The Effects of Gender Sex on Cardiopulmonary Responses to Acute Normobaric Hypoxia

Running title: Sex and Cardiopulmonary Responses to Normobaric Hypoxia

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Abstract

Background

Acute hypoxia leads to a number of recognised changes in cardiopulmonary function including and acute increase in pulmonary artery systolic pressure. However, the comparative responses between men and women have been barely explored.

Methods

Fourteen young healthy adult Caucasian subjects were studied at sea level rest and then after >150 minutes exposure to acute normobaric hypoxia (NH) equivalent to 4800m and again at sea level rest at two hours post NH exposure. Cardiac function, using transthoracic echocardiography, physiological variables and Lake Louise Scores for acute mountain sickness (AMS) were collected.

Results

All subjects completed the study and there was an equal balance of men (n=7) and women (n=7) who were well matched for age (25.9±3.2 vs 27.3±4.4; p=0.51). NH exposure led to a significant increase in AMS scores and heart rate, as well as a fall in oxygen saturations, systolic blood pressure and stroke volume. Stroke volumes and cardiac output were overall significantly higher in men than women and with acute NH heart rate was higher in women (80.3±10.2 vs 69.7±10.7/minute; $p<0.05$). NH led to a significant fall in the estimated left ventricular filling pressure (E/E'), an increase in the septal A' and S' and septal and lateral isovolumic contractile velocities (ICV) and a fall in the E'A'S' ratio. The mitral E, lateral ICV and E' velocities were all higher in men. Acute NH led to a significant increase in right ventricular systolic pressure and

pulmonary vascular resistance. There was no interaction between NH exposure and sex for any parameters measured.

Conclusion

Despite several baseline differences between men and women the cardiopulmonary effects of acute NH are consistent between men and women.

Introduction

Acute and intermediate exposure to hypoxia and high altitude (HA) lead to a number of recognised cardiopulmonary responses. These include pulmonary artery vasoconstriction and an increase in pulmonary artery systolic pressure (Naeije 2010). Resting heart rate and cardiac output tend to increase despite generally neutral or mild decreases in stroke volume (Naeije 2010; Boos et al., 2012 and 2013, Rao et al., 2015). Advances in echocardiography, including tissue Doppler imaging (TDI), have led to improved assessment of both systolic and diastolic cardiac function. Following acute hypoxia mild changes in mitral and tricuspid inflow have been consistently reported in the absence of overt effects on left or right ventricular estimated filling pressure (Boos et al., 2012 and 2013). The reported effects on right ventricular performance have been highly variable and may be partly explained by the differences in the mode, duration and severity of hypoxia between the studies (Boos et al., 2012 and 2013; Pavelescu et al., 2012; Zhou et al., 2012). Differences in temperature, exercise stimulus and hydration may be additional compounding factors (Richardson et al 2009; Naeije., 2013; Mellor et al., 2014).

An area that has been barely explored is that of the effects of sex on cardiopulmonary adaptations to HA. It is already well known that men have larger cardiac chamber sizes and higher resting stroke volume and cardiac output than that of women (Okura et al., 2009; Dalen et al., 2010; Daimon et al., 2011). There is some, albeit very limited data to suggest that there may be sex-related differences in autonomic, vasodilatory and physiological responses to hypoxia (Casey et al., 2014; Lombardi et al., 2013; Patel et al., 2014; Wadhwa et al., 2008; Ricart et al., 2008; Mortola et al., 1996).

In order to overcome some of the challenges of studying subjects at genuine terrestrial HA a number of methods of HA simulation have been utilised and these include hypobaric (reducing the partial pressure of oxygen in a depressurised chamber) and normobaric hypoxia (using either a low FiO_2 chamber or mask) (Boos et al., 2013; Coppel et al., 2015). These simulation methods can accurately replicate the degree of hypoxia for a given altitude, whilst allowing for a more controlled environment for medical research than that afforded with studies at terrestrial HA (Coppel et al., 2015).

In this study we aimed to explore the cardiopulmonary responses of men and women to acute NH in humans in order to determine whether any sex-related differences occur.

Methods

Study population

This was a prospective observational study of 14 fit and healthy British military servicemen aged 22-35 years subjects. This cohort consisted of seven men and seven women who were matched for age and ethnicity. All subjects were required to abstain from caffeine, alcohol, non-steroidal anti-inflammatory drugs and smoking for >12 hours prior to the study and to abstain from strenuous physical activity for 48 hours prior to the experiment. Confirmation of health status was confirmed following a detailed health questionnaire and all subjects were required to have a normal baseline echocardiogram to confirm suitability for inclusion. All the included women had not had a previous pregnancy.

Ethics

The study was approved by the Ministry of Defence Research and Medical Ethics Committee and was conducted according to the standards of the declaration of Helsinki. All subjects were required to provide written informed consent.

Study protocol

The detailed study flow is shown in figure 1. All subjects were examined at rest under normal atmospheric oxygen conditions at near sea level (absolute altitude ~113m; Leeds Beckett University, Centre for Sports Performance, Leeds, UK) followed by a three hour continuous exposure in a NH chamber (TISS, Alton, UK and Sporting Edge, Sherfield on Loddon, UK). For NH exposure the chamber was set to an FiO_2 of 11.4% approximating an altitude of 4800m (fig 1). Participants were then required to complete physiological assessments (heart rate, blood pressure and SpO_2), a detailed transthoracic echocardiogram and assessment of symptoms of AMS. This was performed at rest 60 minutes prior to NH and then after 150 minutes into a three hour exposure to acute NH. All subjects underwent a five minute step test at 90 minutes. The chamber temperature was controlled at 21 °C throughout the study. An additional echocardiogram was performed at rest in normoxia at 120 minutes post NH exposure on all subjects.

Physiological measurements

Resting recordings of oxygen saturations (SpO_2) were performed using a Nellcor N-20P pulse oximeter (Nellcor Puritan Bennett, Coventry, UK). Blood pressure - was measured using an automated blood pressure cuff M6 (Omron Healthcare, Milton Keynes, UK) with the subject sat upright for >10 minutes at rest. Heart rate was obtained from a single lead ECG obtained during the echocardiogram.

Acute mountain sickness (AMS) scores

HA related symptoms were assessed using the Lake Louis Score twice (LLS [Hackett and Oelz, 1992; Roach et al., 1993]). The LLS score allocates a score of 0–3 (symptom not present to severe) for symptoms of AMS (headache, gastrointestinal symptoms, fatigue/weakness, dizzy/light-headedness, difficulty sleeping). A total score of $\geq$3 in the presence of a headache is consistent with AMS and $\geq$6 with severe AMS.

Echocardiographic assessment

All echocardiographic assessments were undertaken using a portable Vivid Q echocardiogram machine (GE Healthcare™, Amersham, Bucks, UK) with a 1.5-3.6 MHz S4 transducer. All scans were performed by a single consultant Cardiologist, with significant experience in echocardiography, and the data was exported for offline viewing and analysis using Xcelera Package (Philips Healthcare, DA Best, The Netherlands).All subjects were scanned semi supine in the left lateral position at 30 degrees head up tilt. Pulsed-wave and two dimensional colour images were acquired in the parasternal short axis and apical four-chamber view during a short end-expiration pause.

Stroke volume and cardiac output were calculated using the aortic systolic flow velocity integral, using pulsed-wave profile of aortic blood flow from the apical five chamber view and the cross sectional area of the left ventricular outflow tract (Boos et al., 2012 and 2013 and 2014; Huez et al., 2005). The Cardiac index and the stroke volume index were calculated by dividing the cardiac output and stroke volume

respectively by the surface area. Ejection fraction was calculated using the Simpson Biplane method.

The pulsed-wave sample volume of the conventional Doppler was placed at the tips of the mitral and tricuspid valve leaflets in order to measure the peak early transvalvular flow velocity (E), and the peak flow velocity (A) of late diastolic filling and the E/A ratios (Paulus et al., 2007). Pulsed-wave TDI volume samples were recorded at the septal and lateral mitral annulus and used to calculate isovolumic contractile velocities (ICV), early (E') and late diastolic (A') and peak systolic (S') long axis velocities (Pavelscu et al., 2012; Boos et al., 2014). The left ventricular EAS index, which is a measure of global cardiac function, (E' / [A' x S']) was calculated using the TDI at the septal annulus as previous described (Boos et al., 2013). Estimation of LV filling pressure was undertaken from the ratio (E/E') using the mitral valve E velocity divided by TDI-derived early annular filling E' velocity at the averaged (septal and lateral lateral) mitral annulus (Paulus et al., 2007). The left ventricular myocardial performance (Tei) index, another measure of global left ventricular function, (IRT [isovolumic relaxation time] + ICT [isovolumic contractile time]/ejection time) was performed using TDI as previously described (Boos et al., 2013).

Right ventricular systolic pressure (RVSP) was estimated from the maximum velocity of the trans-tricuspid gradient using continuous wave Doppler imaging. Pulsed-wave volume sampling at the level of the pulmonary valves was used to assess the pulmonary artery acceleration time. The tricuspid annular plane systolic excursion (TAPSE), which a marker right ventricular log axis systolic function, was recorded using M-Mode echocardiography as previously described (Boos et al., 2013). The

pulmonary artery vascular resistance (PVR) was calculated using the following equation PVR = 80 x TRV/VTI RVOT where TRV was the maximal tricuspid regurgitation velocity and VTI was the velocity time integral of the right ventricular outflow tract (RVOT) velocity measured using pulsed wave doppler at the level of the pulmonary valve in the parasternal short axis view (Abbas et al., 2003).

Statistical Methods and power calculations

Data were analysed using SPSS® statistics version 22 (SPSS Inc., Somers, NY, USA). The Shapiro-Wilk test and inspection of the data was undertaken to assess normality of all continuous data. All data are presented as mean ± standard deviations. Unpaired two-group comparisons of continuous baseline data for men and women were performed using an unpaired T test and a man-Whitney test for parametric and non-parametric data respectively. For categorical data the Fishers Exact test was used. The effects of sex on the time dependent variables (effects of hypoxic exposure) were evaluated by two-way factorial repeated-measures ANOVA. Time at baseline, ≥150 minutes of NH and at 120 minutes post NH were included as levels of within-subjects factor (time effects of hypoxia) and sex (male or female) as between-subjects factors. The Bonferroni multiple comparison test was used when significant differences were found as well as interactions between the effects. A significance level of $P<0.05$ was adopted.

There are no previous published studies that have assessed sex-related differences in cardiac function with acute hypoxia. Our sample size of 14 subjects was based on previously published work which demonstrated significant changes in cardiac function

and hemodynamic indices with acute hypobaric hypoxia with a sample size of 10-14 subjects (Boos et al., 2012, 2103).

Results

All subjects completed the study. Image quality was rated as good to excellent for all of the echocardiographic scans. The average age of the 14 included subjects were 26.6±3.8 (range: 21-33) years with an equal balance of men (n=7; 50%) and women (n=7; 50%) (table 1). They weighed 72.5±12.3kg, were 171.±10.5 cm tall with an average body mass index 24.6±2.4 kg/m^2. The men and women were well matched for age (p=0.51) and were all Caucasian (table 1). Four of the women were on the oral contraceptive pill which was a combined pill in three and progestogen only in one of subjects.

Physiological and haemodynamic variables

The main effects of time and NH exposure were a significant increase in LLS and heart rate, as well as a fall in systolic blood pressure and stroke volume (Table 2). The main effects of sex were that stroke volumes and cardiac output were higher in men despite notably higher heart rates in women (80.3±10.2 vs 69.7±10.7/minute; $p<0.05$) during NH. There was no observed interaction of time (altitude exposure) and sex. Hence, there was no sex-dependent effect of NH on measured variables. There was however a non-significant trend to higher SpO_2 levels among the women compared with men during hypoxia (p=0.09) (Table 2).

Changes in left ventricular function

NH led to a significant fall in Mitral E Velocity (main effect of time [hypoxic exposure] F=10.1; p=0.001), the estimated left ventricular filling pressure (E/E'), an increase in the septal A' and S' and septal (main effect of hypoxic exposure; F=11.9: p=0.002) and lateral (main effect of hypoxic exposure F=9.2; p=0.0007) ICV and a fall in the EAS ratio (Table 3). Mitral E velocity (main effect of sex F=8.1; p=0.02) and lateral ICVs (main effect of sex F=5.3; p=0.04) were overall significantly higher in women (figures 2 and 3) and lateral E' velocities were higher in men (Table 3). There were no significant interactions with NH exposure and sex on any left ventricular functional parameters (p>0.05) (table 3).

Right ventricular function and right ventricular systolic pressure

Acute NH led to a significant fall in pulmonary artery acceleration time and an increase in right ventricular systolic pressure and pulmonary vascular resistance without any main effects of sex or interactions of time and sex (table 4).

Discussion

To the authors knowledge this is the first study to assess the sex-related changes in biventricular cardiac function following acute hypoxia. The main findings of this study were that whilst cross comparative differences in cardiac function exist between men and women at rest during normoxia their responses to acute NH were consistent with the main effect of hypoxia. Hence the cardiac functional responses to hypoxia are similar between men and women despite their recognised baseline differences.

Acute hypoxia leads to a number of well recognised acute physiological and cardiac responses (Naeije., 2013; Boos et al., 2012, 2013 and 2014). This study aimed to

determine whether the additional stimulus of acute hypoxia leads to any specific sex-related differences. This is an important issue as HA exposure, whether as part of recreation or sport, is an interest shared by both men and women and as such either could succumb to the complications of including AMS and high altitude pulmonary oedema (HAPE). Differences in the incidence of AMS between men and women have been variably reported. There is published data to suggest that women may be more prone to AMS than men (Santantonio et al., 2014; McDevitt M et al., 2014) but there is also contrary data to support the exact opposite (Beidleman et al., 2013). The data is similarly conflicting for HAPE where variable sexual predominance have been reported (Hultgren et al., 1996; Sophocles et al., 1986). These reported differences may be explained in part by deficiencies in study design (unequal matching of men and women in numbers and age etc) and failure to adjust for important confounding factors known to influence AMS, such as use of AMS prevention medicines such as acetazolamide, and sex-related differences in the altitude achieved. We did notice that AMS scores were non significantly yet nearly 50% higher during acute NH in men compared with women in our study although this did not reach significance lending some support to previous published work (Beidleman et al., 2013) (Table 2).

Beyond the issue of AMS there is evidence that cardiac adaptations may also be different between men and women. It is well established cardiac chamber sizes, wall thickness and mass are greater in men than women, and are influenced by age, degree of cardiovascular conditioning, ethnicity and body habitus (eg height) (Okura et al., 2009; Dalen et al., 2010; Daimon et al., 2011). Observational studies have highlighted several sex-related differences in left ventricular systolic and diastolic function. These include higher resting mitral E and left ventricular E' velocities in women (Daimon et

al 2011). Our baseline resting data is largely consistent with these published studies. Our data would suggest that the ICV is a very sensitive marker to both the effects of hypoxia which led to marked increase in ICV, and to sex with notably higher lateral ICV and a trend for higher septal peak ICV velocity in men over the time course of the study. It has been previously shown by our group and others (Boos et al., 2013; Huez et al., 2005) that in healthy young adults the ICV increases with acute hypoxia suggesting augmentation of systolic function and that the ICV is higher at rest in men than women with normoxia (Lind et al., 2006). This is, to the authors' knowledge, the first study to assess sex-related changes with acute NH. The left ventricular ICV has been shown to be a robust and validated non-invasive marker of global cardiac contractility and has the advantage over several other functional markers of being less load dependent (Lindqvist et al., 2007).

There is preliminary data to suggest that cardiopulmonary responses hypoxia may be influenced by sex. In a very recent study of healthy young adults exposed to acute isocapnoeic hypoxia it was observed that the increase in pulmonary artery systolic pressure was greater among women than men despite similar ventilatory responses (Fatemian et al., 2015). There is also data to show that with intermittent hypoxia sympathovagal balance was enhanced and parasympathetic nervous system activation were depressed in men but not in women despite again similar ventilatory responses (Wadhwa et al., 2008). Plausible differences between men and women, if genuine, could relate to differences in sex hormones. Sex steroids have overlapping chemical and physiologic properties with corticosteroids that are used to prevent and even treat AMS. Testosterone is a known pulmonary artery vasodilator and may have other properties including immuno-modulation and altering expression of cytokines and

potential anti-thrombotic actions (Smith et al., 2006). The phase of the menstrual cycle has been shown to affect physiological responses in women with attenuation of acute hypoxic pulmonary vasoconstriction in response to endogenous oestrogens (Lahm et al., Pollard et al., 2007). The included women in our study were at differing phases of their menstrual cycle and four were on the oral contraceptive pill which may be important confounding factors. It is unknown whether differences in sex hormonal profiles could influence the efficiency of ventilation-perfusion within the lung and help to explain the observed trend to higher SpO_2 levels in women both at rest and during hypoxia in this study. This is an interesting finding that warrants further exploration in a larger field study at genuine HA. It has been previously shown that women have slightly but significantly higher resting SpO_2 than men although the respective changes with hypoxia have been less well studied (Ricart et al., 2008). Indeed there are recognised differences in red blood cell counts, haemoglobin and 2,3-diphosphoglycerate plasma concentrations between women and men which are additional factors to consider (Ricart et al., 2008). We did not observe any significant differences in the pulmonary vascular responses between men and women with both demonstrating similar increases in pulmonary vascular resistance and pulmonary artery systolic pressure and a fall in the pulmonary artery acceleration time, with acute hypoxia as previously reported (Boos et al., 2012, 2013).

This study has a number of additional limitations which need to be acknowledged. The sample size of this study was small limiting the power to detect a potential significant difference in some of the echo parameters that might have been appreciated with a larger sample size. However, the study is strengthened by the two-way repeated measures design and the two groups were very well matched for age and ethnicity. This

study was performed under experimental NH and cannot necessarily equate to that which would occur with terrestrial HA where the rate of ascent would likely be far slower and the environmental circumstances vastly different. The study cohort includes only young adults and it is unknown whether sex differences might not be manifested until women are menopausal or post-menopausal. Finally, the degree of hypoxia was represented moderate HA at approximately 4800m and there were no cases of significant AMS.

Conclusion

The cardiopulmonary effects of acute NH are not influenced by underlying sex and are consistent with the recognised baseline differences between men and women.

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Author Contributions

Competing interests The authors have no conflicts of interest or financial ties to disclose.

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Table 1 Baseline demographics

	Women	**men**	**P value**
Number (n)	7	7	
Age, years	25.9±3.2	27.3±4.4	0.51
Height, cm	162.7±5.6	179.6±6.4	0.0003
Weight, kg	62.9±6.6	82.2±8.0	0.005
Body Mass index, Kg/m^2	23.8±2.1	25.5±2.4	0.20
Body surface area, m^2	1.67±0.1	2.0±.1	<0.0001
Current Smoker, n	0	1	0.3

Table 2 Changes in key physiological variables

Variable	Baseline	150 minutes NH	120 minutes post NH	Main effects of time (hypoxic exposure)	Main effects of Sex	Interaction (time x sex)
Heart rate, minute^{-1}						
-men	63.6±8.6	69.7±10.7	61.3±1.3	F=9.9	F=2.8	F=2.9
-women	65.4±5.4	80.3±10.2ǂ	69.3±9.5	p=0.0006a,c	P=0.19	p=0.07
Systolic blood pressure, mmHg						
-men	134.3±6.4	124.1±12.2	-	F=7.0	F=2.0	F=1.2
-women	124.7±8.3ǂ	120.5±6.4	-	p=0.02	p=0.18	p=0.30
Diastolic blood pressure, mmHg		71.0±6.1				
-men	75.6±7.8	74.0±4.3	-	F=4.1	F=0.44	F=0.32
-women	76.6±4.6		-	p=0.07	P=0.52	p=0.58
Oxygen saturations, %						
-men	98.6±0.5	77.7±6.1	-	F=229.3	F=3.8	F=3.0
-women	99.0±0.1	82.4±2.8	-	p<0.0001	p=0.08	P=0.11
Lake Louise Scores						
-men	0.0	1.57±1.4	-	F=15.0	F=1.3	F=1.3
-women	0.0	0.86±0.9	-	p=0.002	p=0.28	p=0.28
Stroke volume, ml						
-men	85.3±19.0	75.7±9.1	79.6±10.2	F=2.8	F=11.9	F=0.07
-women	62.3±12.7ǂ	56.4±9.2ǂ	62.0±12.9ǂ	p=0.07	p=0.005	p=0.9
Stroke volume index, ml/minute/m^2						
-men	39.9±6.0	37.4±4.9	39.3±5.5	F=2.7	F=1.4	F=0.1
-women	37.0±5.7	33.7±4.9	36.9±6.5	P=0.09	P=0.27	P=0.9
Cardiac output, l/minute						
- men	5.4±1.6	5.3±1.1	5.0±0.8	F=1.4	F=4.6	F=0.8
- women	4.0±0.9ǂ	4.6±0.5	4.1±1.1	p=0.26	p=0.049	p=0.46
Cardiac Index , l/minute/m^2						
- men	2.7±0.8	2.6±0.3	2.4±0.4	0.6	F=0.07	F=2.1
- women	2.4±0.3	2.2±1.1	2.6±0.4	0.56	P=0.8	P=0.17

ǂ, significant (p<0.05) differences between men and women; Results of post hoc test: a, baseline vs 2.5 hours post NH; b baseline versus 2hours post NH;c, NH versus 2 hours post NH

Table 3 Changes in parameters of left Ventricular function

Variable	Baseline	150 minutes NH	120 minutes post NH	Main effects of time (hypoxic exposure)	Main effects of Sex	Interaction (time X sex)
Systolic function						
Ejection Fraction, % - men - women	 61.9±5.1 59.5±3.5	 61.3±4.1 60.5±3.7	 61.4±5.3 58.5±2.9	 F=0.58 p=0.57	 F=0.92 p=0.36	 F=0.75 p=0.48
Septal S' velocity cm/s - men - women	 9.3±1.5 8.7±1.0	 9.3±0.7 10.3±1.1	 8.8±0.7 9.3±1.0	 F=4.3 p=0.04c	 F=0.4 p=0.54	 F=3.5 P=0.09
Lateral S' velocity cm/s -men -women	 11.3±1.6 12.1±0.9	 12.3±2.4 12.4±2.1	 11.5±1.4 12.8±2.2	 F=0.55 p=0.58	 F=1.3 p=0.28	 F=0.48 p=0.63
Diastolic function						
Mitral A velocity, cm/s - men - women	 60.7±10.1 52.5±14.4	 54.7±13.0 55.6±11.3	 54.4±8.1 52.3±15.4	 F=0.41 p=0.67	 F=0.38 P=0.55	 F=0.80 p=0.46
Mitral E/A ratio - men - women	 1.5±0.2 1.9±0.6	 1.3±0.2 1.6±0.3	 1.4±0.1 1.9±0.7	 F=3.67 p=0.04a	 F=0.6 p=0.53	 F=4.9 P=0.048
Mitral E deceleration time, ms - men - women	 190.0±13.5 192.0±21.2	 206.6±43.0 187.6±20.1	 220.3±41.0 176.6±33.6ǂ	 F=0.3 p=0.76	 F=3.0 p=0.1	 F=2.7 P=0.09
Septal E' velocity cm/s - men - women	 13.6±2.2 13.9±1.5	 11.5±1.0 13.6±1.8	 11.8±1.1 13.7±2.8	 F=3.1 p=0.7	 F=2.7 P=0.13	 F=3.3 p=0.06
Lateral E' velocity cm/s - men - women	 17.0±3.2 19.6±2.9	 16.3±1.6 19.4±2.4ǂ	 16.9±2.1 19.0±3.9	 F=0.17 p=0.85	 F=4.8 P=0.047	 F=0.19 P=0.80
Average E/E' ratio - men - women	 5.8±1.2 5.9±1.6	 4.9±0.9 5.2±0.7	 5.3±0.9 5.7±1.1	 F=4.4p p=0.02a	 F=0.19 p=0.67	 F=0.24 P=0.79
Septal A' velocity cm/s - men - women	 9.1±1.8 7.8±1.3	 9.4±1.5 9.9±1.8	 9.2±1.7 8.5±0.8	 F=5.9 p=0.008ac	 F=0.40 p=0.53	 F=3.3 P=0.06
Lateral A' velocity cm/s - men - women	 9.6±1.3 10.9±3.0	 10.2±2.1 10.8±3.4	 10.6±2.1 10.0±2.3	 F=0.1 p=0.9	 F=0.17 P=0.67	 F=1.1 P=0.35
Combined systolic and diastolic (global) function						
Tei Index - men - women	 0.33±0.05 0.35±0.08	 0.35±0.05 0.35±0.07	 0.33±0.04 0.34±0.08	 F=0.46 p=0.64	 F=0.1 p=0.76	 F=0.13 p=0.88
EAS ratio - men - women	 0.17±0.05 0.18±0.06	 0.14±0.03 0.14±0.04	 0.15±0.04 0.17±0.04	 F=8.3 p=0.002a	 F=0.41 p=0.54	 F=0.19 p=0.83
ǂ, significant ($p<0.05$) differences between men and women; Results of post hoc test: a, baseline vs 2.5 hours post NH; b baseline versus 2hours post NH; c, NH versus 2 hours post NH						

Table 4 Changes in measures of right ventricular function and pulmonary artery pressure

Variable	Baseline	150 minutes NH	120 minutes post NH	Main effects of time (hypoxic exposure)	Main effects of Sex	Interaction (time x sex)
Pulmonary acceleration time, ms						
- men	150.6±8.5	116.9±10.2	135.3±7.7	F=95.1	F=0.9	F=1.0
- women	152.9±12.9	125.4±14.5	140.3±13.8	p<0.0001abc	p=0.36	P=0.38
Right ventricular systolic pressure, mmHg						
- men	14.6±2.2	29.3±3.4	19.1±5.2	F=42.0	F=0.56	F=0.14
- women	14.9±2.5	26.7±6.4	19.0±7.5	p<0.0001abc	p=0.59	P=0.72
Pulmonary vascular resistance dynes / sec / cm^{-5}						
- men	86.9±19.0	140.8±20.0	114.6±27.4	F=29.5	F=1.1	F=1.2
- women	87.6±14.2	124.3±22.7	100.6±27.3	<0.0001abc	p=0.3	p=0.31
TAPSE, cm						
- men	2.5±.04	2.4±0.4	2.5±0.3	F=0.15	F=0.1	F=0.1
- women	2.4±0.2	2.4±0.2	2.5±0.6	P=0.86	p=0.82	p=0.92

TAPSE, trans annular plane systolic excursion; ǂ, significant ($p<0.05$) differences between men and women; Results of post hoc test: a, baseline vs 2.5 hours post NH; b baseline versus 2 hours post NH; c, NH versus 2 hours post NH

Legends for Figures

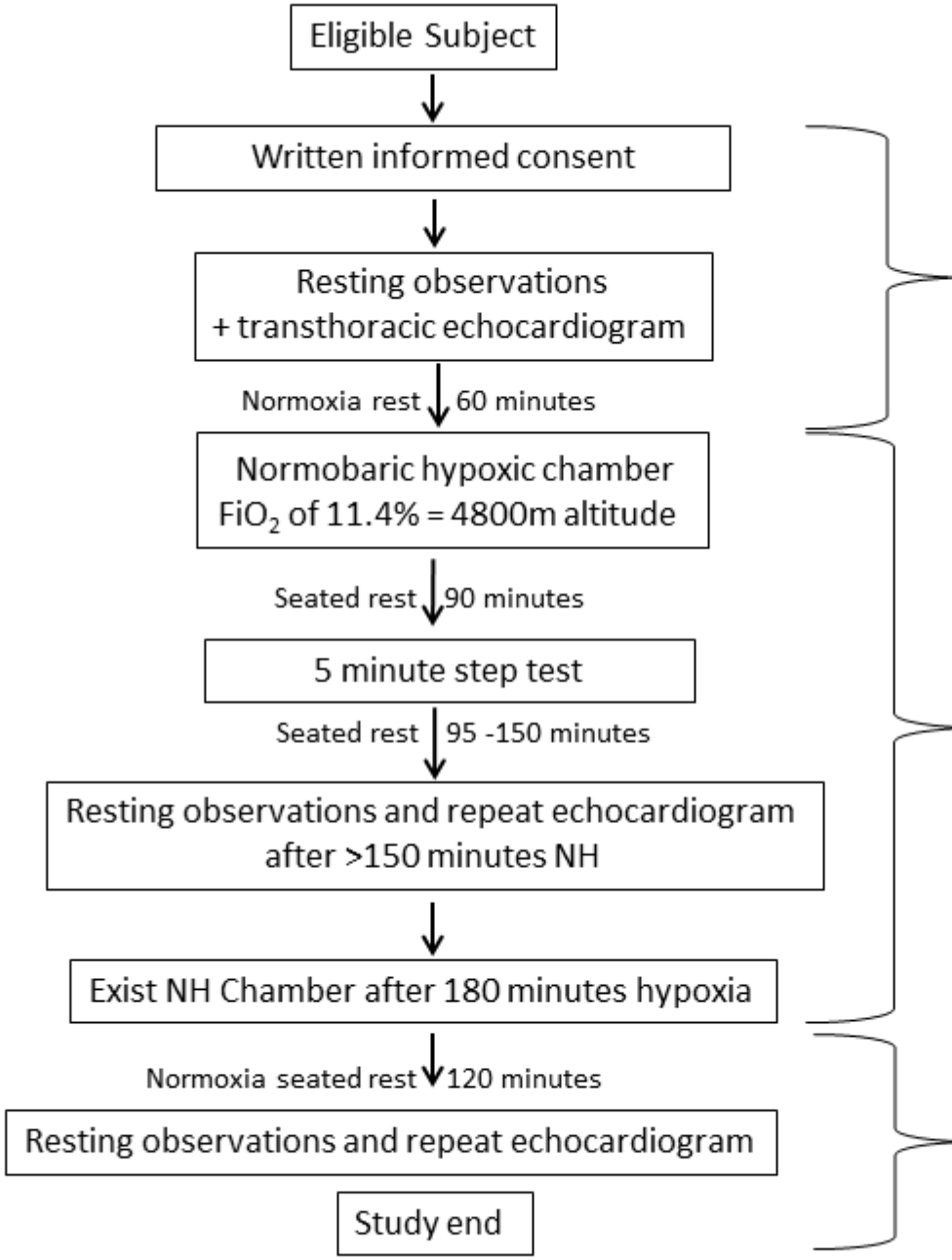
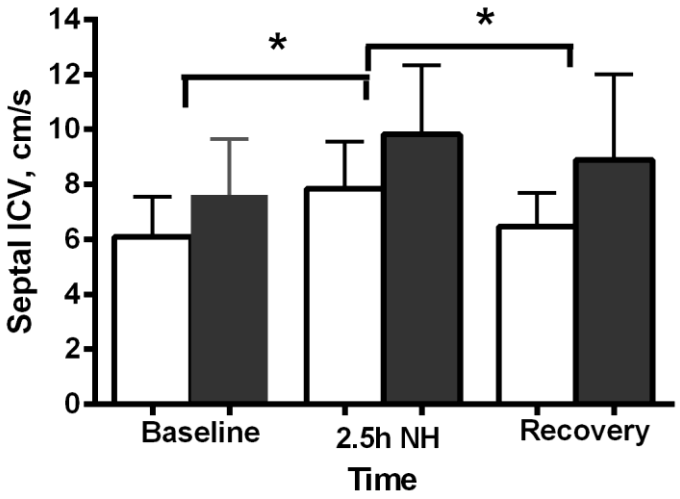


Figure 1: Experimental design flow diagram


Septal ICV, cm/s
14
12
10
8
6
4
2
0
*
*
Baseline
2.5h NH
Recovery
Time

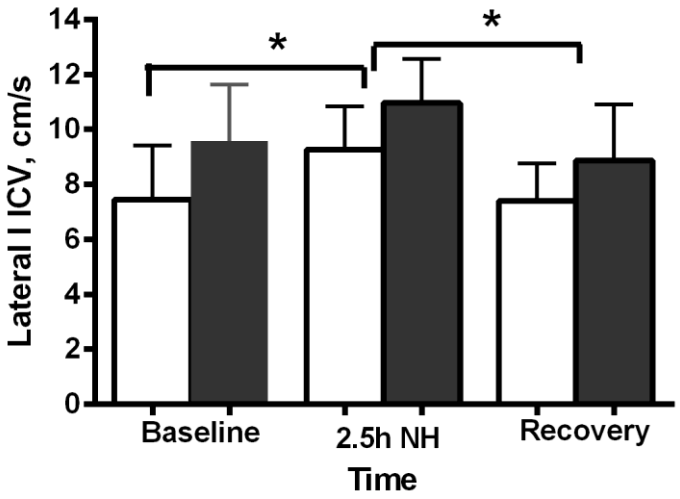


Figure 2 Changes in the Isovolumic contractile velocity (ICV) with exposure to normobaric hypoxia (NH) between women (white shade) and men (dark shade).

* Significance on post test

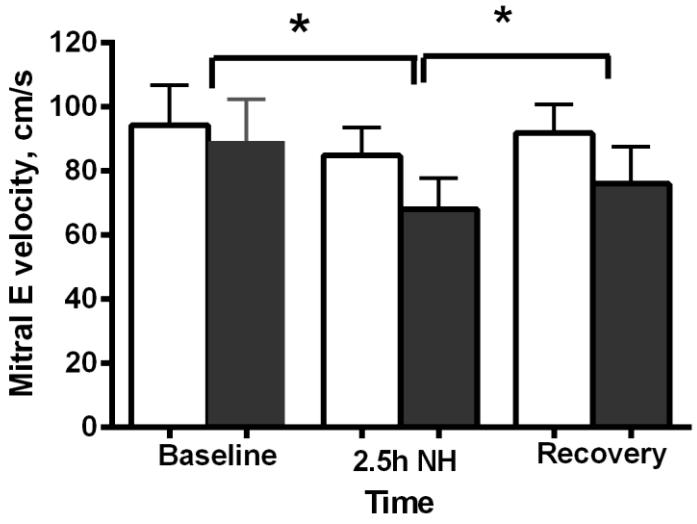


Figure 3 Changes in Mitral E velocity with exposure to normobaric hypoxia (NH) between women (white shade) and men (dark shade).

* Significance on post test