Title

Patent Foramen Ovale and Acute Mountain Sickness

Journal

Cardiology Clinics, 42(4)

ISSN

0733-8651

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Publication Date

2024-11-01

DOI

10.1016/j.ccl.2024.01.009

OKPFO and Acute Mountain Sickness

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Source:
West B, Tobis JM. Patent Foramen Ovale and Acute Mountain Sickness. Cardiol Clin. 2024 Nov;42(4):521-524. doi: 10.1016/j.ccl.2024.01.009. Epub 2024 Feb 28. PMID: 39322342.

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Key words: Patent foramen ovale, right-to-left shunt, acute mountain sickness, high-altitude pulmonary edema

Key points*: List 3 to 5 key points of approximately 25 words each that summarize the main points of the article. Key points appear beneath the article title and authors in print and online.*

1. *Acute Mountain Sickness is thought to result from tissue hypoxia and can cause life-threatening illness in those who travel to altitude.*
2. *Patent foramen ovale is associated with right-to-left shunt and can worsen tissue hypoxia.*
3. *Patent foramen ovale is an independent risk factor for developing acute mountain sickness and high altitude pulmonary edema.*

Synopsis/Abstract: *Acute Mountain Sickness (AMS) commonly plagues people who travel to high altitude and can be life threatening. Clinically AMS is defined by a constellation of symptoms as outlined in the Lake Louise criteria. The underlying etiology is thought to be related to a decrease in partial pressure of oxygen leading to tissue hypoxia. Patent foramen ovale (PFO) bas been postulated to play a role in AMS through right-to-left shunt, which can worsen hypoxemia. Recent data demonstrate a higher prevalence of PFO in hikers with AMS, 15 of 24 (63%) compared with hikers without AMS, 44 of 113 (39%). The presence of a PFO significantly increased the risk for developing AMS: odds ratio 2.61, 95% confidence intervals 1.05 to 6.49; p = 0.038. These findings do not prove causation but instead are hypothesis-generating. Future studies are needed to further elucidate the relationship between PFO and AMS.*

Disclosure: None

Clinics Care Points:

- *When evaluating patients considering ascending to altitude, consider screening for patent foramen ovale as a risk factor for acute mountain sickness.*
- *In patients who develop acute mountain sickness, consider screening for patent foramen ovale.*

The history of acute mountain sickness (AMS) dates back at least 2000 years with a written report from the Chinese Han dynasty warning the Emperor Chung Ti against traveling over the Kilik Pass in the Karakorum Mountains at 4,827 m

(15,837 ft), which was a trade route between China and Afghanistan, because of the risk of getting sick[1]. The report states, "Next, one comes to Big Headache and Little Headache Mountains….they make a man so hot that his face turns pale, his head aches, and he begins to vomit. Even the donkeys and swine react this way."

Mountain sickness is currently described by the Lake Louise Criteria, but still relies heavily on the subjective presence of headache, and gastro-intestinal distress of anorexia, nausea, and vomiting. Hackett and co-workers in the 1970's described 278 hikers who climbed from the airport at Lukla at 2800m to Everest basecamp at 5356m without acclimating during their climb. Over 50% of climbers who ascended rapidly developed symptoms of acute mountain sickness[2]. In 1993, Honigman described that 25% of tourists in Colorado who ascended to relatively lower altitudes of 6300' to 9700', developed mountain sickness[3]. The most common complaints were headache 62%, insomnia 31%, fatigue 26%, shortness of breath 21%, dizziness 21%, loss of appetite 11%, and vomiting 3%.

Additionally in 1993, a consensus committee of respiratory physiologists met at Lake Louise, Canada and developed criteria for making the diagnosis of AMS[4]. Figure 1 presents the original criteria, a score of 3 or more was indicative of a diagnosis of AMS. The Lake Louise criteria were revised in 2018 and sleep disturbance was removed because 1) subsequent data showed that sleep disturbance correlated poorly with the other variables and 2) many studies of AMS have included only daytime exposures. Instead of sleep disturbance, a

functional grading was added to assess the severity of the symptoms[5]. Figure 2 provides the updated criteria. In this scale, AMS was considered to be mild with a score of 3-5, moderate with a score of 6-9, and severe with a score of 10-12.

Fig 1

1. Headache.	0	No headache
	1	Mild headache
	2	Moderate headache
	3	Severe headache, incapacitating
2. Gastrointestinal symptoms.	0	No gastrointestinal symptoms
	1	Poor appetite or nausea
	2	Moderate nausea or vomiting
	3	Severe nausea & vomiting, incapacitating
3. Fatigue and/or weakness.	0	Not tired or weak
	1	Mild fatigue/weakness
	2	Moderate fatigue/weakness
	3	Severe fatigue/weakness, incapacitating
4. Dizziness/lightheadedness.	0	Not dizzy
	1	Mild dizziness
	2	Moderate dizziness
	3	Severe dizziness, incapacitating
5. Difficulty sleeping.	0	Slept as well as usual
	1	Did not sleep as well as usual
	2	Woke many times, poor night's sleep
	3	Could not sleep at all

The original Lake Louise Criteria for acute mountain sickness.

fig 2

Headache
0—None at all
1—A mild headache
2—Moderate headache
3—Severe headache, incapacitating

Gastrointestinal symptoms
0—Good appetite
1—Poor appetite or nausea
2—Moderate nausea or vomiting
3—Severe nausea and vomiting, incapacitating

Fatigue and/or weakness
0—Not tired or weak
1—Mild fatigue/weakness
2—Moderate fatigue/weakness
3—Severe fatigue/weakness, incapacitating

Dizziness/light-headedness
0—No dizziness/light-headedness
1—Mild dizziness/light-headedness
2—Moderate dizziness/light-headedness
3—Severe dizziness/light-headedness, incapacitating

AMS Clinical Functional Score
Overall, if you had AMS symptoms, how did they affect your activities?
0—Not at all
1—Symptoms present, but did not force any change in activity or itinerary
2—My symptoms forced me to stop the ascent or to go down on my own power
3—Had to be evacuated to a lower altitude

A review article in the New England Journal of Medicine in 2013 by Bärtsch described the continuum of altitude sickness from the symptoms of acute mountain sickness to the development of high-altitude pulmonary edema (HAPE) and eventually high-altitude cerebral edema (HACE)[6]. Several authors describe the independent factors that may predispose to acute mountain sickness, which include: a prior history of AMS, days at altitude during the prior 2 months, and the rate of ascent[7,8].

The proposed mechanism of acute mountain sickness is that the decrease in the partial pressure of oxygen with increasing altitude produces progressive hypoxemia with subsequent tissue depletion of essential oxygen. In the lungs

and brain, this causes dysfunction of the vascular endothelium, with release of fluid into the interstitial spaces resulting in pulmonary and cerebral edema.

The potential connection with PFO and altitude related illness is that the right-to-left shunt associated with a PFO, especially during exertion and straining, could increase the hypoxemia, which would exacerbate the hypoxemia produced by the lower partial pressure of oxygen at higher altitudes.

To test the hypothesis that a PFO increases the likelihood of developing high-altitude pulmonary edema, Alleman and colleagues studied 35 experienced mountain climbers, 16 had a history of developing HAPE and 19 climbers who had no history of HAPE[9]. Transthoracic echocardiography with agitated saline was used to determine the presence of a right-to-left shunt. The authors found that climbers with a history of HAPE had a markedly increased frequency of PFO, 69%, compared with 16% in the climbers without a history of HAPE ($p<0.001$). The arterial saturation measured at 4560m was 73% in the HAPE susceptible climbers and 83% in the climbers who did not have an episode of HAPE. These observations are consistent with the hypothesis that a PFO predisposes to developing severe altitude illness.

We were suspicious that the same physiology might be present in the more common type of acute mountain sickness. To test this hypothesis, we assessed the frequency of PFO in hikers in California's Sierra Nevada range who climbed over Mount Whitney (14,500') after acclimating along the John Muir Trail and hikers who did not acclimate but rapidly ascended Mount Whitney from the eastern escarpment at Whitney portal (8000'). (Fig 3).

Mount Whitney, California at 14,500 ft in the middle. Trail camp at 12,000 ft is at the base of Mt. Whitney above the level of the tree line.

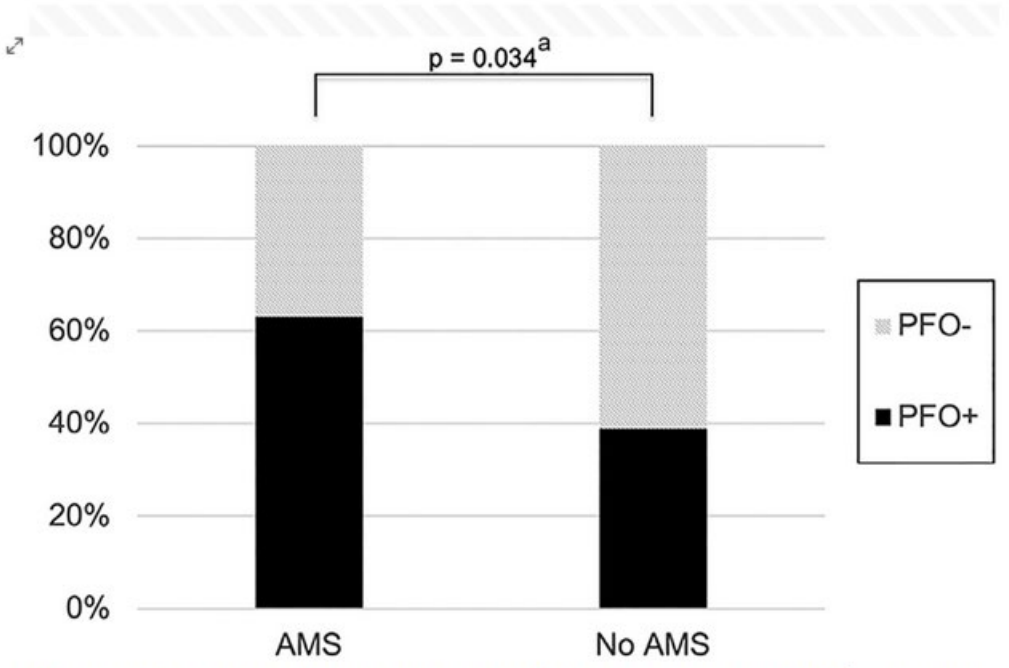
Subjects who had hiked to altitudes above 10,000’ (»3,000 meters) were recruited to this study. The initial group had climbed all or part of the John Muir Trail (JMT) in California. The JMT varies in altitude from 4,000’ in Yosemite Valley to 14,500’ at the top of Mount Whitney. In 2015, the JMT Survey Group conducted a self-reported analysis of 1,500 hikers[10]. 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 (8,2000) and at Whitney Trail Camp (12,000’). Hikers were provided information about the study and were consented before participating. Volunteers were directed to the Southern Inyo Hospital in

Lone Pine, California, in the Owens Valley below Mount Whitney. Upon arrival, they completed an AMS questionnaire. This included the original Lake Louise AMS Scoring System 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.

During the initial recruitment phase as well as during the summers of 2017 and 2018, 137 hikers were recruited into the study[11]. 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.

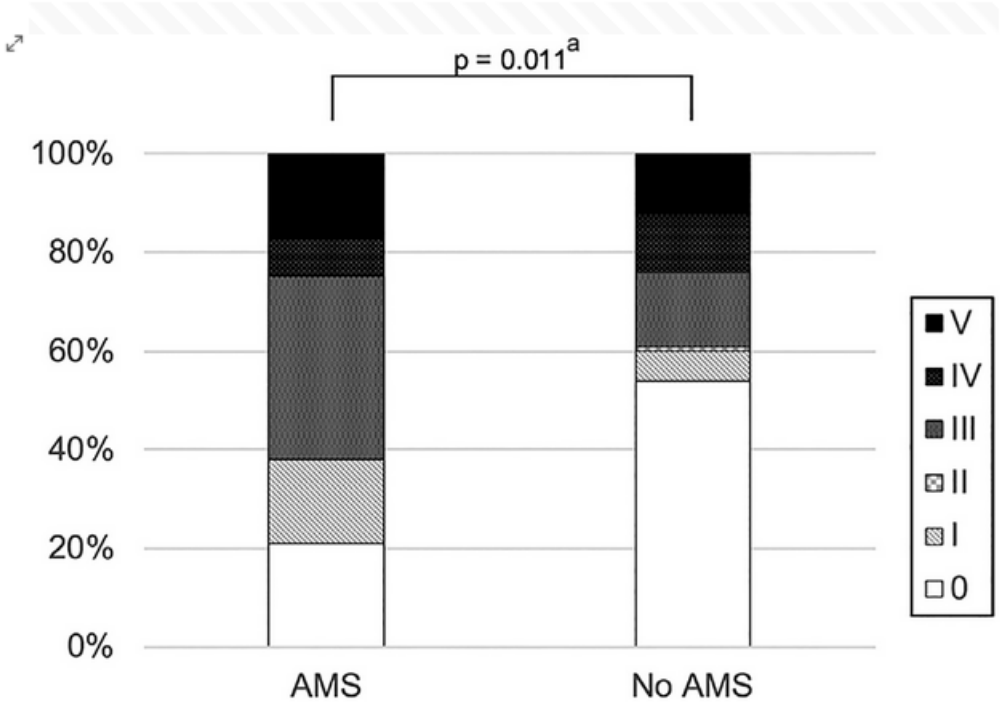
Based on adjudication before TCD testing, 24 (18%) hikers had symptoms consistent with AMS and 113 (82%) hikers did not. There was a higher prevalence of PFO in hikers with AMS, 15 of 24 (63%) compared with hikers without AMS, 44 of 113 (39%; Figure 4). The presence of a PFO significantly increased the risk for developing AMS: odds ratio 2.61, 95% confidence intervals 1.05 to 6.49; $p = 0.038$.



Prevalence of PFO in the subjects with acute mountain sickness (AMS) and those subjects without AMS. [a] Comparison via Pearson $\chi 2$, significant at level $P < .05$.

In the multivariate model, when adjusted for age, gender, AMS prophylaxis, and acclimatization, the relation between PFO and AMS became stronger: odds ratio 4.15, 95% confidence intervals 1.14 to 15.05; p = 0.03. 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 with those who were adjudicated as having no AMS, 7.43 ± 3.04 versus 2.89 ± 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 with those who were adjudicated as having no AMS, 4.67 ± 1.32 versus 1.59 ± 1.49, respectively; p < 0.0001). TCD Spencer grade was significantly higher in those who developed AMS compared with those who did not develop AMS (p = 0.011; Figure 5).



Transcranial Doppler (TCD) degree of right-to-left shunting in subjects with acute mountain sickness (AMS) and those subjects without acute mountain sickness (No AMS). [a] Comparison via Fischer's exact test, significant at level $P < .05$.

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 at 12,000', 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[12,13]. The reason for this is unclear.

The association between PFO and AMS does not prove causation; instead, our findings are hypothesis-generating. Additional studies are needed to further elucidate the relation 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. Clinicians should consider PFO a risk factor in patients who plan to hike to high altitudes.

Figure Legends

Figure 1. The original Lake Louise criteria for Acute Mountain Sickness

Figure 2. The 2018 modified Lake Louise AMS scale

Figure 3. Mount Whitney, California at 14,500' in the middle. Trail Camp at 12,000' is at the base of Mt. Whitney above the level of the tree line.

Figure 4. Prevalence of PFO in the subjects with acute mountain sickness (AMS) and those subjects without acute mountain sickness.

Figure 5. Trans-cranial Doppler (TCD) degree of right to left shunting in subjects with acute mountain sickness (AMS) and those subjects without acute mountain sickness (No AMS).

References:

1. Gilbert, DL. The first documented report of mountain sickness: the China or Headache Mountain story. Respir Physiol. 1983;52(3):315-26.

2. Hackett PH, Rennie D, Levine HD. The incidence, importance, and prophylaxis of acute mountain sickness. Lancet. 1976;2(7996):1149-55.

3. Honigman B, Theis MK, Koziol-McLain J, Roach R, Yip R, Houston C, et al. Acute mountain sickness in a general tourist population at moderate altitudes. Ann Intern Med. 1993;118(8):587-92.

4. Roach R, Bartsch P, Hacket P, Oelz O. The Lake Louise Acute Mountain Sickness Scoring System. Sutton J, Houston C, Coates G, editors. Burlington, VT: Queen City Press; 1993.

5. Roach RC, Hackett PH, Oelz O, Bartsch P, Luks AM, MacInnis MJ, et al. The 2018 Lake Louise Acute Mountain Sickness Score. High Alt Med Biol. 2018;19(1):4-6.

6. Bartsch P, Swenson E. Clinical practice: Acute high-altitude illnesses. The New England journal of medicine. 2013;368(24):2294-302.

7. Schneider M, Bernasch D, Weymann J, Holle R, Bartsch P. Acute mountain sickness: influence of susceptibility, preexposure, and ascent rate. Med Sci Sports Exerc. 2002;34(12):1886-91.

8. Davis C, Hackett P. Advances in the Prevention and Treatment of High Altitude Illness. Emerg Med Clin North Am. 2017;35(2):241-60.

9. Allemann Y, Hutter D, Lipp E, Sartori C, Duplain H, Egli M, et al. Patent foramen ovale and high-altitude pulmonary edema. Jama. 2006;296(24):2954-8.

10. Rozier L, Aksamit I, Meyer K. An unofficial acclimatization guideline for JMT Hikers. https://unofficialacclimatizationguideline.blogspot.com/p/survey-results.html, 2015.

11. West BH, Fleming RG, Al Hemyari B, Banankhah P, Meyer K, Rozier LH, Murphy LS, Coluzzi AC, Rusheen JL, Kumar P, Elashoff D, **Tobis JM**. Relation of Patent Foramen Ovale to Acute Mountain Sickness. Am J Cardiol. 2019 Mar 18.

12. West BH, Noureddin N, Mamzhi Y, Low CG, Coluzzi AC, Shih EJ, et al. Frequency of Patent Foramen Ovale and Migraine in Patients With Cryptogenic Stroke. Stroke. 2018;49(5):1123-8.

13. M. Khalid Mojadidi, MD; Scott C. Roberts, BS; Jared S. Winoker, BS; Jorge Romero, MD; David Goodman-Meza, MD; Rubine Gevorgyan, MD; **Jonathan M. Tobis**, MD. Accuracy of Transcranial Doppler for the Diagnosis of Intracardiac Right-to-Left Shunt: A Bivariate Meta-Analysis of

Prospective Studies. J Am Coll Cardiol Img. Published online February 19, 2014. doi:10.1016/j.jcmg.2013.12.011