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Short-term modulation of the exercise ventilatory response in older men

Helen E. Wood[a,1], Gordon S. Mitchell[b], Tony G. Babb[a,*]

[a] Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas, and University of Texas Southwestern Medical Center-Dallas, 7232 Greenville Ave., Dallas, TX 75231, United States
[b] Department of Comparative Bioscience, University of Wisconsin-Madison, Madison, WI, United States

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ABSTRACT

During exercise with added dead space (DS), the exercise ventilatory response ($\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$) is augmented in younger men, via short-term modulation (STM) of the exercise ventilatory response. We hypothesized that STM would be diminished or absent in older men due to age-related changes in respiratory function and ventilatory control. Men were studied at rest and during cycle exercise with and without added DS. $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$ increased progressively with increasing DS volume ($p < 0.01$), such that CO_2 was not retained with added DS versus without. Hence, the increase in $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$ was not due to increased chemoreceptor feedback from rest to exercise. Increasing exercise intensity diminished the $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$ ($p < 0.01$), and the size of this effect varied by DS volume ($p < 0.05$). We conclude that STM of the exercise ventilatory response is robust in older men; hence, despite age-related changes in lung function and ventilatory control, the exercise ventilatory response can still adapt to increased DS, in order to maintain isocapnia during exercise relative to rest.

1. Introduction

In healthy young men, the exercise ventilatory response is augmented experimentally during exercise with added external dead space via a mechanism termed short-term modulation (STM) of the exercise ventilatory response (Wood et al., 2008a; Poon, 1992; Mitchell and Babb, 2006). STM is an example of modulation within the central respiratory control system and has been proposed to be a general, serotonin-dependent mechanism linking the exercise ventilatory response with resting ventilatory drive (Bach et al., 1993). This mechanism preserves isocapnia during exercise with respect to its new resting level despite altered requirements for ventilation and gas exchange (Mitchell, 1990).

The process of normal aging changes lung function and ventilatory control. For example, aging is associated with a progressive decline in lung function due to a loss of static elastic recoil of the lung, causing reduced maximum expiratory flow rates and increased functional residual capacity (FRC) at rest. Aging is also associated with decreased chest wall compliance, decreased respiratory muscle strength, and increased ventilation–perfusion mismatch (due to increased shunt and physiological dead space), resulting in a lower arterial P_{O_2} (Janssens et al., 1999). Age-related changes in respiratory mechanics decrease ventilatory capacity and increase the effective impedance to ventilatory output. Thus, ventilation does not need to be mechanically limited before the ventilatory response to a respiratory challenge can be altered (i.e. ventilatory output is a balance among ventilatory capacity, respiratory impedance, and ventilatory drive). Age-related changes in gas exchange require greater ventilatory output for a given work rate despite these changes in respiratory mechanics.

A number of studies suggest that the ventilatory response to hypercapnia (HCVR) is reduced in older as compared with younger people (Brischetto et al., 1984; Browne et al., 2003; Kronenberg and Drage, 1973; Naifeh et al., 1989; Peterson et al., 1981). Other groups, however, have reported that the HCVR (Chapman and Cherniack, 1987) is normal in older people. The differing results of these studies may be related to differences in study populations and methods of determining HCVR; overall they suggest the possibility of changes in ventilatory control associated with aging. Such changes would be relevant to the expression of STM since chemoreceptors are involved in the proposed mechanism. It has been proposed that the hypercapnia, resulting from the addition of dead space at rest, stimulates chemoreceptors to increase the resting ventilatory drive. It has been proposed that subsequent increases in brainstem respiratory neuron activity (indirectly) or hypercapnia (directly) augment the serotonergic raphe neuron activity and increase motor neuron excitability. The net result is an augmented exercise ventilatory response with added dead space (i.e. STM) (Mitchell et al., 2008; Mitchell and Babb, 2006).

* Corresponding author. Tel.: +1 214 345 4622; fax: +1 214 345 4618.
E-mail addresses: helen.wood@kcl.ac.uk (H.E. Wood), mitchell@svm.vetmed.wisc.edu (G.S. Mitchell), TonyBabb@TexasHealth.org (T.G. Babb).
[1] Current address: Division of Pharmaceutical Science, King's College London, London, United Kingdom.

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The exercise ventilatory response increases with age (Poulin et al., 1994) due to increased dead space ventilation in older people versus young adults (Johnson et al., 1994). Johnson et al. (1991) directly measured arterial P_{CO_2} (Pa_{CO_2}) during exercise in fit elderly men, and demonstrated that they maintained isocapnia relative to resting values. In older adults, the relationship between expired ventilation ($\dot{V}_E$) and metabolic CO_2 production ($\dot{V}_{CO_2}$) is increased in order to maintain appropriate alveolar ventilation ($\dot{V}_A$). It is not clear how the respiratory controller 'knows' to increase the exercise ventilatory response in order to maintain isocapnia in the elderly.

Little is known concerning the effect of aging on STM expression in humans or animal models. Age-related changes in lung function and ventilatory control could limit the capacity for STM in older adults. For example, since the exercise ventilatory response is already elevated compared with younger people, there may be limited capacity for further increases in response to added dead space (Wood et al., 2009). Further, if the HCVR is reduced in older people, increasing external dead space may have smaller effects on raphe neuron activity, indirectly reducing the magnitude of STM.

In the present study, we tested the hypothesis that STM of the exercise ventilatory response with added external dead space is diminished or absent in healthy older men. Given that breathing pattern is different in older people, with a shallower tidal volume and higher breathing frequency versus younger adults (Janssens et al., 1999), we also hypothesized that breathing mechanics during exercise, added dead space and STM (i.e. combined exercise and dead space) would differ in older men. Contrary to our original hypotheses, STM with added dead space is similar between young and elderly men. Some results of this study have been presented in preliminary form (Wood et al., 2008b).

2. Methods

2.1. Subjects

Men aged 65–75 years were recruited from local advertisements. Subjects were excluded if they had a history of cardiovascular disease, diabetes or asthma, had any musculoskeletal problems that would preclude cycle exercise, or were currently in training for a specific event. None of the subjects smoked currently, although 4 had a history of smoking (3 smoked cigarettes, <1–20 pack-years; 1 smoked a pipe/cigars) but had quit more than 30 years prior to the study. Subjects gave their written informed consent to participate. The study conformed to the standards set by the Declaration of Helsinki and was approved by the Institutional Review Boards of Texas Health Presbyterian Hospital Dallas and the University of Texas Southwestern Medical Center-Dallas. Subjects attended the laboratory on three separate occasions, usually a week apart, and were asked not to eat or consume caffeine for at least 2 h beforehand. They undertook the following tests: visit 1—pulmonary function tests and familiarization with exercise on the cycle ergometer; visit 2—incremental cycle exercise test to exhaustion; and visit 3—constant load submaximal cycle exercise, with and without added external dead space (STM protocol).

2.2. Protocols

The protocols used in the current study were the same as those used in our previous study in younger men (Wood et al., 2008a). Briefly, each subject performed standard measurements of spirometry, lung volumes and diffusing capacity in a body plethysmograph according to American Thoracic Society guidelines (ATS, 1987).

All exercise testing was performed on an electromagnetically braked cycle ergometer. For the incremental exercise test, after a 3-min 'warm-up' at 20 W, the work rate was increased by 20 W every 60 s until the subject could no longer maintain a pedal rate of 50 rpm. Subjects were verbally encouraged to continue to exhaustion. Subjects were monitored throughout with 12-lead ECG, automated blood pressure measurement, and forehead pulse oximetry.

For the submaximal exercise tests (STM protocol) subjects performed five exercise trials, consisting of a 6-min rest period followed by 6 min at each of three constant work rates (10, 30 and 50 W; order not randomized). The first and last trials were controls with no added dead space; for the middle three trials, an external dead space with a volume of 200, 400 or 600 ml (order randomized) was added to the breathing circuit. The dead space tubing was not hidden from the subject's view, but they were not told which dead space volume was used in each trial. Subjects rested off the cycle for 20 min between trials.

2.3. Measurements

2.3.1. Ventilation and gas exchange

The same equipment was used and variables measured as in our previous study in younger men (Wood et al., 2008a). Briefly, expired gas was collected in 200 l Douglas bags at rest and during each level of exercise for determination of O_2 uptake ($\dot{V}_{O_2}$), CO_2 production ($\dot{V}_{CO_2}$) and expired minute ventilation ($\dot{V}_E$, BTPS). End-tidal P_{CO_2} ($P_{ET_{CO_2}}$) was manually recorded from a capnograph, respiratory frequency (f_R) was recorded on a custom-built computerized breath-by-breath system, and tidal volume (V_T) was calculated as $\dot{V}_E/f_R$. Values for $P_{ET_{CO_2}}$, f_R and V_T were averaged over the same periods as the expired gas collections.

2.3.2. Breathing mechanics

Breathing mechanics were measured using a separate data collection system, as described previously (Wood et al., 2009). Briefly, the mouthpiece was attached to a two-way valve connected to separate inspiratory and expiratory pneumotachographs via wide-bore tubing. The flow signals from the separate expiratory and inspiratory pneumotachographs were joined to give a single bi-directional flow signal, which was digitally integrated to give volume. At regular intervals, subjects performed an inspiratory capacity (IC) maneuver, by inhaling maximally to total lung capacity (TLC). End-expiratory lung volume (EELV) was estimated from IC measurement (EELV = TLC − IC) and expressed as a percentage of TLC ([EELV/TLC] × 100). End-inspiratory lung volume (EILV) was calculated (EILV = EELV + V_T) and also expressed as a percentage of TLC ([EILV/TLC] × 100). Ventilation, breath timing (inspired time, T_I, and expired time, T_E), and air flow (mean inspiratory flow, V_T/T_I, and mean expiratory flow, V_T/T_E) were calculated from the dual pneumotachograph volume signal by an interactive computer program developed in this laboratory. Tidal flow-volume loops at rest and during each stage of exercise were generated using this program, and placed within the maximal flow-volume loop (measured in a body plethysmograph on a separate occasion), according to the IC.

2.4. Data analysis

2.4.1. Ventilatory and gas exchange variables

For the incremental exercise test, $\dot{V}_{O_2}$, determined from the expired gas collection at the final work rate was taken as $\dot{V}_{O_2\,peak}$. For the STM protocol, variables were expressed both as absolute values at rest and each work rate and as the change from rest to each work rate, i.e. relative to rest (denoted by Δ). The exercise ventilatory response was defined as the slope of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship ($\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$). This calculation has previously been described in more detail (Wood et al., 2008a). $\dot{V}_E$ and $\dot{V}_{CO_2}$ were