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ORIGINAL ARTICLE

Autonomic cardiovascular response to acute hypoxia and passive head-up tilting in humans

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Abstract Acute hypoxia may alter autonomic cardiovascular reflexes during orthostasis. Heart rate variability (HRV), arterial blood pressure (MAP), and respiratory sinus arrhythmia (RSA) were recorded during supine (SUP) and passive head up tilt (HUT) in eight healthy humans, spontaneously breathing either room air or 10 % O_2 in N_2. In the time domain, heart rate increased and variability decreased with HUT in both trials, with no difference between trials. In the frequency domain, normalized low frequency HRV increased, and normalized high frequency HRV decreased with HUT in both trials, with no difference between trials. MAP was 74.9 (8.6) and 77.5 (11.7) mmHg when SUP in the room air and hypoxia trials, respectively. A significant increase in MAP occurred with HUT in the room air trial but not in the hypoxia trial. In both trials, end tidal CO_2 decreased with HUT, with no difference between trials. In the room air trial, end tidal O_2 increased with HUT, whereas during the hypoxia trial, end tidal O_2 decreased with HUT. The distribution of heart beats relative to the phase of ventilation ($\%HB_{IN}$ and $\%HB_{OUT}$) was similar in both trials: the $\%HB_{IN}$ was 43.5 (3.3) % and $\%HB_{OUT}$ was 56.5 (4.2) % breathing room air when SUP, and 45.5 (3.0) and 54.5 (3.2) when hypoxic and SUP. For both trials, this distribution did not change with HUT. As both HRV and RSA showed similar responses to HUT when spontaneously breathing either room air or 10 % O_2 in N_2, we suggest that autonomic cardiovascular reflexes are preserved during acute hypoxia.

Keywords Autonomic nervous system · Spectral analysis · Cardiac autonomic control

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Introduction

Alternating periods of increasing and decreasing heart rate in phase with breathing [respiratory sinus arrhythmia (RSA)] may improve the efficiency of gas exchange in the lungs (Hayano et al. 1996; Yasuma and Hayano 2004; Grossman and Taylor 2007). Increasing blood flow through the lung during inhalation by the preferential distribution of heart beats during inhalation may reduce intrapulmonary shunt, however, this phasic variation in heart rate is dependent on both body position (Brown et al. 2009a, b; Cooke et al. 1999) and pH (Brown and Howden 2008; Brown et al. 2007). Also, RSA has been shown to increase with hypercapnia but not hypoxemia (Tzeng et al. 2007), in part due to the stimulation of ventilation by an elevated $PaCO_2$. The power of the high frequency (HF) component of heart rate variability (HRV) has been used as a measure of both cardiac vagal tone and RSA since normal resting respiratory frequency is within the HF range (0.15–0.4 Hz). Hypoxia may decrease both low frequency (LF) and HF power (Bernardi et al. 1998; Cornolo et al. 2004; Perini et al. 1996; Ponchia et al. 1994; Saito et al. 2005; Sevre et al. 2001); however, hypoxia may decrease HF power yet increase LF power (Hughson et al. 1994), or have no effect on HF power while increasing LF power (Iwasaki et al. 2006). These equivocal findings emphasize the complex interaction between both inspired PO_2 and

PCO_2, and autonomic nervous system function (Hainsworth et al. 2007; Somers et al. 1991; Kamiya et al. 2005). For example, acute hypoxia may increase both heart rate and blood pressure, although paradoxically, hypoxemia may act on vascular smooth muscle in the systemic circulation causing vasodilation and hypotension. Also, recurrent hypoxic episodes may cause a sustained elevation of mean arterial pressure, although this hypertension appears to be independent of any accompanying hypercapnia. From a clinical perspective, chronic intermittent hypoxia during recurrent apnea syndromes may cause hypertension, increased sympathetic nerve activity, cardiac arrhythmias and myocardial infarction (Prabhakar et al. 2005).

Head-up tilt (HUT) represents a physiological challenge requiring coordinated cardiovascular responses including peripheral vasoconstriction and increasing heart rate—prolonged passive HUT may induce vasovagal syncope. HUT also affects HRV, whereby HF power has consistently been shown to decrease in healthy humans (Cooke et al. 1999; Kamiya et al. 2005; Kochiadakis et al. 1998; Piccirillo et al. 1995). However, directional changes in LF power with HUT appear equivocal, where no changes (Cooke et al. 1999; Kamiya et al. 2005) or increases (Kochiadakis et al. 1998; Piccirillo et al. 1995) have been reported. Impaired cognitive function, spatial disorientation, and syncope, are all characteristics of both acute hypoxia and passive HUT. Indeed, an environment in which a reduced inspired PO_2 occurs with a gravitational-induced redistribution of blood volume will challenge the human body's ability to maintain homeostasis. However, there is currently a paucity of data on the combined effects of acute hypoxia and HUT on both HRV and RSA. Therefore, in the current study, we aimed to quantify these cardiovascular responses in healthy humans to provide further insight into the underlying mechanisms.

Methods

With informed consent, eight healthy adult non-smokers (age range 21–44 years, 4 males, 4 females), with no known cardiovascular or respiratory abnormalities were studied at rest. The female subjects were taking a progesterone-based contraceptive pill and were at least 1 week pre-menstrual. Subjects were at least 4 h post-prandial, and refrained from caffeine containing drinks in the preceding 4 h. All procedures were approved by local Human Ethics Committee.

In a randomized order, subjects were required to breathe either room air (RA: 21 % O_2, 79 % N_2) or normobaric hypoxic air (HYPOXIA: 10 % O_2, 90 % N_2), for a total duration of 12 min, at standard ambient room temperature and atmospheric pressure, i.e., ~20 °C and 760 mmHg. Each 12 min epoch was sub-divided into two 6 min periods. During the first period subjects rested supine (SUP); this was followed by a period of 6 min passive HUT at 85°. Moving from the SUP to the HUT position took <2 s. An allocated washout period between gas exposures was approximately 5 min—during this time subjects could remove the mouthpiece and breathe room air.

During exposures subjects were asked to breathe through a mouthpiece with nasal occlusion. The mouthpiece was connected to a pneumotach (MLT1000L Respiratory Flow Head, AD Instruments, Australia) and a low resistance demand valve connected to a 180L Douglas bag filled with either RA, or HYPOXIA. The mouthpiece and pneumotach added approximately 100 ml ventilatory dead space to each subject. The fractional content of O_2 and CO_2 in the dried air (MLA6024 AD Instruments, Australia) flowing through the pneumotach was continuously measured (response time approximately 100 ms) throughout inhalation and exhalation using a gas analyzer (ML206 AD Instruments, Australia). The O_2 transducer used absorption spectroscopy at λ760 nm and the CO_2 transducer used an infrared sensor. The analyzer was calibrated with samples of known O_2 and CO_2 gas mixtures prior to testing each subject. The length of the sampling lines from the pneumotach to analyzer were minimized to reduce the signal offset—in subsequent data analyses the chart recorder O_2 and CO_2 data streams were time shifted such that the initial changes from typical room air coincided with the start of exhalation, as defined by a continuous positive deflection in ventilatory flow. Ventilatory flow was integrated to determine volume, and this signal was calibrated using a 3-L calibration syringe (Hans Rudolph, USA). Before each test, the pneumotach signal was reset to zero when disconnected from the subject. The mixed expired fractional content of O_2 and CO_2 and the expired end-tidal fractional content of O_2 and CO_2 were recorded.

An electrocardiogram (ECG limb lead 2, band-pass filtered between 10 and 200 Hz, sampling frequency of 1 kHz) was recorded from each subject and collected using a multi-channel analog-to-digital data acquisition system with appropriate software (PowerLab 4/25T and Chart v5.4, AD Instruments, Australia). The ECG was recorded continuously, and was used for HRV analysis using commercially available software (HRV Module for Chart 5, AD Instruments, Australia). Heart rate was calculated by expressing R–R intervals as beats per minute (beats min^{-1}). R–R period data were re-sampled to generate a waveform with uniform time interval. Data were analyzed in the time domain using the mean R–R interval, and the standard deviation of the normal mean R–R interval, and in the frequency domain using a Fourier analysis and a Welch

averaged periodogram method, and banded as very low frequency (VLF: 0–0.04 Hz), LF (0.04–0.15 Hz), and HF (0.15–0.4 Hz). Total power for each spectrum was defined as the area under the spectrum from 0 to 0.5 Hz, and normalized units (%) for the LF and HF components (which take into account any changes in total spectrum power) were calculated.

R waves were identified as occurring during the inhalatory phase ($\%HB_{IN}$) or exhalatory phase ($\%HB_{OUT}$) of ventilation using a peak detection and data logging software routine. These data were used to calculate the relative distribution of heart beats throughout the ventilatory cycle.

Blood pressure was recorded continuously with a non-invasive arterial monitor (Finometer, Ohmeda, UK), and the signal transferred electronically to the chart recorder. The recording was taken from a warmed finger placed at heart level as per manufacturer's instructions, and mean arterial pressure was determined as 1/3 systolic + 2/3 diastolic pressure.

Each variable of interest was analyzed using analysis of variance (significance level at 0.05) following confirmation of distribution normality, and if appropriate, with a post hoc paired sample Student's *t* test to determine where differences occurred (minimum level of significance $P < 0.03$). Values reported are the mean (SD).

Results

All subjects completed both trials, and no syncope episodes were recorded. Heart rate increased and variability decreased with HUT in both ROOM AIR and HYPOXIA trials (Table 1), with no difference between trials. In the time domain, mean R–R decreased by approximately 30 and 25 % in the ROOM AIR and HYPOXIA trials, respectively, and SD R–R decreased by approximately 30 % in both trials. In the frequency domain, LF (%) increased and HF (%) decreased with HUT in both trials.

Changes in the low and HF components of HRV have been plotted against the tilt-induced change (Δ) in heart rate in Fig. 1. This figure describes the relationships between the tilt-induced change (Δ) in normalized frequency components of HRV and the tilt-induced change in heart rate. The upper part of the figure shows Δ LF versus Δ HR—these data indicate that for a larger Δ in heart rate with tilt (further to the right on the *x* axis), the greater the Δ in LF (higher up the *y* axis). However, the relationships are only weak, and the response to tilt for both the room air and the hypoxic conditions are not different. The lower part of the figure shows Δ HF versus Δ HR—these data show that the greater the increase in heart rate with HUT, the greater the decrease in HF (shift to lower values on the *y* axis). Again, the relationships are only weak and appear to be very similar for both room air and hypoxic conditions.

As shown in Fig. 2, mean arterial blood pressure was 74.9 (8.6) and 77.5 (11.7) mmHg when SUP in the ROOM AIR and HYPOXIA trials, respectively. A significant increase ($P < 0.03$) in blood pressure occurred with HUT in the ROOM AIR trial but not in the HYPOXIA trial. Values for end tidal CO_2 and O_2 are also shown in Fig. 2. In both trials, end tidal CO_2 decreased with HUT, with no difference between trials. In the ROOM AIR trial, end tidal O_2 increased from 13.7 (1.2) to 14.4 (0.8) % with HUT ($P < 0.03$), whereas during the HYPOXIA trial, end tidal O_2 decreased from 5.3 (0.4) to 4.8 (0.4) % with HUT ($P < 0.03$).

The distribution of heart beats relative to the phase of ventilation ($\%HB_{IN}$ and $\%HB_{OUT}$) was not different with HYPOXIA compared to ROOM AIR. The $\%HB_{IN}$ was 43.5 (3.3) % and $\%HB_{OUT}$ was 56.5 (4.2) % breathing ROOM AIR when SUP, and the $\%HB_{IN}$ was 45.5 (3.0) and $\%HB_{OUT}$ was 54.5 (3.2) breathing HYPOXIA when SUP. Also, for both trials, there was no change in the distribution of heart beats relative to phases of ventilation with HUT.

Discussion

This study quantified autonomic cardiovascular responses to the combined stressors of acute hypoxia and passive head-up tilt in healthy humans during spontaneous breathing. The $\%HB_{IN}$ and $\%HB_{OUT}$ are novel measures to describe the distribution of heart beats relative to the phase of ventilation—this study is unique in that this method has been applied to the combined stressors of acute hypoxia and HUT. This study reported that the distribution of heart beats throughout phases of ventilation was unaffected by either hypoxia or head-up tilt. Also, this is the first study to report both MAP and Δ in HRV with combined hypoxia and HUT, and presents the novel finding of a tilt-induced decrease in the HF component of HRV yet no change in the distribution of heart beats relative to stages of ventilation, a finding consistent with RSA–vagal dissociation. A further unique finding of this study is that cardiac autonomic reflexes induced by orthostatic challenge appear to be preserved during acute hypoxia—albeit in healthy subjects.

The increased heart rate with reduced time domain variability during passive HUT is well documented (Cooke et al. 1999), as are the directional changes in frequency components of HRV (Kamiya et al. 2005). Hypoxia during HUT appeared to have no effect on these responses. Resting heart rate when supine was elevated during hypoxia, with no change in MAP—this is consistent with the homeostatic requirements imposed by hypoxia-induced peripheral vasodilatation. The elevation of MAP with HUT

Table 1 Heart rate variability measures in both time and frequency domains during spontaneous breathing of atmospheric air (ROOM AIR) or normobaric hypoxia (10 % O_2 in N_2), when either resting supine (SUP) or during passive head-up whole body tilting to 80° (HUT)

	Mean R–R (ms)	SD R–R (ms)	Mean HR (beats min^{-1})	LF (ms^2)	HF (ms^2)	LF (%)	HF (%)
ROOM AIR							
SUP	1,073 (178)	96 (42)	63 (17)	3,345 (3,599)	6,130 (5,083)	36.3 (23.6)	61.0 (22.6)
HUT	754 (125)	64 (17)	82 (14)	1,766 (980)	985 (658)	64.2 (11.7)	33.5 (10.7)
Δ (HUT-SUP)			18.36 (9.37)			27.86 (21.87)	−27.56 (20.44)
HYPOXIA							
SUP	850 (105)	122 (50)	70 (10)	2,895 (4,140)	2,364 (1,940)	45.5 (26.3)	49.7 (24.2)
HUT	639 (60)	87 (58)	95 (9)	1,653 (1,139)	706 (917)	71.2 (14.7)	25.7 (11.9)
Δ (HUT-SUP)			24.28 (6.98)			25.65 (20.56)	−24.02 (19.36)

Values are mean (SD) for eight subjects

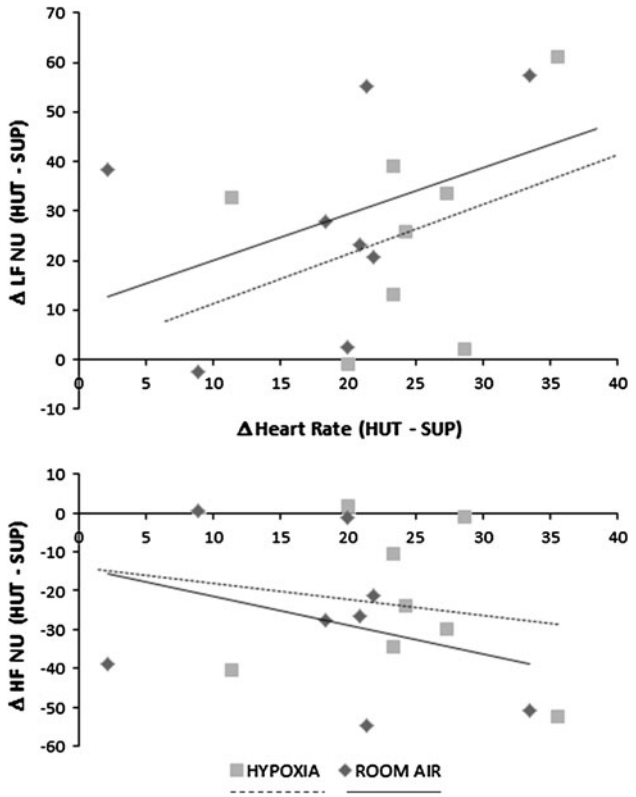

Fig. 1 Change (Δ) in low frequency (LF_{NU}) and high frequency (HF_{NU}) components of heart rate variability as a function of Δ in heart rate induced by passive head-up tilt (HUT), when spontaneously breathing either room air or 10 % O_2 in N_2(Hypoxia)

in the room air trial was consistent with a tilt-induced peripheral vasoconstriction and increased heart rate-reflexes concordant with the maintenance of cerebral perfusion (Rosner and Coley 1986; Toska and Walloe 2002). Hypoxia did not change MAP when SUP was compared to HUT, and it has previously been reported that mild systemic hypoxia had no effect on MAP, and did not affect baroreflex responses to neck suction or pressure (Eckberg et al. 1982).

In the current study, hypoxia was caused by spontaneous ventilation of 10 % O_2 in N_2, thus both pulmonary hypoxia and circulating hypoxemia are potential origins for changes in cardiac auto-regulation. In the hypoxia trial, MAP was not significantly increased with HUT, possibly indicating that a local hypoxemia in the peripheral circulation reduced or abolished any tilt-induced vasoconstriction. However, we can speculate that the tilt-induced increase in heart rate during the hypoxia trial was sufficient to maintain cerebral perfusion and prevent the onset of syncope. Acute hypoxia increases sympathetic activity and may increase both heart rate and blood pressure (Hainsworth et al. 2007)—responses possibly attributable to elevated circulating catecholamine concentration (Mazzeo et al. 1998). Paradoxically, hypoxia also acts on vascular smooth muscle in the systemic circulation (Marshall 1994), potentially causing vasodilation and hypotension. In the current study, MAP did not increase with hypoxia despite an increase in heart rate. We suggest that the increased heart rate is mediated by the arterial baroreflex, whereby arterial pressure is maintained despite a possible reduction in total peripheral resistance initiated by hypoxia-induced peripheral vasodilation. HF_{NU} was unchanged with hypoxia when compared to room air, and there was no evidence of any changes in the distribution of heart beats during either the inhalatory or exhalatory phases of ventilation with hypoxia—these findings suggest that hypoxia had no effect on either vagal tone (Hirsch and Bishop 1981) or RSA.

In the current study, MAP remained above 50 mmHg in all subjects throughout SUP and HUT. Lower values of cerebral tissue oxygenation may be more common with a systolic blood pressure lower than 80 mmHg during HUT (Suzuki et al. 2008), and it has been suggested that systolic pressures <80 mmHg and MAP <60 mmHg are the lower

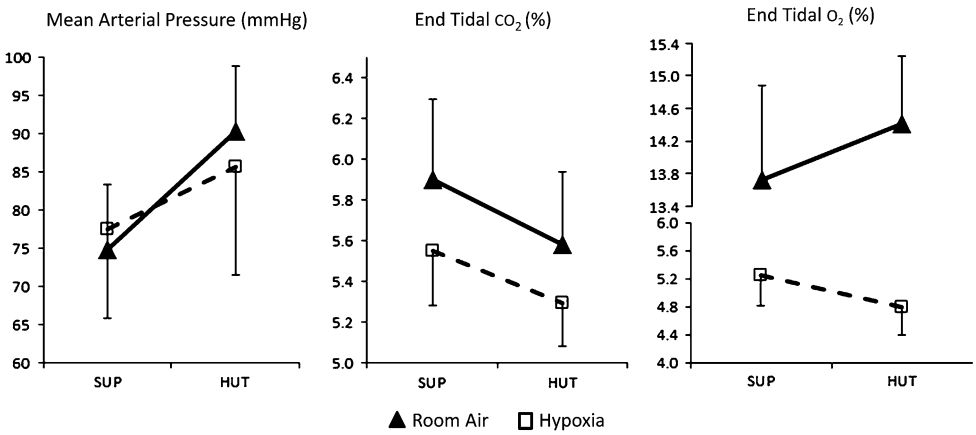

Fig. 2 Mean (SD) tilt-induced changes in mean arterial blood pressure (MAP), end tidal CO_2, and end tidal O_2, when spontaneously breathing either room air or 10 % O_2 in N_2 (Hypoxia). Values are the mean for eight subjects when supine (SUP) and when in a head up tilt position (HUT)

limits for cerebrovascular autoregulation (Novak et al. 1998). However, others (Thomas et al. 2010) have shown independence of both systolic blood pressure and MAP on cerebral oxygenation during cerebral hypo-perfusion.

In the current study, normobaric hypoxia using 10 % O_2 in N_2 is equivalent to an inspired PO_2 of approximately 70 mmHg—this acute hypoxia will potentially cause pulmonary vasoconstriction and pulmonary hypertension, and severely limit the capacity for physical work. Without acclimatization, such a level of hypoxia is poorly tolerated and may lead to adverse physiological consequences if prolonged. All our subjects tolerated the hypoxia for the required period, but signs of pre-syncope were evident in some (two) subjects during HUT when hypoxic. Thus, although our results suggest the preservation of autonomic integrity during combined orthostatic challenge and hypoxia, similarly reported by others (Rickards and Newman 2002; Henriksen and Rowell 1986), prolonged exposure to acute hypoxia (without acclimatization) and HUT may decrease orthostatic tolerance. Although the work carried out in the current study was on healthy subjects, brief periods of hypoxia may be experienced during sleep apnea (SA) and chronic obstructive pulmonary disease (COPD)—thus, the data presented here may have relevance in the study of these conditions. The data presented in this study support the notion that typical cardiovascular reflexes in healthy subjects are preserved in acute hypoxia, however, we speculate that clinical populations (SA and COPD) may not have this preservation, and may experience altered autonomic regulation. No data are available to support this suggestion, but we suggest that initially studying the healthy may provide an ideal starting point to perform these studies on patients.

Hypoxia induced by inhalation of 10 % O_2 in N_2 has some similarities with breath-hold diving—a procedure shown to influence both HRV and RSA (Lemaitre et al. 2008). However, in the current study, subjects maintained pulmonary ventilation during the acute hypoxia exposure, and thus the respiratory effect on both HRV components and RSA were potentially modified by changes to ventilatory patterns—this is different to the hypoxia induced by breath holding. We also imposed an orthostatic challenge with passive, whole body, head-up tilt. During submerged diving procedures (both free diving and SCUBA), ambient hydrostatic pressure induces a shift in blood volume which can increase central venous pressure and venous return which is in contrast to the typical cardiovascular responses to orthostatic challenges.

A decrease in end tidal PCO_2 with HUT reflects the distribution of pulmonary perfusion relative to ventilation. An upright lung has under-perfused but ventilated alveoli in the proximal regions of the lung, adding physiological dead space, therefore end tidal PCO_2 is reduced due to mixing with ambient air. A surprising result in the present study was the decrease in end tidal $\%O_2$ with HUT in the hypoxia trial. Mixing of end tidal exhaled gas with ambient inhaled air containing 10 % O_2 should increase end tidal $\%O_2$ with HUT, as shown in the room air trial. Although speculative, we suggest that hypoxia-induced pulmonary vasoconstriction may reduce physiological dead space in the upright lung—a mechanism which potentially improves ventilatory efficiency when hypoxic.

In summary, these data suggest that cardiovascular reflexes and cardiac autonomic regulation are preserved during acute hypoxia. The vagal withdrawal associated with moving from a supine to a passive head-up position appeared unaffected by acute hypoxia, however, the appearance of pre-syncope signs in some subjects during HUT when hypoxic requires further investigation.

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