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Prediction of Susceptibility to Acute Mountain Sickness Using Hypoxia-Induced Intrapulmonary Arteriovenous Shunt and Intracardiac Shunt Fractions

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14. ABSTRACT

We have spent the first year getting IRB approval and meeting with other experts in high altitude physiology and medicine to ensure that our research approach is solid. The following organizations have approved our protocol: a) Sacred Heart Medical Center IRB, the review board for Oregon Heart and Vascular Institute; b) Oregon Public Health and Safety (OPHS) and the University of Oregon Radiation Safety Committee; c) The State of Oregon; d) The University of Oregon IRB; e) The Department of Defense IRB. Robert Roach, Ph.D., Director of the Altitude Center at the University of Colorado School of Medicine provided us with an enormous amount of insight and assistance in ensuring that we will succeed in our aims. The hyperbaric chamber was set up and potential subjects have begun to be recruited. Two subjects have completed part of the protocol. The data thus far support our hypothesis that individuals who are susceptible to Acute Mountain Sickness (AMS) will have significantly greater amounts of shunt in hypoxia and/or have an intracardiac shunt such as a PFO and thus a greater degree of arterial hypoxemia than individuals who are not AMS susceptible.

15. SUBJECT TERMS
Acute Mountain Sickness Susceptibility, intrapulmonary shunt, intracardiac shunt

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Introduction:
Previous research has shown that some individuals are more susceptible to acute mountain sickness (AMS) than others and that the development of arterial hypoxemia hours before the onset of AMS can predict with great accuracy, who is will get sick upon further ascent (1, 2). However, why some people develop greater degrees of hypoxemia than others remains unresolved. We proposed that greater degrees of intrapulmonary and intracardiac shunting (through patent foramen ovale(PFO)) are responsible for the greater degree of arterial hypoxemia in AMS susceptible subjects compared to AMS resistant subjects. In this study we aim to identify which subjects will develop a greater degree of arterial hypoxemia in hypoxic environments in advance of ascent to high altitude. To do this we will evaluate hypoxia-induced intrapulmonary and intracardiac shunt using saline contrast echocardiography to determine bubble/shunt scores. We will also use nuclear medicine imaging to determine shunt fractions following acute exposures to hypoxia to correlate bubbles scores with shunt fractions. We will also determine which subjects develop AMS by exposing them to 10 hrs of 11.5% oxygen in an environmental chamber. This will allow us to link AMS score (susceptibility to AMS) to intrapulmonary and intracardiac bubble scores/shunt fractions and thus be able to predict who will get sick before ascent to high altitude using non-invasive, inexpensive ultrasound technology.

Body:
For **Task #1.2** "Detect shunt during 30 min hypoxic exposure with ultrasound – PFO- subjects." 18 PFO- subjects have completed saline contrast echocardiography while breathing hypoxic gas mixtures. – TASK COMPLETED.

For **Task #1.3** "Quantify shunt during hypoxic exposure with SPECT CT – PFO- subjects." This **Task** has been initiated. We expect to be working on this task for the next two quarters.

For **Task #2.1** Quantify AMS after 10 hr exposure to 11.5% O_2 - PFO- subjects" – All 18 PFO- subjects that have completed the acute exposure in **Task #1.2** have also completed the 10 hr exposure. Nine subjects were classified as AMS+ and 9 as AMS- (Fig. 1, solid circles). – TASK COMPLETED.

For **Task # 2.2** "Determine if shunt predicts AMS susceptibility – PFO- subjects" – Based on bubbles score obtained in **Task #1.2**, we have determined a PFO- subject's bubble score after breathing an FIO_2=0.14 (~ 3,320 m) for 30 min is the best to determine AMS susceptibility (Fig. 1). **Based on our current data we can predict with 67% accuracy whether PFO- subjects who have completed the saline contrast echo-cardiography while breathing an FIO_2=0.14, will be susceptible or resistant to developing AMS after 10 hr hypoxic exposure.** – TASK COMPLETED.

For **Task #3.1** "Detect shunt during 30 min hypoxic exposure with ultrasound – PFO+ subjects." 19 PFO+ subjects have completed saline contrast echocardiography while breathing hypoxic gas mixtures for 30 min. One PFO+ subject that had completed the **Task #3.1** had to be excluded after the subject revealed, after completing the study, that they had consumed excessive amounts of alcohol and had a hangover on the day prior to entering the chamber. Therefore, of the PFO+ subjects still included, 18 have completed **Task #3.1** – TASK COMPLETED.

For **Task #3.2** "Quantify shunt during hypoxic exposure with SPECT CT – PFO+ subjects." This **Task** has been initiated. We expect to be working on this task for the next two quarters.

For **Task #3.3** "Determine if shunt predicts AMS susceptibility – PFO+ subjects" –
19 of the 19 subjects in **Task #3.1** have also completed the 10 hr exposure (FIO_2=0.115) to determine AMS susceptibility. One PFO+ subject that had completed the study had to be excluded after the subject revealed, after completing the study, that they had consumed excessive amounts of alcohol and had a hangover on the day prior to entering the chamber. Therefore, of the PFO+ subjects still included, 18 have completed "AMS susceptibility after 10hr exposure." Of the 18 that have completed the 10hr hypoxic exposure, 7 have been classified as AMS susceptible and 11 have been classified as AMS resistant.

As we expect subjects that are PFO+ to demonstrate some level of hypoxia induced intrapulmonary shunt we have also looked at bubble score after breathing an FIO_2=0.14 for 30 min to determine if this can predict AMS susceptibility in PFO+ subjects as well as it does in PFO- subjects (Fig. 1). **Based on our current data we can predict with 83% accuracy whether PFO+ subjects who have completed the saline contrast echo-cardiography while breathing an FIO_2=0.14, will be susceptible or resistant to developing AMS after a 10 hr hypoxic exposure**. – TASK COMPLETED.

Summary:
In summary, a total of 36 subjects (18 PFO- & 18 PFO+) have completed a 30 min hypoxic exposure at FIO_2=0.14 and have also completed the 10 hr exposure (FIO_2=0.115). Of these, 16 subjects were classified as AMS+ (9 PFO-, 7 PFO+) and 20 were classified as AMS- (9 PFO-, 11 PFO+). Bubble scores achieved after breathing an FIO_2=0.14 for 30 min were **predictive of AMS susceptibility in 75% of all subjects**. For this prediction, PFO- subjects with a bubble score ≥ 2 and PFO+ subjects with a bubble score ≥ 3 after breathing a FIO_2 = 0.14 for 30min were predicted to be AMS+. Interestingly, of the subjects classified as AMS+, the PFO- subjects had an average LL score = 4 after 10 hrs and PFO+ subjects had an average LL score = 5.7 after 10hrs, which was statistically significantly difference.

AMS classification was determined using LL scores, ESQ scores, and headache severity as determined by the ESQ. AMS susceptible subjects met the criteria for AMS+ at least twice during the 10 hr exposure and/or were AMS+ at 10 hrs. Criteria used to determine AMS+ were as follows, a LL score ≥ 3 and an ESQ ≥ 0.7 OR a LL score ≥ 3 and ESQ ≥ 0.4 and a headache score ≥ 2 on the ESQ.

Intrapulmonary arteriovenous anastomoses, patent foramen ovale and nuclear medicine shunt fraction quantification

Post-doctoral fellow JJ Duke is working to complete **Task #1.3** "Quantify shunt during hypoxic exposure (14% and 11.5% O_2) with SPECT-CT" in PFO- subjects and **Task #3.2** "Quantify shunt during hypoxic exposure (14% and 11.5% O_2) with SPECT-CT" in PFO+ subjects. Since the Quarter 11 report we have collected data on two additional subjects in a separate pilot study that is being used to optimize the data collected for these Tasks (see **Figures 2 & 3**). The new subjects add strength to the relationship between bubble score obtained using saline contrast echocardiography and our nuclear quantification technique (**Figure 2**). Our data currently support the idea that the bubble scores are not linear with shunt fraction, however, our data clearly show that bubble scores greater than 1 result in significant increase I shunt fraction, i.e. greater that 1% of the cardiac output. **Figure 3** is an updated figure showing the difference in the percent of cardiac output flowing through intrapulmonary arteriovenous anastomoses while breathing normoxic and hypoxic gas, note we can detect significant differences.

Non-Task Specific Accomplishments:
Collaboration with Dr. Robert Roach, role of patent foramen ovale in symptoms of acute mountain sickness: field study

As reported for Quarter 10, Data collected on a collaborative trip to Mt. Chacaltaya Bolivia (5260m) were used to determine if our chamber study data may have applicability in the field as well. These data were consistent with our chamber data and we are in the process of writing up these data for publication. Submission is tentatively scheduled for 01 March 2014.

Key Research Accomplishments:

Completed Milestones:
Milestone #1 2, 4 – 6 & 8 are now completed.

- 36 subjects have completed both the prediction and chamber days, and we have been able to predict with ~80% accuracy which subjects will get sick within 10 hrs at 11.5% O_2
- Nuclear imaging techniques have been extensively refined and being used for data collection. We currently have data on n = 7 PFO- men and have discovered a body position effect that could explain some of our findings with saline contrast.
- Completed data collection for validation of our results in a field study.

12th Quarter Research Accomplishments:

- 18 PFO- and 18 PFO+ subjects completed both the prediction day breathing 14% O_2 for 30 min and the chamber day visit, breathing 11.5% O_2 for 10 hrs.
- Nuclear imaging techniques has been extensively refined and being used for data collection.
- Completed data collection for validation of our results in a field study.

Reportable Outcomes:

- Using saline contrast echocardiography, bubble score obtained after 15-30 minutes breathing 14% O_2 can predict with ~80% accuracy who will develop AMS during 10 hrs breathing 11.5% O_2.

- Using saline contrast echocardiography to detect the presence and determine the characteristics of a patent foramen ovale predicts that subjects who demonstrate intracardiac shunting without performing a Valsalva maneuver will develop AMS within 10 hrs at 11.5% O_2.
- PFO+ subjects are not more susceptible to AMS unless intracardiac shunting occurs without performing a Valsalva maneuver, in which case, we are able to predict that these individuals are AMS susceptible with 100% accuracy.

Conclusion:

After having 36 subjects breathe 14% O_2 for 30 minutes and detecting intrapulmonary and intracardiac shunt with saline contrast echocardiography we can predict with ~80% accuracy that subjects who achieve a bubble score of 3 after breathing 14% O_2 for 15-30 minutes are predicted to be AMS susceptible. **Using saline contrast echocardiography to detect the presence and characteristics of a patent foramen ovale, can predict AMS susceptibility with ~75% accuracy in PFO- and PFO+ combined.**

So what? For years now people have tried, without much success, to implicate the hypoxic ventilatory response in determining individual susceptibility to AMS and have achieved a ~50% rate of success. Alternatively, it is well known that shunt plays a negative role in pulmonary gas exchange efficiency and that decreased gas exchange efficiency is well correlated with AMS susceptibility. What isn't known is who will have the worst gas exchange efficiency and thus the greatest susceptibility to AMS. Our results clearly support the idea that bubble score and/or the presence of an intracardiac shunt such as a PFO can clearly be used to determine who will get sick at high altitude as we can currently predict AMS susceptibility with ~75% certainty in PFO- and PFO+ combined.

References:

1. **Burtscher M, Szubski C, and Faulhaber M**. Prediction of the susceptibility to AMS in simulated altitude. *Sleep Breath* 12: 103-108, 2008.
2. **Loeppky JA, Icenogle MV, Charlton GA, Conn CA, Maes D, Riboni K, Gates L, Melo MF, and Roach RC**. Hypoxemia and acute mountain sickness: which comes first? *High Alt Med Biol* 9: 271-279, 2008.

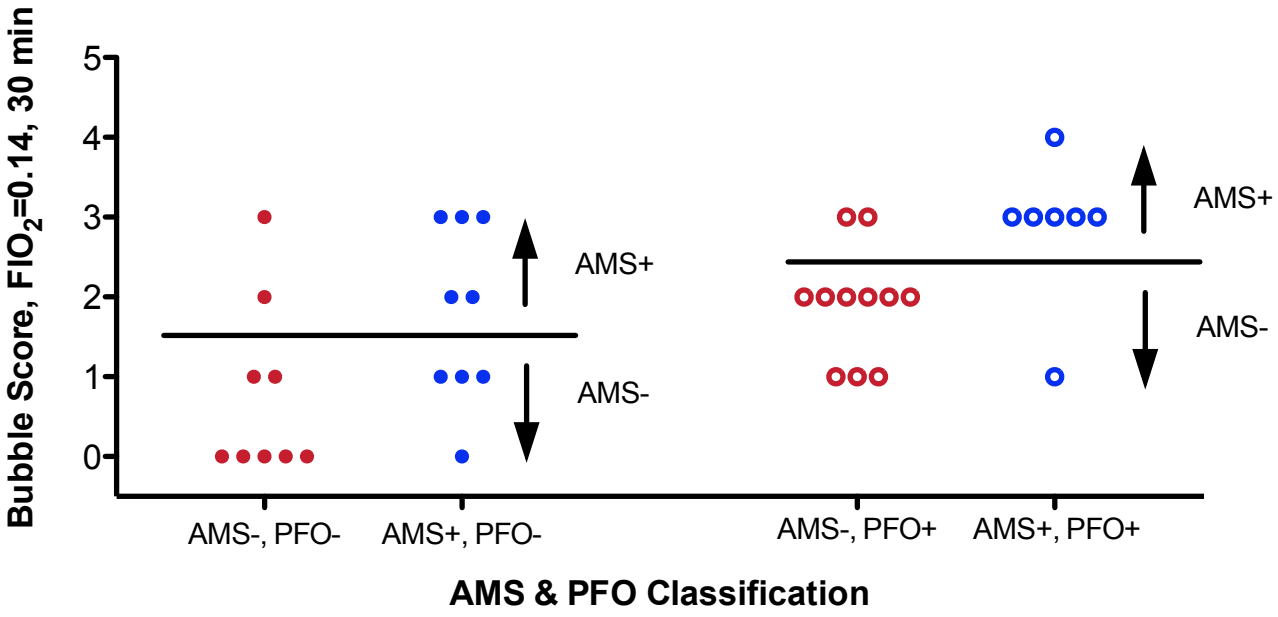

Fig. 1 shows bubble score obtained after breathing a hypoxic gas mixture (FIO_2=0.14) for 30 minutes. Each data point represents 1 subject and subjects are divided by AMS susceptibility; AMS susceptible (AMS+), represented in blue, or AMS resistant (AMS-), represented in red. PFO- subjects (n=18) are solid circles, PFO+ subjects (n=18) are open circles.

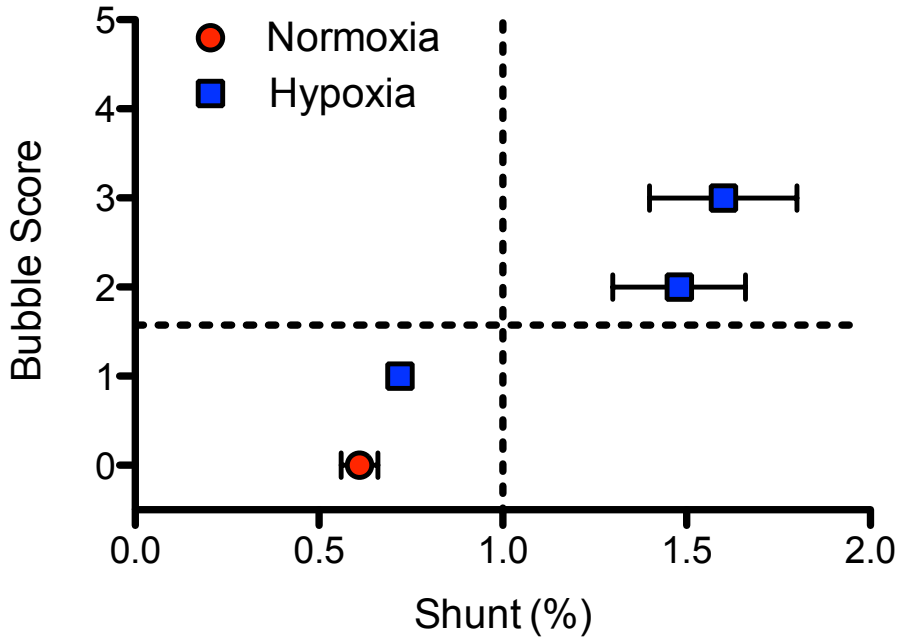

Fig. 2 Bubble score obtained via saline contrast echocardiography versus percent of cardiac output flowing through intrapulmonary arteriovenous anastomoses (shunt%; n=7). Note that as bubble score increases, shunt% also increases and that a significant amount of shunt% occurs once bubble score is >1.

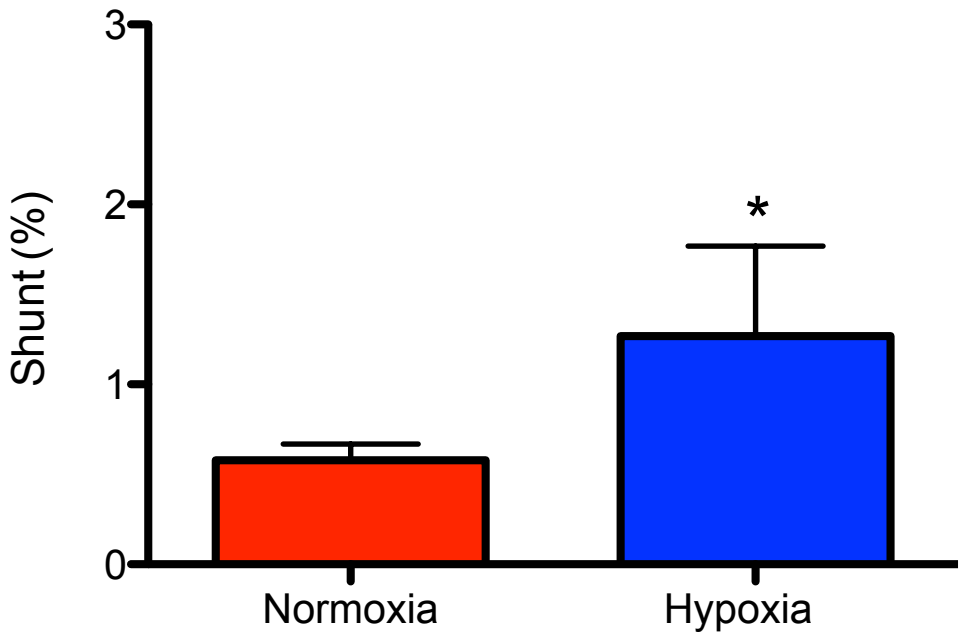

Fig. 3 Percent of cardiac output flowing through intrapulmonary arteriovenous anastomoses while breathing room air and hypoxic gas for 30 min each at rest. * Denotes a statistically significant difference between conditions (n=7).