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## **Relation of Patent Foramen Ovale to Acute Mountain Sickness**

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**Running head:**

Patent Foramen Ovale and Mountain Sickness

**Abstract**

Over 50% of people who rapidly ascend to extreme altitudes develop various symptoms known as acute mountain sickness (AMS), which rarely can be life threatening. It is unclear why some people are more susceptible to AMS than others. Our objective was to determine whether patent foramen ovale (PFO) is a risk factor for AMS. Subjects who had hiked to altitudes above 10,000' (~3,000 meters) on the John Muir Trail in California were recruited. Participants completed a questionnaire and two-physician adjudication was performed in regard to AMS status. A transcranial Doppler with agitated saline contrast injection was performed to evaluate the presence or absence of PFO. The primary outcome was the development of AMS. From 2016 to 2018, 137 hikers were recruited into the study. There was a higher prevalence of PFO in hikers with AMS 15/24 (63%) compared to hikers without AMS 44/113 (39%);  $p = 0.034$ . In the multivariate model, the presence of a PFO significantly increased the risk for developing AMS: OR 4.15, 95% CI 1.14 - 15.05;  $p = 0.030$ . In conclusion, hikers with a PFO had significantly higher risk of developing AMS relative to hikers

without a PFO. Clinicians should consider PFO a risk factor in people who plan to hike to high altitudes.

**Keywords:**

Patent foramen ovale; acute mountain sickness; right-to-left shunt

Over 50% of people who rapidly ascend to significant altitudes develop Acute Mountain Sickness (AMS) <sup>1-4</sup>. The symptoms, as defined by the Lake Louise Scoring System, include headache, gastrointestinal upset, fatigue, difficulty sleeping, and lightheadedness <sup>5,6</sup>. Up to 25% of individuals visiting only moderate altitudes, from 6,300' to 9,700', have become symptomatic <sup>7</sup>. AMS can progress to life threatening conditions such as High-Altitude Pulmonary Edema (HAPE) and High-Altitude Cerebral Edema (HACE) <sup>1,8</sup>. It is unclear why some people are more susceptible to AMS than others. A history of AMS, the number of days spent at high altitude during the preceding two months, and the rate of ascent are major independent determinants of the incidence of AMS <sup>3,9</sup>. These factors likely contribute to the degree and rate of onset of hypoxemia, which has been proposed to initiate the cascade of events leading to AMS <sup>10</sup>. Patent foramen ovale (PFO) is an embryologic

residual right-to-left cardiac shunt found in 18.0% – 27.3% of the general population <sup>11,12</sup>. Depending on the severity of the shunt, this can lead to hypoxemia. Previous evidence has implicated PFO in HAPE <sup>13</sup>. In this study, we investigated whether hikers who developed AMS were more likely to have a PFO than hikers who did not develop AMS symptoms.

## **Methods**

Subjects who had hiked to altitudes above 10,000' (~3,000 meters) were recruited to this study. The initial group had climbed all or part of the John Muir Trail (JMT) in California. The JMT varies in altitude between 4,000' in Yosemite Valley to 14,500' at the top of Mount Whitney. In 2015, the John Muir Trail Survey Group conducted a self-report analysis of 1,500 hikers <sup>14</sup>. These survey participants were asked to come to UCLA to complete an AMS questionnaire and to undergo a transcranial Doppler (TCD) study.

To increase enrollment, a second method for recruiting subjects was devised. Permission was obtained from the Inyo National Forest Service to recruit hikers along the Mount Whitney Trail during the 2017 and 2018 summers. Recruiters were stationed both at Whitney Portal (8,200') and at Whitney Trail Camp (12,000'). Hikers were provided information about the study and were consented prior to participating. Volunteers were directed to the Southern Inyo Hospital in Lone Pine,

California, at the foot of Mount Whitney. Upon arrival, they completed an AMS questionnaire. This included the original Lake Louise Acute Mountain Sickness Scoring System <sup>5</sup> as well as questions regarding acclimatization and premedication, and whether climbers had to stop their ascent due to symptoms or if their symptoms were alleviated by descent.

The original Lake Louise Acute Mountain Sickness Scoring System is a self-reported metric that quantitates the degree of discomfort experienced for the following five variables: headache, gastrointestinal symptoms (nausea, vomiting, and/or changes in appetite), fatigue and/or weakness, dizziness and/or lightheadedness, and difficulty sleeping; a total score cutoff for AMS is 3 or higher <sup>5</sup>. This score was revised in 2018 and difficulty sleeping was removed and replaced with an AMS functional score representing the impact an individual's symptoms had on their climb <sup>6</sup>.

Each questionnaire was reviewed, and two-physician adjudication was performed in regard to AMS status. The overall Lake Louise Acute Mountain Sickness Score was considered as was functional status. Adjudication was completed prior to PFO testing.

After antecubital sterilization, an intravenous line was inserted into a forearm vein and a TCD study was performed using a portable machine (Spencer technologies, Seattle, WA). TCD is the most sensitive method for determining if an individual has a right-to-left

shunt (RLS) when compared with direct probing of the septum during cardiac catheterization<sup>15,16</sup>. This test requires an intravenous injection of 8 mL agitated saline mixed with 1 mL of blood and 0.5 mL of air, while the middle cerebral arteries are assessed with Doppler ultrasound at a frequency of 2 MHz<sup>17</sup>.

Shunts were graded using the Spencer Logarithmic Scale, which counts the number of bubbles detected per minute in the middle cerebral arteries and ranges from 0-5, with 0 denoting the absence of a shunt and 5 denoting the presence of a large shunt (>300 bubbles/minute)<sup>15,18</sup>. Measurements were taken both at rest and following a Valsalva maneuver. Manometry was used to obtain consistency of Valsalva effort. The cutoff for a positive test is Grade 3, which corresponds to the presence of a PFO at cardiac catheterization<sup>15</sup>.

Although the TCD examination reveals the presence of a RLS, it does not distinguish between a PFO and pulmonary arteriovenous malformation. In our experience of 1500 TCD studies, the rate of pulmonary arteriovenous malformation is only 1% in patients referred without hereditary hemorrhagic telangiectasia, thus, a positive RLS examination by TCD was used to define the prevalence of PFO<sup>19,20</sup>.

Baseline characteristics were collected and compared between hikers with and without PFO; continuous and categorical variables were compared via t-test and Pearson  $\chi^2$ , respectively. A simple logistic



model was created for PFO predicting AMS. Additionally, a multivariate logistic regression model adjusted for age, gender, the use of AMS prophylaxis, and acclimatization was created. AMS prophylaxis included taking medications which can mitigate symptoms of high altitude, such as acetazolamide and/or a non-steroidal anti-inflammatory, prior to ascent <sup>21,22</sup>. Participants were considered acclimatized if they spent more than two days at altitude above 8,000' prior to attempting the Mount Whitney summit <sup>23</sup>.

Lake Louise AMS Scores were compared between hikers who were adjudicated as experiencing AMS versus those who were adjudicated as not having AMS via t-test. Additionally, this comparison was repeated with the categories of "Difficulty Sleeping" and "Fatigue and/or Weakness" removed; these modifications were made to reflect the conditions of hiking up to 22 miles/day to the top of Mount Whitney as well as the change in the Lake Louise AMS Score which occurred while this study was ongoing <sup>6</sup>. TCD Spencer grade was compared between those who developed AMS and those who did not develop AMS via Fisher's exact test.

This project was approved by the UCLA Institutional Review Board and the Inyo National Forest Ranger Office.

## **Results**

During the initial recruitment phase as well as during the summers of 2017 and 2018, 137 hikers were recruited into the study. Of these participants, 59 (43%) hikers were diagnosed with a PFO and 78 (57%) hikers were negative for a PFO. There were no significant baseline differences between these groups [Table 1].

Based on adjudication prior to TCD testing, 24 (18%) hikers had symptoms consistent with AMS and 113 (82%) hikers did not. There was a higher prevalence of PFO in hikers with AMS 15/24 (63%) compared to hikers without AMS 44/113 (39%) [Figure 1]. The presence of a PFO significantly increased the risk for developing AMS: OR 2.61, 95% CI 1.05 - 6.49;  $p = 0.038$ .

In the multivariate model, when adjusted for age, gender, AMS prophylaxis and acclimatization, the relationship between PFO and AMS became stronger: OR 4.15, 95% CI 1.14 - 15.05;  $p = 0.030$ ) [Table 2]. None of the other variables in the model were significant predictors for AMS.

Lake Louise AMS Scores were significantly higher in hikers who were adjudicated as having AMS compared to those who were adjudicated as having no AMS,  $7.43 \pm 3.04$  versus  $2.89 \pm 2.27$ , respectively;  $p < 0.0001$ . When the categories of "Difficulty Sleeping" and "Fatigue and/or Weakness" were removed, the scores remained significantly higher in the hikers who were adjudicated as having AMS compared to those who were adjudicated as having no AMS,  $4.67 \pm$

1.32 versus  $1.59 \pm 1.49$ , respectively;  $p < 0.0001$ ). TCD Spencer grade was significantly higher in those who developed AMS compared to those who did not develop AMS ( $p = 0.011$ ) [Figure 2].

## **Discussion**

In our study, hikers with a PFO had significantly higher risk (3x) of developing AMS relative to hikers without a PFO. This relationship was seen in our unadjusted model and was strengthened when we controlled for other variables that have previously been associated with AMS. Clinicians should consider PFO a risk factor in people who plan to hike to high altitudes.

There is prior work to suggest that PFO may play a role in HAPE. In 2006, Allemann et. al. demonstrated that a PFO was 4 to 5 times more likely to be identified in professional mountain climbers who were HAPE-susceptible compared to those who were HAPE-resistant. The authors demonstrated that climbers with a PFO developed a greater degree of hypoxemia compared to those without a PFO<sup>13</sup>. These findings supported a previously-postulated hypothesis regarding HAPE pathophysiology, the cyclic interplay of hypoxic pulmonary hypertension and right-to-left shunting<sup>24</sup>.

However, if the development of AMS was solely related to right-to-left shunting, one would expect to see a significant difference in oxygen saturations between those who develop AMS and those who do

not, particularly at altitude. We did not find this association but the oxygen saturation was obtained at rest, not during exercise.

Additionally, there was a significant portion of participants with PFO in our study who did not develop AMS. It is interesting to note there were a large number of hikers, both with and without AMS, who had a PFO in our study. The prevalence in our population was 43%, which is higher than typical rates seen in other populations <sup>11,12</sup>. The reason for this is unclear.

PFO is associated with a wide variety of clinical conditions, including stroke in young people, migraine headaches with aura, exacerbation of sleep apnea, platypnea-orthodeoxia syndrome, and decompression illness <sup>25-28</sup>. One unifying hypothesis for these associations is that an embolus or biochemical trigger, normally restricted to the venous circulation, enters the systemic circulation to produce these clinical syndromes. This hypothesis would also explain the multi-organ involvement in AMS due to excessive hypoxemia from the RLS.

The JMT and Mount Whitney have become very popular trails even for inexperienced hikers or backpackers. Thousands of hikers with various levels of experience attempt these trails every year <sup>29</sup>. It is possible to climb to the top of Mount Whitney (14,500') in one day, although the task is daunting with an elevation delta of 6500' and 11 miles in each direction. The Lake Louise AMS Scoring System does not

function well for single day hikes. This is due to both the “Difficulty Sleeping” and “Fatigue and/or Weakness” subcategories. Hikers often get only a few hours of sleep before they start out at Whitney Portal between 2 - 4 AM. It is not surprising that many describe poor sleep and excessive fatigue. These are not necessarily due to the hypoxemia of high altitude but to the degree of exertion and lack of conditioning of the hikers.

Due to these considerations, only three sections of The Lake Louise AMS Scoring System were used in the adjudication of AMS. The degree to which each hiker’s symptoms impacted their ability to continue climbing, or symptoms that improved upon descent, were also considered. In support of this approach, while this study was ongoing, a new Lake Louise Acute Mountain Sickness Scoring System was released, which replaced the “Difficulty Sleeping” category with a “Clinical Function Score” <sup>6</sup>.

One limitation of this study was the self-report questionnaires on symptoms of AMS. To help reduce biases and improve data capture, we reviewed responses with each participant prior to adjudication. However, participant surveys were not always complete. Another limitation of this study was its observational nature and the biases inherent in this design. The association between PFO and AMS does not prove causation; instead, our findings are hypothesis generating. Additional studies are needed to further elucidate the relationship

between PFO and AMS. Moreover, a prospective randomized trial of PFO closure versus standard therapy is warranted to determine whether PFO closure could alleviate the symptoms of AMS.

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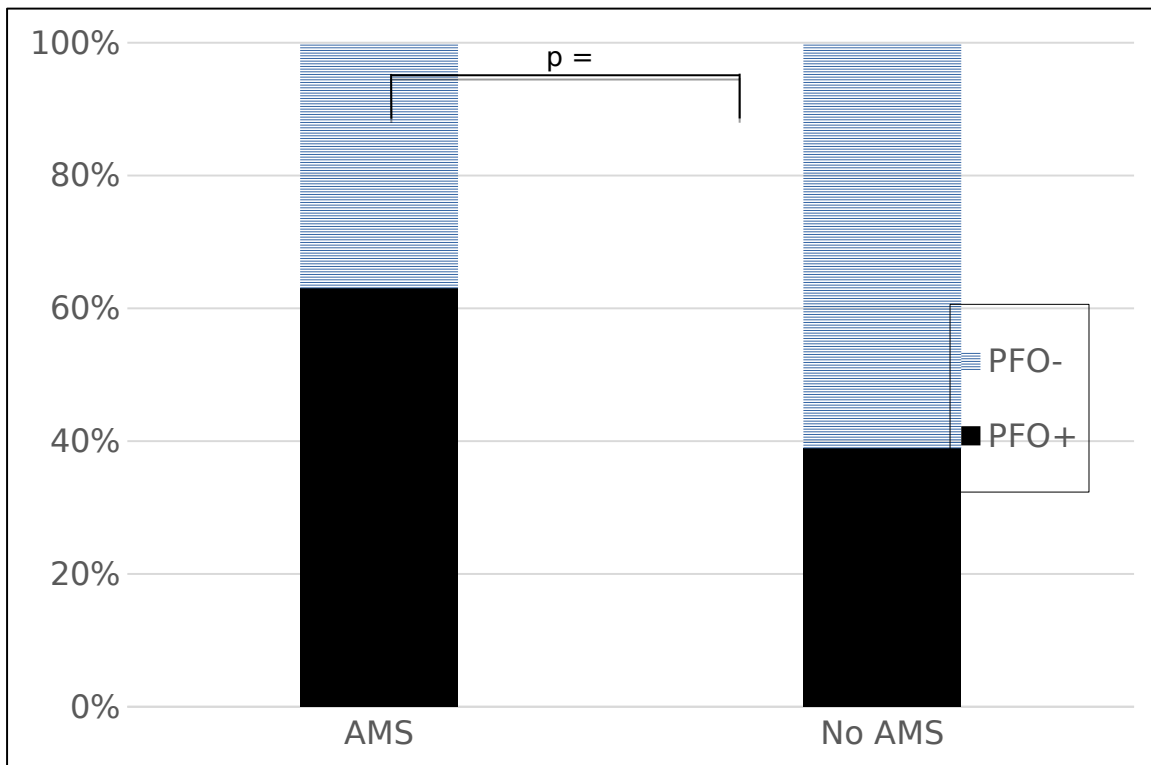
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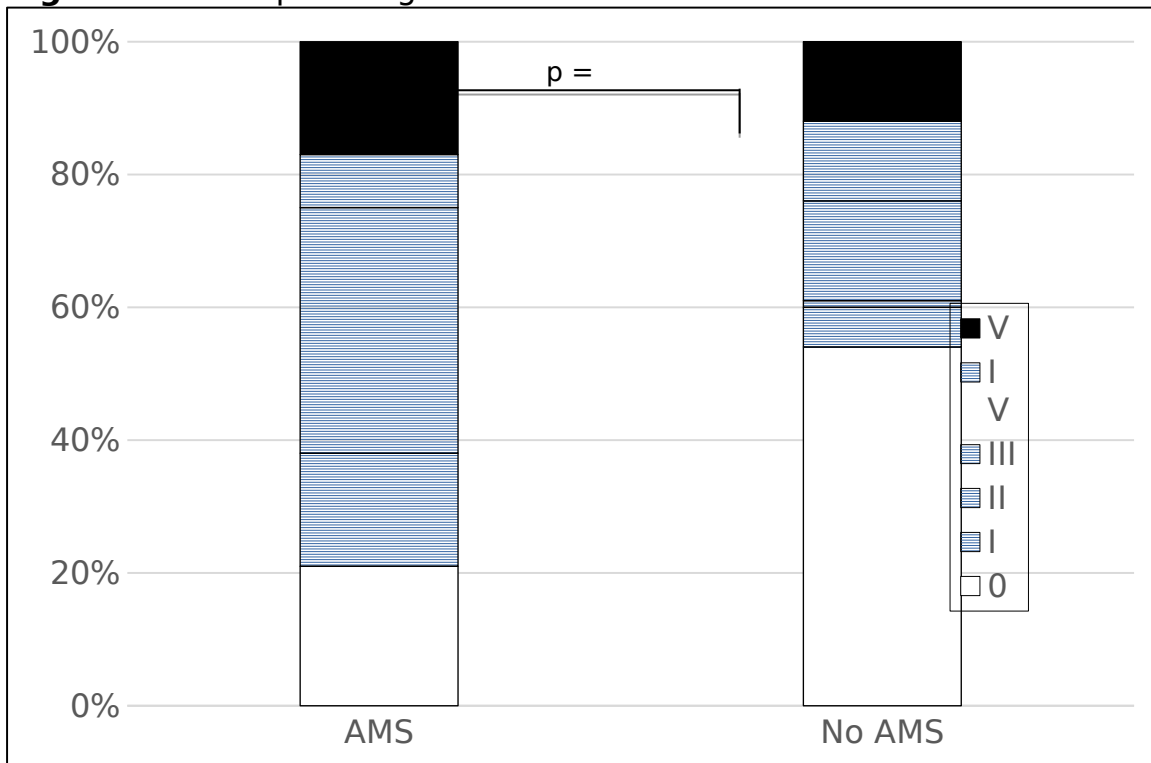
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**Figure 1:** Prevalence of PFO in hikers with and without AMS



\*Comparison via Pearson  $\chi^2$ , significant at level  $p < 0.05$ .

**Figure 2:** TCD Spencer grade in hikers with and without AMS



\*Comparison via Fischer's exact test, significant at level  $p < 0.05$ .

**Table 1:** Baseline characteristics

<b>Variable</b>	<b>Patent Foramen Ovale</b>		<b>P-value</b>
	<b>Yes (n = 59)</b>	<b>No (n = 78)</b>	
Age (years)	46.5 [42.6 - 50.5]	44.8 [41.4 - 48.2]	0.52
Women	20 (34%)	32 (41%)	0.39
Body mass index (kg/m <sup>2</sup> )	23.7 [22.7 - 24.6]	24.1 [23.3 - 24.9]	0.48
Pack weight (lbs)*	31.8 [26.5 - 37.1]	32.1 [28.3 - 35.9]	0.92
History of smoking (yes)	3 (6%)	5 (7%)	0.75
AMS prophylaxis (yes)	9 (15%)	15 (19%)	0.54
Acclimatization (yes) <sup>†</sup>	26 (58%)	27 (56%)	0.88
Saturation at 3,000' (%)	95.8 [95.3 - 96.2]	96.1 [95.7 - 96.5]	0.33
Saturation at 12,500' (%) <sup>‡</sup>	85.3 [80.2 - 90.3]	83.7 [77.9 - 89.5]	0.64

Continuous variables were compared via t-test, median [inter-quartile range]. Categorical variables were compared via Pearson  $\chi^2$ , n (%).

\*Based on data for n = 55 patients with overnight gear. <sup>†</sup>Based on data for n = 93 patients. <sup>‡</sup>Based on data for n = 15 patients.

**Table 2:** Multivariate model for AMS

	<b>OR</b>	<b>95% CI</b>	<b>p-value</b>
Age (per year)	1.00	0.96 - 1.04	0.126
Gender (female)	0.61	0.18 - 2.01	0.441
AMS prophylaxis (yes)	1.23	0.28 - 5.35	0.780
Acclimatization (yes)	0.51	0.16 - 1.68	0.270
<b>PFO (positive)</b>	<b>4.15</b>	<b>1.14 -</b>	<b>0.030*</b>

**15.05**

\*Significant at level  $p < 0.05$