Special Topic:  
Aging and High Altitude

Going High with Heart Disease:  
The Effect of High Altitude Exposure in Older Individuals and Patients with Coronary Artery Disease

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Abstract

Levine, Benjamin D. Going high with heart disease: The effect of high altitude exposure in older individuals and patients with coronary artery disease. High Alt Med Biol 16:89–96, 2015.—Ischemic heart disease is the largest cause of death in older men and women in the western world (Lozano et al., 2012; Roth et al., 2015). Atherosclerosis progresses with age, and thus age is the dominant risk factor for coronary heart disease in any algorithm used to assess risk for cardiovascular events. Subclinical atherosclerosis also increases with age, providing the substrate for precipitation of acute coronary syndromes. Thus the risk of high altitude exposure in older individuals is linked closely with both subclinical and manifest coronary heart disease (CHD). There are several considerations associated with taking patients with CHD to high altitude: a) The reduced oxygen availability may cause or exacerbate symptoms; b) The hypoxia and other associated environmental conditions (exercise, dehydration, change in diet, thermal stress, emotional stress from personal danger or conflict) may precipitate acute coronary events; c) If an event occurs and the patient is far from advanced medical care, then the outcome of an acute coronary event may be poor; and d) Sudden death may occur. Physicians caring for older patients who want to sojourn to high altitude should keep in mind the following four key points: 1) Altitude may exacerbate ischemic heart disease because of both reduced O2 delivery and paradoxical vasoconstriction; 2) Adverse events, including acute coronary syndromes and sudden cardiac death, are most common in older unfit men, within the first few days of altitude exposure; 3) Ensuring optimal fitness, allowing for sufficient acclimatization (at least 5 days), and optimizing medical therapy (especially statins and aspirin) are prudent recommendations that may reduce the risk of adverse events; 4) A graded exercise test at sea level is probably sufficient for most clinical decision making and will allow for assessment of exercise capacity, and provokable ischemia. Given these considerations, most older individuals with CHD should be able to tolerate exposure to high altitude safely, and with minimal increased risk.

Key Words: aging; altitude; coronary artery disease; hypoxia; sudden cardiac death

Introduction

Despite recent advances in the management of cardiovascular diseases and declines in overall death rates from CVD, ischemic heart disease remains the largest cause of death in older men and women in the United States, and across the western world (Lozano et al., 2012; Roth et al., 2015). The process of atherosclerosis progresses with age, and thus age is the dominant risk factor for coronary heart disease (CHD) (generally MI, coronary heart disease death, or revascularization) or cardiovascular disease (CHD+stroke) in virtually any algorithm used to assess risk for cardiovascular events, including the recent AHA pooled cohort risk equations (Goff et al. 2014). Subclinical atherosclerosis also increases with age (Cheng et al. 2003), providing the substrate for precipitation of acute coronary syndromes. Thus the risk of high altitude exposure in older individuals is linked inexorably with both subclinical and manifest coronary artery disease.

Effect of High Altitude on the Circulation

Ascent to high altitude reduces the partial pressure of oxygen, causing systemic hypoxia and reduced oxygen...
availability to the tissues. The acute and chronic cardiovascular response/adaptation to high altitude is beyond the scope of this essay, and is reviewed in detail elsewhere (Baggish et al., 2014). A summary of the key adaptations is provided in Figure 1 of this review.

A few points deserve emphasis: 1) the acute response to high altitude is dominated by sympathetic activation from stimulation of arterial chemoreceptors that is prominent, proportional to the magnitude of hypoxia, and is sustained or even enhanced with increasing duration at high altitude (Hansen and Sander, 2003; Saito et al., 1988). An example of this physiology is provided in Figure 2 (Hansen and Sander, 2003); 2) this global alerting response is then modulated by local vasodilator mechanisms that preserve systemic O2 delivery with remarkable precision (Rowell et al., 1986; for review, see Casey and Joyner, 2012); 3) with acclimatization, stroke volume at rest and with exercise falls prominently, though the regulation of cardiac output in response to increases in metabolic demand remains remarkably preserved (Sutton et al., 1988).

**Problems at High Altitude for Patients with Cardiovascular Disease**

There are four major problems associated with taking patients with CHD to high altitude: 1) The reduced oxygen availability may cause or exacerbate symptoms; 2) The hypoxia and other associated environmental conditions (exercise, dehydration, change in diet, thermal stress, emotional stress from personal danger or conflict) may precipitate acute coronary events; 3) If #1 or #2 occur and the patient is far from advanced medical care, then the outcome of an acute coronary event may be poor; and 4) Sudden death may occur.

![Diagram showing cardiovascular hemodynamic changes at sea level, acute hypoxia, and chronic hypoxia](image_url)
Functional capacity

As far as symptoms are concerned, the most obvious and indeed universal symptom is a reduced work capacity. Maximal oxygen uptake decreases by ~1% for every 100 m above 1500 m (Fulco et al., 1998). The magnitude of this reduction is remarkably similar (and predictable) in the elderly (Levine et al., 1997) as well as in patients with known coronary artery disease (CAD) (Erdmann et al., 1998; Schmid et al., 2006), independent of the presence of depressed ejection fraction (Erdmann et al., 1998). Such a reduction in exercise capacity is generally well tolerated in younger individuals who have substantial functional reserve such that even a 20%–30% reduction in work capacity (at an altitude of 3500–4500 m) will have a minimal impact on relatively low intensity activities such as mountain walking or climbing. However, for an older patient with CAD, who might have a peak VO\(_2\) of only 20 mL/kg, such a reduction might bring peak work capacity below that required for activities of daily living (~4 METS = 14 mL/kg). Therefore knowledge of a patient’s functional capacity at sea level, as well as the anticipated altitude exposure and planned activity levels are essential to making recommendations regarding travel to high altitude for older individuals and patients with CAD.

Provocable ischemia

In addition to knowledge of functional capacity, it is also important to determine whether, and at what workloads, patients develop provocable ischemia during exercise. Exercise-induced ischemia is fundamentally an imbalance between oxygen supply and oxygen demand to the myocardium. Both sides of this equation are altered at altitude. Most obviously, the reduction in oxygen content under hypoxic conditions reduces oxygen transport. In addition, the driving pressure for oxygen from the capillaries into the muscle cells is reduced, even if O\(_2\) content is partially restored by acclimatization (reduced plasma volume increasing Hgb concentration, and respiratory alkalosis increasing Hgb binding of oxygen). Because the heart has a high O\(_2\) extraction at rest, the only way it can increase O\(_2\) availability is by increasing perfusion (though the RV has a greater extraction reserve than the LV (Zong et al., 2005).

In normal individuals, coronary blood flow clearly increases with high altitude hypoxia (Kaufmann et al., 2001; Wyss et al., 2003; Beaudin et al., 2011). Perhaps less well appreciated is the fact that atherosclerosis can lead to paradoxical vasoconstriction in the face of stresses like exercise (Gordon et al., 1989). Hypoxia may have similar effects (Arbab-Zadeh et al., 2009), particularly in the setting of marked sympathetic activation, thereby exacerbating the reduction in oxygen supply to the heart during hypoxic exposure. Figure 3 shows quantitative coronary angiograms from a patient with normal coronary anatomy demonstrating appropriate vasodilation in response to severe hypoxia; in contrast, a patient with coronary atherosclerosis demonstrates paradoxical vasoconstriction in response to the same degree of hypoxia.

Indeed, before the advent of routine exercise stress testing, many in the cardiology community used the “Levy test” which employed 10% FIO\(_2\) in patients with symptoms of angina to provoke ischemia (Fig. 4) (Levy et al. 1939). The combination of intense sympathetic activation and coronary vasoconstriction may provide the conditions for takotsubo or “stress” cardiomyopathy (Vaccaro et al., 2014). Anecdotal reports suggest that this syndrome may be not uncommon at high altitude (Warren Johnson, personal communication), though true epidemiological incidence/prevalence data are lacking.

Hypoxia also alters the demand side of the equation. As shown in Figure 1, the heart rate for any given work rate is higher at altitude than it is at sea level (even though maximum HR may be lower after acclimatization). Blood pressure, although reduced with very acute exposure, is also

FIG. 2. Mean voltage neurograms in three individual subjects at baseline, after 30 days acclimatization to 5260 m, and after return to sea level. Each spike represents a burst of efferent muscle sympathetic nerve activity (SNA). Note marked increase in SNA at altitude, which persists in recovery. Figure reproduced with permission from Hansen and Sander, 2003.
elevated, thereby increasing the rate-pressure product and myocardial oxygen demand (internal work) for any external work rate. Thus for patients with known or subclinical CAD, exercise at high altitude causes ischemia at lower absolute external work rates (because of increased myocardial demand) and lower internal work rates (because of coronary vasoconstriction) (Levine et al., 1997). For patients who have normal LV function, and have been well vascularized, either with coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), there is little evidence that exercise with acute high altitude exposure causes ischemia or arrhythmias that were not previously present at sea level,

**FIG. 3.** Top panel shows quantitative coronary angiograms from a patient with normal coronary vessels at rest in normoxia (left) and hypoxia (right) demonstrating normal vasodilation. Bottom panels from a patient with atherosclerosis shows paradoxical vasoconstriction. Figure reproduced with permission from Arbab-Zadeh et al., 2009.

**FIG. 4.** Original recordings from Levy et al., 1939 showing ECG at baseline with normal ST segments (left panel), after 1 and 5 minutes of 0.10% FIO2 hypoxia equivalent to an altitude of ~ 5000 m (middle two panels), which show progressive ST segment depression, followed by recovery (last panel). Figure reproduced with permission from Levy et al., 1939.
even at altitudes as high as 3500 m (Schmid et al., 2006). Even for patients with documented CAD and mildly depressed LV function (average ejection fraction: 0.39) who do not have ischemia at sea level, there does not appear to be an unexpected ischemia at altitude, at least up to 2500 m (Erdmann et al. 1998). It is important to emphasize, though, that patients may underestimate the intensity of exercise associated with some mountain activities. For example, Holter monitoring of downhill skiers showed that the majority of individuals achieved HR > 80% of predicted maximum (Grover et al., 1990).

There are not enough data to provide firm evidence-based recommendations as to how to manage older patients with chronic cardiovascular disease at altitude. Given the above physiology, it seems reasonable to ensure that patients with known cardiovascular disease be in stable condition, with all risk factors controlled as well as possible at sea level. It is the author’s opinion that patients who are fit and active at sea level without symptoms, do not need a screening exercise test as an absolute precondition for travel to high altitude. However, the older the patient, the more extensive the risk factor burden, and the lower the patient’s functional capacity, the more strongly a case could be made for testing. For example, a 50-year-old man with a right coronary stent after unstable angina 5 years previously, who has normal LV function, runs regularly, has no angina, with excellent risk factor control is likely to do well, and the information obtained from an exercise test is not likely to alter patient outcome since there is no evidence that any intervention (such as PCI or CABG) would benefit the patient. This argument is similar to that demonstrated for cardiovascular risk assessment prior to elective vascular surgery in patients with peripheral vascular disease. (McFalls et al., 2004)

Conversely, a 70-year-old patient with incomplete revascularization, stable angina, limited work capacity at sea level, and impaired LV function, probably should have an exercise test at sea level—not to drive revascularization, but to assess functional capacity, the presence of provokable ischemia, and perhaps alter therapy (e.g., increase beta blockade dosage, add a calcium channel blocker) to optimize performance and minimize ischemia at altitude. Other factors such as the planned activity level at altitude, rate of ascent, adequacy of acclimatization, all might be mitigating factors that could alter the final decision.

For patients with chronic hypertension, there exists the possibility of worsening control of hypertension because of high altitude-induced sympathetic activation. Conversely, there is also a risk of orthostatic hypotension due to hypoxic vasodilation, though this problem generally occurs early in the time course of altitude exposure (Nicholas et al., 1992). Recent unpublished data from trekkers in Nepal suggest that, although BP may be slightly elevated at night in patients with pre-existing hypertension, episodes of severe hypertension are rare (Young et al., 2015). Given the recent recommendations to be more permissive of blood pressure, especially in older individuals (James et al., 2014), there is probably little risk for moderate hypertension in the elderly, especially for short-term exposures (weeks) typical of a high altitude sojourn. Therefore for patients who are well controlled at sea level without complications, this author does not recommend routine monitoring of blood pressure during short duration sojourns.

For more prolonged exposure (months) or for those patients that may either be poorly controlled at sea level, or have suffered serious consequences of hypertension (such as a stroke, or hypertensive emergency), then a plan for regular monitoring and enhanced therapy should blood pressure increases be more than moderate (i.e., sustained SBP > 180) would be reasonable. Drugs aimed at the renin–angiotensin–aldosterone system may be relatively less effective at high altitude (Parati et al., 2014), and drugs aimed at the sympathetic nervous system may be more so (Bilo et al., 2011), though comparative effectiveness studies have not been performed in patients with hypertension at altitude (Velasco et al., 2014). Such studies would be fruitful areas of investigation.

Although intense exercise transiently increases the risk for cardiac events [for example, Siscovick et al., (1984); for review, see Parker and Thompson (2012)], high degrees of fitness are protective, both against sudden death (Siscovick et al., 1984; Parker and Thompson, 2012) as well as cardiovascular events, even in patients with substantial atherosclerosis (LaMonte et al., 2006). This protective effect of regular exercise may be in part mediated by improved endothelial function and flow mediated vasodilation (Hambrecht et al., 2000). Altitude acclimatization also appears to improve and perhaps abolish paradoxical vasoconstriction due to hypoxic exercise (Levine et al., 1997), so that ST depression occurs at the same rate-pressure product at altitude after acclimatization as compared to acute exposure.

Although overall blood coagulation does not appear to be upregulated at altitude (Bärtisch et al., 1989), there is a modest effect of acute altitude exposure augmenting platelet activation (Lehmann et al., 2006), so that the risk of a platelet mediated spontaneous acute coronary syndrome (ACS) may be slightly higher at altitude than it is at sea level. However, this risk has not been assessed in clinical trials. Certainly the use of aspirin should be strongly considered for all patients with CHD who go to altitude, as well as the use of thienopyridines, though the risk of dual antiplatelet therapy must be balanced against the risk of bleeding, especially in remote environments where trauma may be a significant risk.

**FIG. 5.** Data from Bürtscher et al. 1993 showing the relationship between number of sudden cardiac deaths (SCDs) in the Austrian Alps (left axis, solid bars for males and females), and the % of the total number of SCDs (right axis, solid line) as a function of 10 year age groupings (horizontal axis). Figure reproduced with permission from Bürtscher et al., 1993.
Risk of remote environments

In this context, it is important to emphasize that regardless of the specific effect of altitude exposure, for patients with CAD, events happen, even to those who appear to be at relatively low risk. Indeed, more than half of patients who present with their first MI would not have been considered to be at high risk by standard Framingham criteria (Akoshah et al., 2003), the so-called “prevention paradox.” This problem of the difficulty in predicting events, especially in the short term as would be relevant for a patient with CAD wanting to sojourn to altitude, raises one of the most important aspects of managing such patients; that is, the often remote environments in which such activities take place. If a patient has an ACS in a major US city, emergency medical services will likely be there in minutes, and a patient can be in a high level cath lab with a “door-to-balloon” time of <1 hour. If an event happens on a trek or climb in a remote part of the world, no such advanced help is available and the patient will experience the true “natural history” of their disease. All patients with cardiovascular disease, including those who just have risk factors, must then accept the risk of having an acute cardiovascular event far from advanced medical assistance and without modern intervention. Of course, there are many risks associated with foreign travel to high altitude environments, and this one of remoteness must be factored into the complex risk-benefit assessment equation that is different for every patient.

Sudden cardiac death

The most catastrophic event that can occur in patients with CAD is sudden cardiac death (SCD). According to the “Biological Model of Sudden Death” elaborated by Myerburg et al. (1989), underlying structural abnormalities including myocardial infarction (both acute and chronic), cardiomyopathic processes (hypertrophic, ischemic, dilated), or intrinsic electrical abnormalities are influenced by functional abnormalities such ischemia/reperfusion, systemic factors (exercise, hypoxia), and neurohumoral effects (sympathetic activation), ultimately leading to circulatory collapse. For older patients, such as older athletes (Maron et al. 1980), the most common underlying medical problem causing SCD is coronary artery disease. Autopsy studies have confirmed that for exertion-related SCD, the majority of individuals have plaque rupture as the cause, with a smaller minority having only plaque hemorrhage, and a larger minority having no change in plaque (Burke et al., 1999). During high altitude activities such as skiing, the majority of SCDs occur in patients with a previous MI (~40%) or cardiovascular risk factors such as hypertension (50%), and the vast majority (>95%) did not do any regular exercise prior to their skiing vacation (Burtscher et al., 2000).

Perhaps the best estimates of the risk of SCD during mountain activities come from the work of Martin Burtscher in Austria who has tracked SCD in the Alps for decades. A key figure from his NEJM paper (Burtscher et al., 1993) is reproduced in Figure 5.

A few points are worth emphasizing from these data: 1) the risk of SCD in the mountains begins to climb steeply after age 40 for men, and is highest in the group > age 60, similar to the epidemiology of CAD; 2) the risk of SCD is extremely low in females of all ages. The investigators estimated the number of individuals exposed in this period of time and calculated the incidence as one SCD for every 780,000 hiking hours and one SCD/1,630,000 skiing hours (Burtscher et al., 1993). More recently, Ponchia examined similar data from the Italian Alps and estimated 1 SCD/2,940,000 mountain hours (Ponchia et al., 2006), with one “cardiac event,” including non-fatal MI, of 1/957,000 mtn hours. These figures should be compared with the data from joggers in Rhode Island, where Paul Thompson estimated 1 death/3,000,000 jogging hours (Thompson et al., 1982). Thus the risk of mountain activities at altitude may be slightly greater than the risk of jogging at sea level.

Most recently, the Burtscher group has shown that even one night of acclimatization at an altitude > 1300 m prior to exercising at altitude may lead to a nearly 6-fold reduction in the risk of sudden cardiac death in the mountains (Lo et al., 2013). Therefore, fitness and acclimatization remain the best protective measures to limit the risk of adverse events at high altitude in patients with CAD.

Conclusion

In summary, the key take home messages from this essay are presented in Table 1. Older patients who may be harboring subclinical CHD, or patients with known and manifest disease, can generally tolerate high altitude exposure well, given an adequate amount of fitness, and stable disease with optimal medical therapy. The remoteness of many high altitude environments must be taken into account when a patient is trying to weigh the risks and benefits of a high altitude sojourn.

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Author Disclosure Statement

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References


Table 1. Take Home Messages

| 1) Altitude may exacerbate ischemic heart disease because of both reduced O_2 delivery, as well as paradoxical vasoconstriction; |
| 2) Adverse events, including acute coronary syndromes and sudden cardiac death are most common in older unfit men, within the first few days of altitude exposure; |
| 3) Ensuring optimal fitness, allowing for sufficient acclimatization (at least 5 days), and optimizing medical therapy (especially statins and aspirin) are prudent recommendations that may reduce the risk of adverse events; |
| 4) A graded exercise test at sea level is probably sufficient for most clinical decision making and will allow for assessment of exercise capacity, and provocative ischemia. |


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