years) non-smoking male subjects participated in the study (Table 1). All subjects were physically active, were free from cardiovascular and lung disease, and had pulmonary function within normal limits (Table 1). The experimental procedures were approved by the Mayo Clinic Institutional Review Board and each subject provided written informed consent prior to participation.

2.2. Experimental procedures

The experimental procedures were conducted during two laboratory sessions that were separated by at least 48 h but no longer than 2 weeks. The subjects abstained from caffeine for 12 h and exercise for 24 h before each session. During the first session, pulmonary function was assessed via body plethysmography (MedGraphics Elite Series Plethysmograph, Medical Graphics Corporation, St. Paul, MN, USA) according to standard procedures (Miller et al., 2005). Subjects then performed a maximal incremental exercise test (20 W every 2 min starting at either 60 W, 80 W or 100 W) on an electromagnetically braked cycle ergometer (Lode Corvial, Lode B.V. Medical Technology, Groningen, The Netherlands). Peak work rate (W_{peak}) was calculated as the sum of the final completed work rate plus the fraction of the partially completed work rate performed before exhaustion. Peak O_2 uptake (V_{O_2peak}) was the highest mean value recorded over the final 30 s of exercise. At the second session, subjects cycled for 6 min at 25%, 6 min at 50% and 6 min at 75% of W_{peak} before cycling at 90% of W_{peak} to the limit of tolerance (Fig. 1). The subjects rested quietly for 4 min between each exercise bout. Lung diffusing capacity for carbon monoxide (DLCO) and its component parts alveolar–capillary membrane conductance (D_m) and pulmonary capillary blood volume (V_c) were assessed before exercise, during the final minute of each exercise bout, and 15 min after exercise by measuring the disappearance of small amounts of carbon monoxide (CO) and nitric oxide (NO) during a rebreathe technique (Fig. 1).

2.3. Lung diffusing capacity and alveolar–capillary membrane conductance

DLCO, D_m and V_c were assessed by simultaneously measuring the disappearance of CO and NO using a rebreathe technique, as we have described previously (Ceridon et al., 2010; Snyder et al., 2006a; Taylor et al., 2011). Subjects sat upright on the cycle ergometer and breathed through a two-way switching valve (Hans Rudolph 4285 series, Hans Rudolph, Kansas City, MO, USA) that was connected to a pneumotachometer (MedGraphics prevent Pneumotach, Medical Graphics Corporation, St. Paul, MN, USA), a mass spectrometer (Marquette 1100 Medical Gas Analyser, Perkin-Elmer, St. Louis, MO, USA) and a NO analyser (Sievers 280i NOA, Sievers, Boulder, CO, USA). The inspiratory port of the switching valve was set to either room air or a 5 L anesthesia bag that was filled with 0.3% CO ($C^{18}O$), 40 parts per million (ppm) NO (diluted in the bag immediately before the rebreathe maneuver from an 800 ppm gas mixture), 35% O_2 and N_2 balance. The total volume of gas in the anesthesia bag was determined by the resting tidal volume (V_T) of each subject. This was not different before vs. 15 min after exercise for either the YNG (group mean $V_T = 1.16 \pm 0.30$ vs. 1.19 ± 0.45 L) or the OLD subjects (group mean $V_T = 0.93 \pm 0.29$ vs. 0.95 ± 0.33 L). To ensure the volume of the test gas was consistent across multiple rebreathe maneuvers the bag was filled using a timed switching circuit that, given a constant flow rate from the tank, resulted in the desired volume. The test gas volume given by the switching circuit was verified before and after exercise using a 3 L syringe. Before each rebreathe maneuver, the subjects were instructed to breathe normally on room air for 4–5 breaths. At the end of a normal expiration, the subjects were switched to the rebreathe bag and told to "nearly to empty the bag" with each breath for 10–12 consecutive breaths. To ensure that data could be collected over 8–10 breaths before the NO in the test gas decayed completely, the subjects maintained respiratory frequency at 32 breaths/min during each maneuver by following a metronome with distinct inspiratory and expiratory tones. Following each maneuver, the rebreathe bag was emptied with a vacuum pump before being refilled for the next maneuver. Each subject performed the rebreathe in triplicate before and 15 min after exercise. The post-exercise rebreathe measures were initiated 15 min after exercise and took ~6 min to complete. The rebreathe maneuver was also performed in duplicate during the final minute of each exercise bout. DLCO, D_m and V_c were computed using custom analysis software.

2.4. Exercise responses

Following the pre-exercise rebreathe maneuvers, subjects cycled at 25%, 50% and 75% of W_{peak} (each for 6 min) before they cycled at 90% of W_{peak} to the limit of tolerance (i.e. until they were unable to maintain pedal cadence above 60 rpm). A 1 min "warm-up" at 40% of the workload about to be completed was allowed before each exercise bout and four min of recovery was given between each exercise stage (Fig. 1). Ventilatory and pulmonary gas exchange indices were measured throughout exercise using the mass spectrometer and pneumotachometer. Heart rate (HR) and arterial oxygen saturation (SaO_2) were measured beat-by-beat using a pulse oximeter (Nellcor N-595, Tyco Healthcare Group,