

# RESPONSES TO ISOCAPNIC HYPOXIA IN A HOT WORK ENVIRONMENT DIFFER IN YOUNGER AND OLDER MALES

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## INTRODUCTION

Climate change is impacting the health of the population, especially the elderly population. Michelozzi *et al.* (2009) emphasize that high temperatures increase respiratory-related hospital admissions, particularly in the elderly population, but the underlying mechanisms are poorly understood. The impact of extreme heat events on hospital admissions is expected to increase in European cities as a result of global warming and a progressively aging population [1]. In Denver, Colorado, higher temperatures were found to be an important factor in increasing the frequency of hospitalization for acute myocardial infarction and congestive heart failure in men and women over 65 years of age, reinforcing that this is a global issue [2].

Older individuals have reduced thermoregulatory responses relative to those of younger individuals [3]. Some of these changes include reduced sweat rate [4] and attenuated cutaneous blood flow [5]. Respiratory evaporative heat loss is one of the body's principal cranial heat loss mechanisms [6]. Respiratory responses to heat in the older population have not been analysed in detail and resolving the nature of these ventilatory responses in such conditions promises to the further understanding this groups ability to thermoregulate. This has special relevance given the increased breathing-related illness in older populations during heat waves.

In temperate conditions, hypoxic ventilatory responses may or may not be reduced in the elderly. Peterson *et al.* (1981) found ventilatory responses to hypoxia were reduced by approximately 50% in 65-79 year old males [7]. Kronenberg and Drage (1973) found similarly a  $P_{A}O_2$  of 40 mmHg in young healthy males resulted a pulmonary ventilation of  $40.1 \pm 4.7$  L/min (mean  $\pm$  SEM) whereas this increment was a significantly smaller  $10.2 \pm 1.2$  L/min in older healthy males [8]. In contrast to these results, septuagenarians were shown to have similar ventilatory responses to acute hypoxia as younger controls [9]. The ventilatory response to hypoxia consists of 2 phases [10]. The peripheral chemoreflex sensitivity to a diminished partial pressure of oxygen in the arterial blood ( $P_aO_2$ ) drives a preliminary acute increase in pulmonary ventilation [11]. With sustained hypoxia, the initial increase in pulmonary ventilation is followed by a subsequent decline, reaching a new steady state by approximately 20 min; this is known as the Hypoxic Ventilatory Decline (HVD). The HVD is thought to represent peripheral chemoreceptor desensitization and other centrally mediated mechanisms [12].

In order to assess the effect of heat on the thermoregulatory and ventilatory responses of older individuals, the effect of an isocapnic hypoxic ventilatory challenge was assessed both under

normothermic (NT) core temperatures and hyperthermic (HT) core temperatures in older and younger volunteers. It was hypothesized that: 1) older individuals will have an impaired ventilatory response to hypoxia and 2) this ventilatory response will be less augmented under HT conditions than for younger individuals.

## METHODS

*Volunteers:* A sample size of 4 volunteers with a mean difference in peak HVR  $1.20 \pm 0.49 \text{ L} \cdot \text{min}^{-1} \cdot \%^{-1}$  [10] with an  $\alpha=0.05$  gave a power of 0.9. Volunteers included 5 older males (mean  $\pm$  SD): age  $57.4 \pm 5.4$  years, weight  $88.9 \pm 12.0$  kg, height  $1.84 \pm 0.16$  m) and 5 younger controls (4 male 1 female; age  $30.0 \pm 9.2$  years, weight  $71.3 \pm 10.9$  kg, height  $1.75 \pm 0.07$  m). All were non-smokers, non-asthmatics and refrained from caffeine, alcohol, and heavy exercise for 24 h prior to testing. The office of research ethics at SFU granted approval for the study in accordance with the Helsinki Declaration. Each volunteer gave a written, informed consent after being thoroughly familiarized with the experimental protocol, instrumentation, and risks of participation.

*Instrumentation:* Each participant wore a nose clip and was fitted with a mouthpiece mounted on a 2-way flow sensor housing. Inspired gases were delivered to the flow sensor housing using a 2-way non-rebreathing valve (NRB 2700, Hans Rudolph Inc, Kansas City, Mo.). Breath-by-breath gas samples, for measurement of pulmonary ventilation ( $V_E$ ) and its components, were drawn from the inspired and expired air to a metabolic cart (Model: Vmax 229, SensorMedics, Yorba Linda, Calif.) at a rate of  $\sim 600 \text{ mL} \cdot \text{min}^{-1}$ . The details of the calibration of the metabolic cart have already been reported (Chu et al 2007).

Arterial hemoglobin oxygen saturation ( $\text{SaO}_2$ ) was measured using a pulse oximeter (Masimo Radical, Irvine, Calif.) attached to the participant's left ear lobe. In each volunteer a calibrated nasopharyngeal esophageal temperature ( $T_{ES}$ ) thermistor probe (Mon-a-therm, Mallinckrodt Med. Inc., St Louis, Mo.) was positioned at the T8/T9 level [13].

The data acquisition system (Nat. Instr., Austin TX, USA) included a program written in LabVIEW (v. 7.0, Nat. Instr., Austin) operating on a Windows<sup>TM</sup>-based personal computer. This system controlled an End Tidal Forcing (ETF) system so as to control end-tidal gases at the appropriate levels, presented in Koehle *et al.* (2009) [14]. An analog signal from the flow sensor for each breath from the metabolic cart was also used to trigger breath-by-breath collection of pulmonary ventilation, HR,  $\text{SaO}_2$ , and  $T_{ES}$  by the data acquisition system. A walk-in climatic chamber (L - 5.08 m, W - 3.75 m and H - 2.49 m; Tenney Engineering Inc., Union, NJ, USA) was employed for the passive heating portion of the study.

*Protocol:* In a NT environment resting data were collected from each volunteer for a 30-min period before an isocapnic Hypoxic Ventilatory Response (iHVR) test was conducted in method similar to that of Steinback and Poulin [10]. This test consisted of a 5-min rest period, followed by 20-min isocapnic exposure to a  $P_{ET}\text{O}_2$  of 50 mmHg. End-tidal  $\text{CO}_2$  was maintained at each participant's resting level over the 20-min HVR test that was followed by a 5-min rest period. Approximately 1 h rest was given and a second iHVR was conducted. Prior to the second test the volunteer was passively heated in a climatic chamber at  $50^\circ\text{C}$ ,  $\sim 20\%$  RH until their  $T_{ES}$  had risen by  $\sim 1.5^\circ\text{C}$ . Each volunteer wore shorts, T-shirt and running shoes and a tightly sealed vapour impermeable rain suit. When the  $T_{ES}$  was increased to the target level seals on the rain suit were

opened and  $T_{ES}$  was maintained at that level. The both iHVR tests were performed on the same day to remove day-to-day variations in the iHVR [15].

The iHVR and HVD responses were determined as presented in Steinbeck and Poulin [10]. To express iHVR as a linear function of the hypoxic stimulus,  $P_{ET}O_2$  was converted to a calculation of  $O_2$  saturation ( $ScO_2$ ) using the transform described by Severinghaus (1979) [16]:

$$ScO_2 = (((P_{ET}O_2^3 + 150 P_{ET}O_2)^{-1} \times 23400) + 1)^{-1} \times 100$$

The iHVR was calculated as peak HVR (peakHVR) and every 5-min through the duration of the 20-min hypoxic test. iHVR was calculated as the change in  $V_E$  divided by the change in  $ScO_2$ .

$$iHVR (L \min^{-1} \%^{-1}) = \frac{\Delta V_E}{\Delta ScO_2}$$

The HVD was calculated as the % decrease of  $V_E$  from peakHVR as the % return to control  $P_{ET}CO_2$  following 20-min of hypoxia.

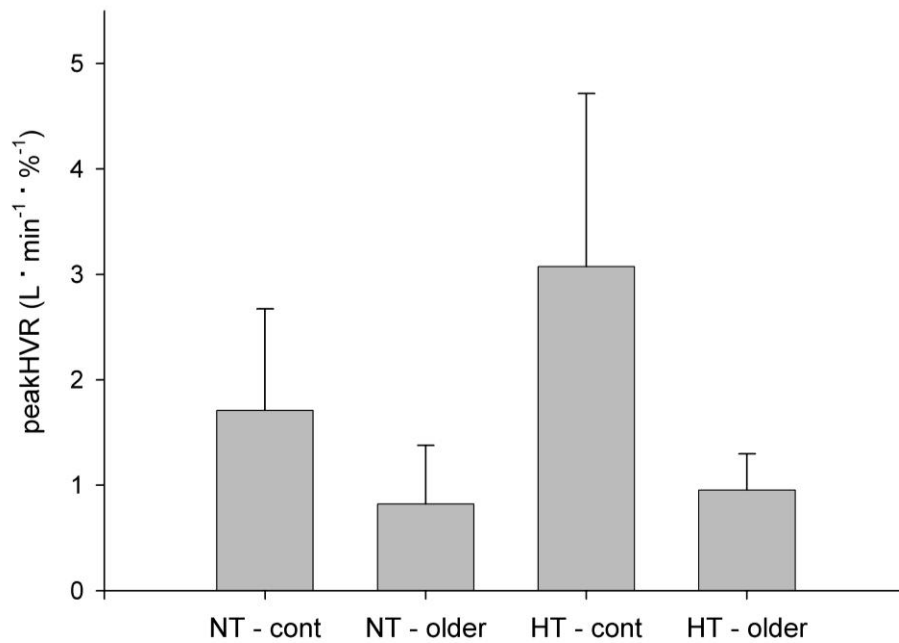
$$HVD (\%) = 100 \left( 1 - \left( \frac{HVR_t}{peakHVR} \right) \right)$$

All delta values were calculated in relation to the time point occurring immediately prior to the onset of hypoxia (time = -1 min).

*Statistical Analysis:* Univariate ANOVA were employed to analyse the NT and HT effects with fixed factors of the Age (control and older), time (+5, +10, +15 and +20 min). A post-hoc mean comparison at each of the time points was conducted with unpaired t-tests. A univariate ANOVA was employed to assess the differences in between HT and NT conditions using the mean of the 4 iHVR time points for each volunteer using fixed factors of Temperature (NT and HT) and Age (control and older). Core temperature, peakHVR and HVD responses were assessed with univariate ANOVAs with factors Age (control and older) and Temperature (NT and HT). The level of significance was set at an  $\alpha < 0.05$ . Analyses were performed with SPSS<sup>®</sup> (version 16.0) statistical software package for Windows<sup>®</sup> (SPSS Inc., Chicago, Ill.).

## RESULTS

For  $T_{ES}$  there was a main effect of the Temperature ( $P < 0.0001$ ,  $n=10$ ) but no Age effect ( $P=0.723$ ,  $n=10$ ) nor interaction between the Temperature and Age (Control group-NT:  $37.03 \pm 0.60^\circ C$ , HT:  $38.22 \pm 0.55^\circ C$ ; Older group-NT:  $37.05 \pm 0.48^\circ C$ , HT:  $38.41 \pm 0.25^\circ C$ ;  $P=0.669$ ,  $n=10$ ). All volunteers completed the NT- but only 3/5 of the older group in the HT-environment completed the iHVR test. Of the two volunteers who could not complete the iHVR, one completed the first 6 min and the other volunteer was unable to complete any of the iHVR test; both volunteers experienced presyncopal symptoms. Irrespective of Temperature, between groups peakHVR was significantly reduced ( $P=0.007$ ) for the older vs. the younger group (Fig. 2). There was a significant main effect of Age for iHVR in NT ( $P=0.001$ ) but not in HT ( $P=0.147$ ) with means comparisons given in Table 1. Neither Temperature nor Age affected HVD (Table 2).



**Figure 2.** Peak isocapnic hypoxic ventilatory response (peakHVR) in normothermic (NT) and hyperthermic (HT) conditions in control (cont) and older age group.

Time (min)	Isocapnic Hypoxic Ventilatory Response (L·min <sup>-1</sup> ·% <sup>-1</sup> )			
	Control NT	Control HT	Older NT	Older HT
+5	0.95 ± 0.29	1.64 ± 1.13	0.23 ± 0.12*	0.19 ± 0.26
+10	0.64 ± 0.22	1.39 ± 1.35	0.13 ± 0.28*	0.07 ± 0.21
+15	0.52 ± 0.25	0.86 ± 0.72	0.08 ± 0.13*	0.23 ± 0.42
+20	0.43 ± 0.21	0.79 ± 0.80	0.04 ± 0.12*	0.43 ± 0.70

**Table 1.** iHVR responses (mean ± SD) at 5, 10, 15 and 20 min in control and older age groups in normothermic (NT) and hyperthermic (HT) environments. (\**p* < 0.05 between groups).

	Hypoxic ventilatory decline (%)	
	NT	HT
<b>Control Group</b>	64.68 ± 29.74	74.58 ± 19.16
<b>Older Group</b>	96.87 ± 12.57	68.18 ± 49.00

**Table 2.** Hypoxic ventilatory decline in control and older volunteer in a normothermic (NT) and hyperthermic (HT) environment.

## DISCUSSION AND CONCLUSIONS

Heat loss from the upper airways, occurs at a site directly beside the hypothalamus. This is the principal integrative tissue in thermoregulation. Increased ventilation will increase the heat loss due primarily to evaporation of the airway mucus [17]. The difference between the groups for iHVR (Table 1) and peakHVR (Fig.1) indicated that under both NT and HT conditions the older group had a blunted response to hypoxia. This reduced ventilatory response to iHVR worsened in the HT environment, again, reducing the older volunteer's ability to respond to the HT environment.

Core temperatures increased in both the control and the older groups by over 1°C in the HT environment, an amount that is enough to induce a hyperventilation [18]. However, under these conditions 3/5 of the older volunteers were unable to complete iHVR test due to presyncopal symptoms. This results help explain why older have individuals increased hospital admissions during heat waves. They appear to have both reduced ventilatory responses to hypoxia and a reduced capacity for thermoregulation [1, 2].

This pilot study indicates that for future studies less severe conditions are needed to assess the HVR. These conditions could be achieved by aiming to raise  $T_{ES}$  by only ~1.0°C and by reducing the level of hypoxia to a  $P_{ET}O_2$  to 60 mmHg. The results support that the control of breathing is impaired in older people and this effect is augmented in a HT environment. Respiratory control in older people is something that requires further research, especially in light of the imminent climate change.

## REFERENCES

1. Michelozzi P, Accetta G, De Sario M, D'Ippoliti D, Marino C, Baccini M, Biggeri A, Anderson HR, Katsouyanni K, Ballester F, et al: High temperature and hospitalizations for cardiovascular and respiratory causes in 12 European cities. *Am J Respir Crit Care Med* 2009, 179:383-389.
2. Koken PJ, Piver WT, Ye F, Elixhauser A, Olsen LM, Portier CJ: Temperature, air pollution, and hospitalization for cardiovascular diseases among elderly people in Denver. *Environ Health Perspect* 2003, 111:1312-1317.
3. Kenney WL, Munce TA: Invited review: aging and human temperature regulation. *J Appl Physiol* 2003, 95:2598-2603.
4. Shoenfeld Y, Udassin R, Shapiro Y, Ohri A, Sohar E: Age and sex difference in response to short exposure to extreme dry heat. *J Appl Physiol* 1978, 44:1-4.
5. Weiss M, Milman B, Rosen B, Eisenstein Z, Zimlichman R: Analysis of the diminished skin perfusion in elderly people by laser Doppler flowmetry. *Age Ageing* 1992, 21:237-241.
6. Rasch W, Samson P, Cote J, Cabanac M: Heat loss from the human head during exercise. *J Appl Physiol* 1991, 71:590-595.
7. Peterson DD, Pack AI, Silage DA, Fishman AP: Effects of aging on ventilatory and occlusion pressure responses to hypoxia and hypercapnia. *Am Rev Respir Dis* 1981, 124:387-391.
8. Kronenberg RS, Drage CW: Attenuation of the ventilatory and heart rate responses to hypoxia and hypercapnia with aging in normal men. *J Clin Invest* 1973, 52:1812-1819.
9. Smith WD, Poulin MJ, Paterson DH, Cunningham DA: Dynamic ventilatory response to acute isocapnic hypoxia in septuagenarians. *Exp Physiol* 2001, 86:117-126.
10. Steinback CD, Poulin MJ: Ventilatory responses to isocapnic and poikilocapnic hypoxia in humans. *Respir Physiol Neurobiol* 2007, 155:104-113.
11. Weil JV, Zwillich CW: Assessment of ventilatory response to hypoxia: methods and interpretation. *Chest* 1976, 70:124-128.
12. Bascom DA, Clement ID, Cunningham DA, Painter R, Robbins PA: Changes in peripheral chemoreflex sensitivity during sustained, isocapnic hypoxia. *Respir Physiol* 1990, 82:161-176.
13. Mekjavic IB, Rempel ME: Determination of esophageal probe insertion length based on standing and sitting height. *J Appl Physiol* 1990, 69:376-379.
14. Koehle MS, Giles LV, Curtis AN, Walsh ML, White MD: Performance of a compact end-tidal forcing system. *Respir Physiol Neurobiol* 2009.
15. Sahn SA, Zwillich CW, Dick N, McCullough RE, Lakshminarayan S, Weil JV: Variability of ventilatory responses to hypoxia and hypercapnia. *J Appl Physiol* 1977, 43:1019-1025.
16. Severinghaus JW: Simple, accurate equations for human blood O<sub>2</sub> dissociation computations. *J Appl Physiol* 1979, 46:599-602.
17. White MD: Components and mechanisms of thermal hyperpnea. *J Appl Physiol* 2006, 101:655-663.
18. Cabanac M, White MD: Core temperature thresholds for hyperpnea during passive hyperthermia in humans. *Eur J Appl Physiol Occup Physiol* 1995, 71:71-76.

