PRIFYSGOL BANGOR UNIVERSITY

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The Effect of Biological Sex on Cardiovascular Response to Acute Hypoxia

1 Introduction

- **Hypoxia** is defined as a deficiency of oxygen (O_2) in bodily tissues *(Faarc, 2000)*, specifically at saturations [SpO_2 (%)] of < 90% *(Myatt, 2017)*.
- Hypoxia can predispose to hypoxaemia thus the activities of oxygen consuming metabolic pathways are restricted *(Thompson, 2016)*.
- **Cardiac output (Q)** is a measure of the pumping function of cardiac tissue. Maintaining Q ensures adequate oxygen delivery to tissues.
- **Heart rate (HR)** is a component of Q *(Kumar & Clark, 2016)* and is considered an indirect measure of cardiac function *(Freeman, 2006)*.
- In hypoxia, HR (and Q) increases via autonomic sympathetic stimulation *(Thomson et al., 2006)*.
- Mediated through the baroreceptor reflex *(DeMers & Wachs, 2021)*, **mean arterial pressure (MAP)** is considered to be the perfusion pressure of bodily tissues.
- In hypoxia, MAP increases as a function of Q increasing and systemic vascular resistance decreasing.
- It is well documented that the **physiologies of males and females differ**, especially through the action of sex-specific steroid hormones, but this difference in biological sex has only been adequately acknowledged in recent scientific literature *(Blair, 2007)*.
- Indeed, a recent hot topic review conducted by Mugele, Oliver, Gagon & Lawley (2020) showed no evidence of literature comparing the effects of hypoxic and cold stress featuring a **sex comparison.**

2 Research question:

Does CV response to acute hypoxia differ based on biological sex?

Null hypothesis 1: *Under acute hypoxia, resting HR and MAP will not significantly increase in both sexes, whilst SpO2 will not significantly decrease in both sexes.*

Null hypothesis 2: *Under acute hypoxia, the aforementioned changes to HR, MAP and SpO2 will not be significantly different between males and females.*

3 Methodology:

Participants: convenience sample of 10 individuals, mean age of 21.7 (range 18-36), mean BMI 23kg/m^2 *(Friend et al,. 2021)*. Strict inclusion criteria met (age, medical fitness, acclimatisation specifications). Female specific opt in/out questions on menstrual cycle and contraceptive methods (impact of sex-specific steroid hormones). **Ethics:** granted by Bangor University Ethics Committee.

Design: Quasi-experimental design to investigate the separate and combine effects of two independent variables (IV) on each dependent variable (DV).

Variables: IV1 FiO_2 (20.9% normoxia or 12% hypoxia). IV2 biological sex (male or female). DV's resting HR (bpm), MAP (mmHg), SpO_2 (%).

Equipment and trialling: successful trial conducted. Proof of environmental manipulation from SpO_2 changes. Poikilocapnic hypoxia generated using a normobaric hypoxico chamber. HR measured with Acuson 3-lead ECG. MAP measured using Omron brachial cuff and monitor. SpO_2 measured using Nonin pulse oximeter.

Main procedure: participants exposed to each FiO_2% for 90 minutes respectively (with counterbalancing) whilst data for each DV was measured at four timepoints before being meaned into one datapoint per sex per unit time. Temperature set at 26.0ºC, humidity set at 30% for all.

Statistical analysis: SPSS software utilised to conduct a 2-factor x 2-level Mixed Model ANOVA. Factor 1 (IV1 - FiO_2%) being a within-subject variable. Factor 2 (IV2 - sex) being a between-subject variable.

4 Results

- No significant interaction effects between 'FiO_2%' 'sex' on SpO_2 (p = *.211)*, HR (p = *.337)* or MAP (p = *.280)* were observed.
- A significant main effect for FiO_2 on SpO_2 was observed, with mean SpO_2 decreasing in hypoxic stress [sample mean: 98.6% (± 0.7) to 83.6% (± 4.6), male-specific mean: 98.1% (± 0.5) to 81.4% (± 4.4), female-specific mean: 99.1% (± 0.5) to 85.8% (± 4.0), all p = < *.001*].
- This observation provides the proof of environmental manipulation.
- However, no significant main effect for sex on SpO_2 was observed (p = *.086*).
- A significant main effect for FiO_2 on resting HR was seen, with mean HR increasing in hypoxia [sample mean: 57.7 bpm (± 6.0) to 70.0 bpm (± 9.8), male-specific mean: 54.4 bpm (± 5.5) to 69.6 bpm (± 12.3), female-specific mean: 61.1 bpm (± 4.9) to 70.3 bpm (± 8.1), all p = *.003*].
- But no significant main effect for sex on resting HR was observed (p = *.418*).
- No significant main effect for FiO_2 on MAP was present, with MAP not changing significantly in hypoxic stress [sample mean: 84.3 mmHg (± 4.4) to 86.4 mmHg (± 6.6), male-specific mean: 84.1 mmHg (± 5.1) to 87.9 mmHg (± 6.5), female-specific mean: 84.4 mmHg (± 4.3) to 84.9 mmHg (± 7.0), all p = *.164*].
- Lastly, no significant main effect for sex on MAP was seen (p = *.693*).
- Figure 1 displays mean resting HR in the different biological sexes when under normoxic and hypoxic conditions respectively.
- Figure 2 displays MAP in the different biological sexes when under normoxic and hypoxic conditions respectively.

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Figure 1 – *Mean heart rate in the different biological sexes when under normoxic and hypoxic conditions respectively.*

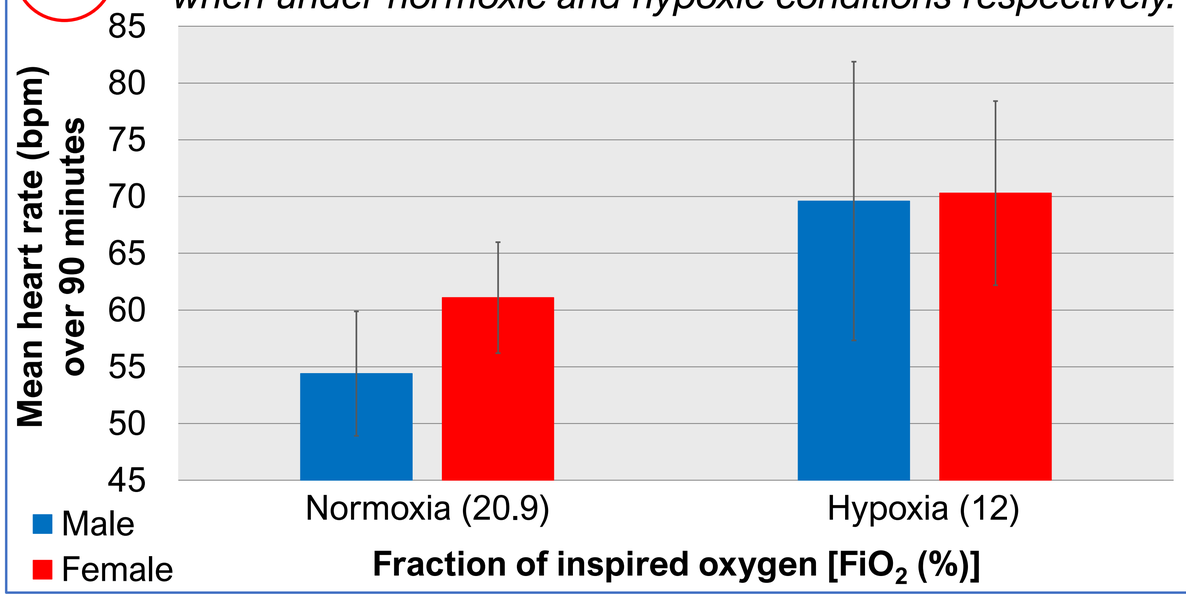

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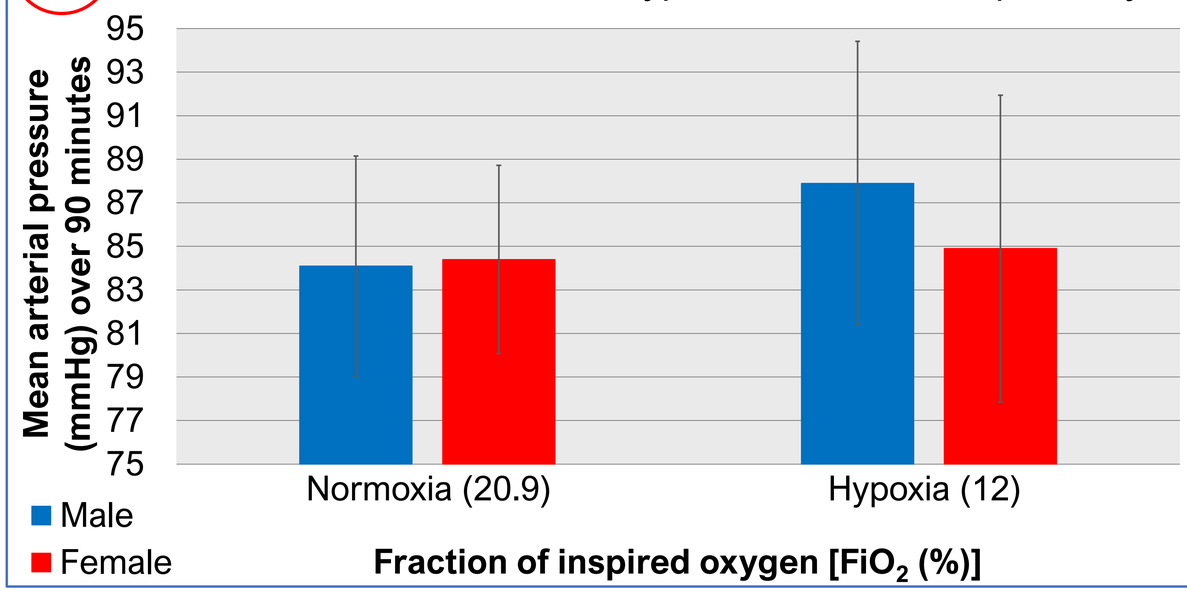
Figure 2 – *Mean arterial pressure in the different biological sexes when under normoxic and hypoxic conditions respectively.*



7 Conclusion and Future Directions

- **Summary:** In a convenience sample of ten individuals, an acute reduction in FiO_2 to 12.0% (hypoxia) of 90 minutes duration significantly increased HR (p = *.003*) and significantly decreased SpO_2 (p = < *.001*) compared to 90 minutes of FiO_2 20.9% (normoxia). However, no significant change to MAP (p = *.164*) was observed. Null hypothesis (a) is therefore partially rejected as only MAP displayed no significantly variation under hypoxia.
- **Summary:** No significant sex-based differences across all measured parameters were observed when under hypoxic stress (SpO_2: p = *.086*, HR: p = *.418* and MAP: p = *.693*). As such, null hypothesis (b) must be accepted.
- **Heart rate:** HR increased under hypoxia as expected due to sympathetic drive. Despite no observable sex differences in this study, literature does show that some may be present under a duration of 150 minutes *(Boos, Mellor, O'Hara, Tsakirides, & Woods, 2016)*.
- **Mean arterial pressure:** A physiological balance between the renin-angiotensin-aldosterone-system and sympathetic nervous system aiming to vasoconstrict and thus preserve central perfusion under hypoxia, versus peripheral vasodilation to conserve peripheral oxygenation, could explain why MAP did not significantly change under hypoxic stress. Literature both for and against MAP sex differences exist.
- **SpO_2:** With decreasing FiO_2, the partial pressure oxygen in the lungs falls and subsequently blood oxygen saturations also decline. With regards to the respiratory system, hyperventilation and pulmonary hypertension ensue to uphold the partial pressure of oxygen in the lungs and the ventilation-perfusion ratio *(Calbet & Lundby, 2009)*. Literature does support the presence of sex difference in respiratory parameters more broadly *(Sheel, MacNutt, & Querido, 2010)*.
- **Sample size and demographics:** studying a larger sample size may enable sex-based differences in the physiological outcomes to be observed *(Lenth, 2001)*.
- **Timeframe:** individuals often spend prolonged periods of time in high-altitude regions. Studying the acute, sub-acute and chronic changes to CV physiology in a hypoxic state would provide a useful insight for high-altitude casualty rescuers for example *(Mugele et al., 2020)*.
- **Alpine environment replication:** hypoxia is not found in isolation in high-altitude regions. A grave risk is posed by acute or prolonged cold exposure leading to peripheral cooling or hypothermia. Studying the physiological effects of hypoxic and cold jointly has received little scientific attention. This field subsequently holds substantial research potential, as do any potential sex-based differences here.
- **Parameters:** a limited number of parameters were assessed at rest in this study due to logistical constraints. More measures would allow for greater insight into alterations to CV physiology under hypoxic stress. For example, examining CV physiological changes under hypoxia and cold when active in recreationalist or athletes *(Buchheit et al., 2004)*.

8 References

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