Risks Associated With Traveling to High Altitudes for Patients with Coronary Artery Disease: A Systematic Review.

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Abstract
Background: The purpose of this paper is to systematically review the studies which look at the risk of cardiac function on patients with known coronary artery disease during travel to higher altitudes. The body of evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool developed by the GRADE Working Group.

Method: An exhaustive literature search was performed using PubMed, Medline, CINHAL and Web of Science through the Pacific University Library system. The following keywords were searched individually and in combination: coronary artery disease, (CAD), altitude, travel.

Results: Two studies were reviewed on this topic. The first study reviewed 22 patients and reported a resting heart rate increase of 19% at 3454m compared to that at low altitude. Maximum O2 uptake at 3454m decreased significantly going from 28.3 ml/kg/min at sea level to 22.9 ml/kg/min at altitude. Another study was a case control study that took 10 healthy nonacclimatized male controls and eight non acclimatized men with CAD and measured rate pressure products (RPP) a clinical indicator of myocardial oxygen. The RPP increased significantly at rest in hypoxic conditions and the ECG evaluation had four out the eight CAD patients with significant ST-segment depression, whereas all eight patients had ST-depression at simulated altitude.

Conclusion: CAD patients should be advised traveling to altitude with rest and exercise is a risk. The grade score was moderate for these studies.

Keywords: coronary artery disease, CAD, altitude, travel

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Risks Associated With Traveling to High Altitudes for Patients with Coronary Artery Disease: A Systematic Review.

Todd Heron

A course paper presented to the College of Health Professions in partial fulfillment of the requirements of the degree of Master of Science

Pacific University School of Physician Assistant Studies

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ABSTRACT

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INTRODUCTION

Background

Annually an estimated 35 million tourists visit the Western United States, 40 million visit the Alps and there are over 100 million tourists worldwide (Burtscher et al., 2001). Traveling to mountainous regions is becoming more of a leisure time activity for the whole family and may include skiing, hiking and mountain climbing. Visiting mountainous regions offers a wide range of outside entertainment that can be enjoyed by healthy people as well as those with chronic health conditions.

One of the top five health issues today is coronary artery disease (CAD). According to the World Health Organization (WHO, 2011) coronary vascular disease ranks as number one in death of adults in the world.

CAD is defined as a narrowing of the small blood vessels that supply blood and oxygen to the heart. This can lead to myocardial infarctions (MI), stable and unstable angina and even death. The concern for patients with CAD is the lack of blood and oxygen flow to the heart tissue in essence depriving the heart muscle of what it needs most. When traveling to higher altitudes the demand on the heart muscle takes on more stress for increasing oxygen to areas where it is needed. When moving from sea level to high altitude, there are reductions in atmospheric pressure, oxygen pressure, humidity, and temperature (Higgins, 2010). Wyss et al. (2003) observed a significant decrease in exercise induced coronary flow reserve in CAD patients during inhalation of a hypoxic gas
mixture corresponding to an altitude of 2500m compared with baseline measurements at 450m. This would suggest that patients with CAD and/or a history of cardiac events may have to work harder with limited resources in order to compensate for the change in altitude. The responsibility of the heart is hindered by the lower oxygen pressure at altitude that is needed for maintaining stability in the body during this time of transition to higher altitude. Lower oxygen pressure means the heart is being stressed, and tries to compensate for that, by working harder. The heart beats faster and pumps harder trying to increase more oxygen to the tissue, but there is only so much oxygen the heart can bring in, due to the limited oxygen carrying capacity of hemoglobin that is found within red blood cells of patients at sea level. So more red blood cells are produced which increases volume load on the heart thereby increasing more cells moving through the already narrowed arteries which can potentially result in an MI.

Flow is linked to oxygen demand. This is necessary because the heart has very high basal oxygen consumption (8-10 ml O$_2$/min/100g) and the highest A-VO$_2$ difference of a major organ (10-13 ml/100 ml) (Klabunde, 2007). In non-diseased coronary vessels, whenever cardiac activity and oxygen consumption increases, there is an increase in coronary blood flow (active hyperemia) that is nearly proportionate to the increase in oxygen consumption (Klabunde, 2007). Adenosine is an important go-between of increased blood flow and auto regulation. It serves as a metabolic link between oxygen consumption and coronary blood flow (Klabunde, 2007).
Limiting or conflicting information has been given on the topic of traveling to high altitude (defined as greater than 500m) and having a prior cardiac event such as an (MI). Conflicting results show that living at high altitude with CAD actually helps in lowering an MI event where as another study showed living at high altitude was an environmental risk factor (Baibas, Trichopoulou, Voridis, & Trichopoulos, 2005; Al-Huthi, Raja’a, Al-Noami, & Rahman, 2006). With CAD patients who live at high altitude there was a 15 year cohort study from 1981 to 1996 by Baibas, et al. (2005) there were 1198 inhabitants (504 men & 646 women) that were researched to see if there was a relation to total and coronary mortality for residence in mountainous versus lowland areas within Greece. This study took into account multiple variables including, age, smoking, drinking, systolic blood pressure, glucose, cholesterol, uric acid and cell volume. Coronary cumulative mortality was somewhat lower among the mountainous village residents than among lowland residents.

One study cautiously recommends performing physical exercise even at moderate altitude (Wyss et al., 2003) and yet, another study suggests that residents in mountainous regions with increased activity under moderate hypoxia seemed to have a “protective effect” from total and coronary mortality (Baibas et al., 2005). A recommendation from (Tuttle et al. 2010) states both ascending to altitude and exercising at altitude can be safe in patients with stable coronary artery disease or a remote history of an acute coronary event.
PURPOSE

The purpose of this paper is to systematically review the effect that traveling to higher altitudes has on the cardiac function of patients with known CAD. In addition, the body of evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool developed by the GRADE Working Group (Guyatt et al., 2008)

METHOD

An extensive literature search was performed using PubMed, Medline, CINHAL and Web of Science through the Pacific University Library system. The following keywords were searched individually and in combination: coronary artery disease (CAD), altitude, travel. The search was limited to the English language, results published since 2000 and human subjects. This resulted in 17 articles. Duplicates, narrative reviews, editorials and letters to the editor were excluded. The remaining six articles were included in this systematic review involving randomized trials and cohort studies. Studies were taken from all over the world.

RESULTS

The first study reviewed was performed by Schmid et al., (2006) who enrolled 22 patients with a history of an MI to be revascularized either by percutaneous coronary angioplasty or by coronary bypass surgery. All participants underwent eight to 10 weeks of cardiac rehab following their MI. They
were then given a stress test at 540m in Switzerland and then rapidly ascended a railway to simulate the “touristic” approach for altitude which brought the participants up to 3454m. At this altitude they were given another stress test to compare to the original stress test. All beta blocker medicines were held for one week to give maximal effect of stress testing. The authors reported a resting heart rate increase of 19% at 3454m compared to that at low altitude (Schmid et al., 2006). In correlation to maximum oxygen uptake (VO2 max), which is the body’s ability to transport and use O2 during aerobic activity, this increased equally during sub maximal exercise at both altitudes but at 3454m it decreased significantly going from 28.3 ml/kg/min at sea level to 22.9 ml/kg/min at altitude. Lactate levels, levels showing hypoxia in the blood, were also taken at two minute intervals which showed marginal differences until six minutes which indicated a significant increase at altitude of 3.4 (Range .5-2.2 mmol/L) compared to that of 2.3 (Range .5-2.2 mmol/L) at sea level. At peak, lactate levels were actually higher at sea level (7.1) than at altitude (6.9) but not shown to be of statistical significance (p=0.715). Despite these changes, no complications were observed and no stress tests had to be stopped prematurely. No evidence of stress induced ischemia or arrhythmias were noted during the stress test and recovery (Schmid et al., 2006).

The next study reviewed was conducted by Wyss et al. (2003) who studied the “Influence of Altitude Exposure on Coronary Flow Reserve.” This was a case control study that took 10 healthy nonacclimatized male controls and eight non acclimatized men with CAD and simulated hypoxic conditions during rest,
adenosine stress testing and exercise. The healthy controls were simulating altitude at 4500 m where as the CAD patients would simulate altitude at 2500 m.

One of the outcomes measured was rate pressure products (RPP); a clinical indicator of myocardial oxygen demand is calculated by multiplying the heart rate by the systolic blood pressure. The RPP in both groups increased significantly at rest in hypoxic conditions. However, when adenosine was introduced into the equation, hypoxia was more pronounced in CAD patients. RPP had no significant change at maximal exercise in normoxia and hypoxia. With ECG evaluations, four out the eight CAD patients had significant ST-segment depression, whereas all eight patients had ST-depression at simulated altitude, two patients experienced angina pain at baseline, but seven did so at altitude (Wyss et al., 2003). The authors reported that myocardial blood flow (MBF) in controls at altitude had a 24% increase compared to that at baseline which was similar to that of the CAD participants. When exercise was introduced there was a 38% increase in reserve coronary blood flow (CBF) for controls whereas for CAD patients it actually decreased 18%. There seemed to be no significant change for either the CAD or control patients when adenosine was introduced into the study.

**DISCUSSION**

Clinicians should be able to advise patients on the effects of travelling to higher altitudes. Taking into account different studies is important because it gives a perspective of how to best treat the patient and what one can do for recommendations. Data was used for traveling from high to low altitude with use
of exercise and rest to give the best possible information for the treatment of a patient. This systematic review has attempted to answer what effect a change in altitude can have for CAD patients, giving the practitioner the best knowledgeable answer to give a patient. Could a practitioner have confidence in counseling a CAD patient for traveling to higher altitude?

Schmid et al. (2006) studied patients with stable CAD going to high altitudes. This study confirmed stress put on the heart by comparing rest and exercise at sea level and higher elevation which could potentiate ischemia or an acute MI event.

Stress was put on the heart just at rest in higher elevations, in which the heart rate increased 19%. This would indicate a compensatory mechanism by the heart for O2 when someone with CAD is taken to altitude. The body is adjusting its supply and demand for the decreased O2 on the myocardial tissue. This study did take into consideration removing beta blocker medications in order to get maximal effort out of the injured heart from the participants; this could possibly help understand why there was such an increased heart rate in CAD participants.

In exercise testing, increased systolic BP at different stages signified increased heart tissue demand. When hypoxic conditions arise, sympathetic responses occur and can cause coronary vasoconstriction in regions with abnormal endothelial vasomotor control and can further compromise myocardial oxygen delivery (Wyss et al., 2003). With increased BP and increased sympathetic response it would seem reasonable to advise BP control especially
during an activity that involves exercise. The decrease in O2 of 19% suggests that there would be a limited supply of O2 on an already damaged heart and tissues. With an increase in heart rate and then a lower pressure of O2 for tissues it would seem rational to suggest there is another risk factor in traveling at elevation. Increased lactate blood levels coincide with lower partial pressure at altitude and a decrease in O2 uptake on the heart. All these variables indicate stress on the heart and there is a decrease of O2 in the blood with increased stress in an elevated location to supply the heart.

There were some limitations in this study (Baibas et al., 2005). The first being that only lactate blood samples were taken and no hematocrit or hemoglobin levels were sampled. These samples would help specify levels of capacity to carry O2. Although not specified, it is possible that not all patients were from the same climate. “Living in a mountainous village as compared with residence in the lowland ones exhibited an apparent “protective” effect…” (Baibas et al., 2005 p.276). Having a patient from a higher altitude in which they are already acclimatized and exercising them at an elevation that they are used to would result in the reported numbers being less significant. Second, they had taken patients, revascularized them with bypass surgery or angioplasty and rehabilitated them for 8-10 weeks, there were no indications of other co-morbidities, and Schmid et al. (2006) stated that the data do not apply to patients at a higher risk than that of the population studied. This suggests that patients with lower ejection fraction, left ventricular dysfunction, with incomplete revascularization or not consistently rehabilitated may not benefit from the
findings of this study. Third, patients who did participate in this study were limited to 20 men and two women not giving us help on what to recommend for women when approached with this question. Future studies should deal with men and women more equally. Last, the study was also in a controlled environment with professionals on hand to maintain and monitor stress levels. It is possible that the estimate of effects given could be underestimated due to the controlled environment. Exposure to outside influences such as weather could have impact on the patient’s well being.

Wyss et al. (2003) studied the information for CAD patients at moderate altitude of 2500m as opposed to the control group at 4500m using rest, adenosine and exercise induced hypoxia. The rate pressure product (RPP) with sea level versus high elevation is significantly higher at rest for both control and CAD participants. This is indicating that there is a demand for myocardial O2. After adenosine was introduced to CAD participants, a medicine that decreases the heart rate in a high altitude versus low altitude simulation, the RPP was found to be significant representing an increase in demand for O2 on the heart. Two explanations are still possible on this, first, one can still have a flow of blood to the areas of the heart, but in a hypoxic condition have a decrease of O2 being delivered to tissue. Second, it is also possible that MBF was exhausted due to a decrease in coronary flow rate. Partial pressure is a key factor when a patient is taken to a higher elevation.

Some limitations of the present study were noted (Wyss et al, 2003). First, the participants were using a bicycle stress test as opposed to the treadmill
stress test which is not typical physical activity in the mountains. Hiking, downhill skiing and even walking around town are the typical touristic forms of movement. Maximal workload may have been limited by this scenario of the bike to achieve a capacity equal of that to travelers at higher elevations. Second, it was stated in the article that “Data was acquired in the post exercise period” (Wyss et al. 2003). This circumstance of data collection would indicate that maximal output of hemodynamics had fallen before the data was obtained. The time period for participants to stop exercising and the time period to collect data would decrease actual information due to the recovery state of the participant. Lastly, the mean age for controls was 23 whereas the mean age for CAD patients was 56 and no women were involved in this study. The younger age of the control group could result in the difference in their numbers without any other consideration. If participants in the control group were better matched to the actual participants in age the numbers would have been closer in MBF and RPP.

During this review, the GRADE classification was used evaluate the quality of evidence in the studies. The outcomes reviewed were increased stress on the heart at rest and with exercise at high altitudes. The observational studies assisted in the findings of high versus low elevation stress on the heart for CAD patients in both exercise and at rest. Two studies qualified to be in the low quality category based on a case control study as well as a cohort study.

The quality of evidence is classified by the GRADE Working Group into one of four levels: very low, low, moderate, and high. The interpretation of each classification is as follows:
High quality— Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality— Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality— Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality— any estimate of effect is very uncertain (Guyatt et al., 2008, 926).

The outcomes evaluated in this review are increased stress on the heart at rest and with exercise (Appendix, Table 1). For the outcome measurement of increased stress on the heart at rest, two observational studies were evaluated. The two observational studies had a starting grade of low but were upgraded based on controlling of confounders. The resulting grade for the outcome was moderate, indicating that the two studies presented had enough of a comparison in their results to be of value in medical decision making.

For the outcome of increased stress on the heart with exercise, two observational studies were evaluated. The first was a cohort study by Schmid et al. (2006) which studied the methods of exercise and rest at sea level and at elevation the second was from Wyss et al. (2003) which was a case-control study using exposure to altitude in determining coronary reserve.

The overall GRADE across both outcomes was determined to be moderate with the upgrading of the confounders. This is interpreted to mean that
these sources were reliable and could be used to rely on in this question of traveling to high altitudes with CAD.

This study set out to find a legitimate answer to the question “Would it be a risk to send a patient to higher elevation knowing that they have CAD?” This topic is clinically relevant since there are multiple family members with CAD going to higher elevations for leisure time activities including walking and exercise. As patients proceed to higher elevations there is an increase in partial pressure that stresses the heart for maximal uptake of O2 and increases heart rate to deliver blood to the body and tissues. This stress on the heart could potentiate a cardiac event for that CAD patient. There is a risk in traveling to higher altitudes according to the studies reviewed. CAD patients should be given the information for risks involved when traveling to higher elevations and should take precautions. Furthermore, those with CAD should be advised to refrain from exercising at higher elevations. Each patient is different and should be considered to have specific needs met before advising them to proceed to higher altitude. The Grade supported certain reliability in the results of the studies by assessing a moderate score. Increasing research is likely to have an important impact in the estimate of effect and may change the estimate.
REFERENCES


### APPENDIX A

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<th>Comparison</th>
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<th>Quantity and type of evidence</th>
<th>Findings</th>
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<th>Grade of Evidence for Outcome</th>
<th>Overall GRADE of Evidence</th>
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<td>(2) Observational</td>
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