GENDER CONSIDERATION IN EXPERIMENT DESIGN FOR AIR BREAK IN PREBREATHE

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ABSTRACT

Introduction: If gender is a confounder of the decompression sickness (DCS) or venous gas emboli (VGE) outcomes of a proposed air break in oxygen prebreathe (PB) project, then decisions about the final experiment design must be made. **Methods:** We evaluated if the incidence of DCS and VGE from tests in altitude chambers over 20 years were different between men and women after resting and exercise prebreathe protocols (1). Nitrogen washout during PB is our primary risk mitigation strategy to prevent subsequent DCS and VGE in subjects. Bubbles in the pulmonary artery (venous blood) were detected from the precordial position using Doppler ultrasound bubble detectors. The subjects were monitored for VGE for four min at about 15 min intervals for the duration of the altitude exposure, with maximum bubble grade assigned a Spencer Grade of IV.

DCS and VGE Outcomes with Gender and Type of Prebreathe

PB Condition	n	%DCS	%VGE	%Grade IV VGE
Resting				
male	453	15.6	43.9	25.1
female	96	11.5	24.0	10.4
χ^2 p-value		0.37	**0.00045**	**0.0027**
Exercise				
male	166	11.4	44.5	10.8
female	51	21.5	39.2	7.8
χ^2 p-value		0.10	0.60	0.72

Results: There was no difference in DCS incidence between men and women in either PB protocol. The incidence of VGE and Grade IV VGE is statistically lower in women compared to men after resting PB. Even when 10 tests were compared with Mantel-Haenszel χ^2 where both men (n = 168) and women (n = 92) appeared, the p-value for VGE incidence was still significant at 0.03. The incidence of VGE and Grade IV VGE is not statistically lower in women compared to men after exercise PB. Even when six tests were compared with Mantel-Haenszel χ^2 where both men (n = 165) and women (n = 49) appeared, the p-value for VGE incidence was still not significant at 0.90. **Conclusions:** Our goal is to understand the risk of brief air breaks during PB without other confounding variables invalidating our conclusions. The cost to additionally account for the confounding role of gender on VGE outcome after resting PB is judged excessive. Our decision is to only evaluate air breaks in the exercise PB protocol. So there is no restriction to recruiting women as test subjects.

INTRODUCTION

- Key to any experiment design is to hold all variables constant except the one in question.
- Statistical power is seriously reduced if two variables modify the DCS and VGE outcomes.
- In essence, you increase the chances of NO statistical result given confounding variables.

NULL HYPOTHESIS: Gender is not a confounder of DCS or VGE outcome in a proposed project about brief air break in resting and exercise PB.

METHODS

- Original design was to have 25 subjects perform resting PB and 25 subjects perform exercise PB.
- We want to know if a brief air break during oxygen PB increases the risk of DCS or VGE, and if the late or early break is more significant after either a resting or exercise PB.
- Exercise consists of 10 min of dual-cycle arm and leg ergometry at 75% of VO2 peak.
- Following the PB, subjects ascend to 4.3 psia in an altitude chamber and performs four hrs of EVA-simulation exercise.
- Measured outcomes are incidence of DCS and VGE.

ANALYSIS OF EXPERIMENT DESIGN

- Advancing age is often associated with increased risk of DCS and VGE so the same age distribution is planned between resting and exercise PB protocols to control for age.
- There is uncertainty if gender is a confounder of DCS and VGE outcome, or if there is an additional interaction between gender and exercise during PB.
- We evaluated past research data about resting (n=549) and exercise (n=217) PB in relation to gender.

RESULTS

TABLE I. DCS and VGE Results after **Resting Prebreathe**

variable	N = 96 females	N = 453 males	p-value
mean TR360 ± SD	1.58 ± 0.26	1.56 ± 0.26	0.59
mean altitude ± SD	5.83 ± 1.42 psia	5.07 ± 1.31 psia	<0.01
mean time ± SD	4.12 ± 1.41 hrs	4.02 ± 1.33 hrs	0.48
% DCS (n)	11.5 (11 / 96)	15.6 (71 / 453)	0.37
% VGE (n)	24.0 (23 / 96)	43.9 (199 / 453)	0.00045
% GIV VGE (n)*	10.4 (10 / 96)	25.1 (114 / 453)	0.0027
% GIV VGE (n)**	43.4 (10 / 23)	57.2 (114 / 199)	0.29

TR360 is a computed index of decompression dose (2).
* is proportion of Grade IV VGE based on total exposures.
** is proportion of Grade IV VGE based on those exposures with detected VGE.
Note: first three p-values from z-test, last four from χ^2.

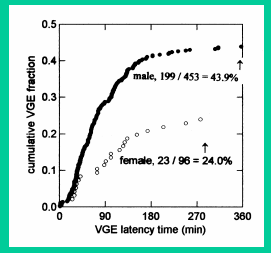

Figure 1. The cumulative VGE fraction for the first VGE detected in men and women who performed resting PB procedures increases to 43.9% for men and 24.0% for women. The difference in VGE incidence and Grade IV VGE incidence is statistically significant, $p < 0.01$ (see Table I). When 10 tests were compared with Mantel-Haenszel χ^2 where both men (n = 168) and women (n = 92) appeared, the p-value for VGE incidence is still significant at 0.03. Finally, based on Kaplan-Meier estimate of the survival function accounting for censored observations stratified by gender and using Mantel-Haenszel log-rank test, the survival curves between men and women are statistically different ($\chi^2 = 12.67$ with 1 df, $p < 0.001$). The incidence of DCS is not different in these data (15.6% for men versus 11.5% for women, p = 0.37).

TABLE II. DCS and VGE Results after **Exercise Prebreathe**

variable	N = 51 females	N = 166 males	p-value
mean ETR ± SD	1.91 ± 0.04	1.89 ± 0.04	<0.01
mean altitude ± SD	4.30 ± 0 psia	4.30 ± 0 psia	1.0
mean time ± SD	4.0 ± 0 hrs	4.0 ± 0 hrs	1.0
% DCS (n)	21.5 (11 / 51)	11.4 (19 / 166)	0.10
% VGE (n)	39.2 (20 / 51)	44.5 (74 / 166)	0.60
% GIV VGE (n)*	7.8 (4 / 51)	10.8 (18 / 166)	0.72
% GIV VGE (n)**	20.0 (4 / 20)	24.0 (18 / 74)	0.29

ETR is a computed index of decompression dose that accounts for exercise during prebreathe (2).
* is proportion of Grade IV VGE based on total exposures.
** is proportion of Gade IV VGE based on those exposures with detected VGE.
Note: first three p-values from z-test, last four from χ^2.

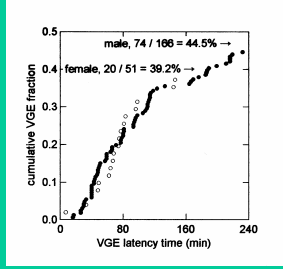

Figure 2. The cumulative VGE fraction for the first VGE detected in men and women who performed exercise PB procedures increases to 44.5% for men and 39.2% for women. The difference in VGE incidence is not statistically significant, $p > 0.05$ (see Table II). The cumulative VGE fraction for men (filled circles) is about the same as in Fig. 1, regardless if resting or exercise PB procedures were performed. But the cumulative VGE fraction for women (open circles) looks very different than in Fig. 1. When six tests were compared with Mantel-Haenszel χ^2 where both men (n = 165) and women (n = 49) appeared, the p-value for VGE incidence is still not significant at 0.90. Finally, based on Kaplan-Meier estimate of the survival function accounting for censored observations stratified by gender and using Mantel-Haenszel log-rank test, the survival curves between men and women are not statistically different ($\chi^2 = 0.33$ with 1 df, p = 0.56). Women are responding more so than men with different incidence of VGE and different cumulative VGE fractions depending on the type of PB procedure. The incidence of DCS is not statistically different in these data (11.4% for men versus 21.5% for women, p = 0.10).

CONCLUSIONS

- Gender is a confounder of VGE outcome after resting PB, but not DCS incidence.
- Gender is not a confounder of VGE or DCS incidence after exercise PB.
- To increase statistical power, and have no restrictions on gender it was decided to just perform exercise PB with a goal of 50% female participation.

DISCUSSION

- There is a "strong" desire by the NIH, and therefore NASA, to evaluate any biomedical pr with 50% women.
- Women will continue to have an important role in space walks (EVA's).
- If gender is a confounder of DCS or VGE outcomes, then one decision is to increase the sample size to essentially conduct a study within a study.
- This is a costly decision, but you are gaining additional insight for the cost and effort.
- If gender is not a confounder of DCS and VGE outcome, then there should be no restricti for inclusion.
- Our decision was to include women and eliminate the resting PB protocol where gender shown to confound the VGE outcome.
- We now satisfy the desire to include women in this biomedical research, maximize our statistical power to address the fundamental question about break in PB, and stay within th budget constraints of the proposal.

REFERENCES

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