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People with Pre-existing Cardiovascular Conditions Going to the Mountains

Intended for physicians, interested non-medical persons and trekking or expedition operators

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Hamlet: Give me that man
That is not passion's slave, and I will wear him
In my heart's core, ay, in my heart of heart
As I do thee

Hamlet, act 3, scene 2, 71-74.
William Shakespeare

Content

1 Introduction

1.1 Rational

Mountainous regions occupy 40 million km^2 and account for approximately 27% of the Earth's surface. It is estimated that 38 million people live permanently above 2500m, with an additional 100 million visitors travelling to mountain regions for work and recreation each year [1].

Mountains are inherently dangerous. Mountaineering activities are typically characterized by strenuous exercise in a particular environment where the combination of falling barometric pressure and consequent ambient hypoxia, temperature and humidity together with increases in solar radiation and wind speed may trigger a series of important physiological responses that affect principally the respiratory, cardiovascular, neuro-endocrine and renal systems. These events can contribute to serious physical problems in subjects at risk [1]. The exact altitude at which these physiological changes affect cardiopulmonary performance varies between individuals, however significant changes typically begin at >2.500m.

Despite the challenges faced by falling barometric pressure, regular physical activity and exposure to moderate altitudes up to 2500m under certain conditions may contribute to well-being and longevity [2, 3].

Literature on whether people with pre-existing cardiovascular conditions should go to high altitude is limited. Making a decision depends upon what altitudes are likely to be encountered, activities chosen, the nature of the pre-existing disease and other factors such as the general medical condition of the subject.

1.2 Epidemiological data

Cardiovascular diseases (CVDs) are the commonest cause of death globally: more people die annually from CVDs than from any other cause. Mortality data for 2007 show that CVDs accounted for 33.6% of all deaths, or 1 in every 2.9 deaths in the United States [4, 5].

CVDs are a group of disorders of the heart and blood vessels that include:

- coronary heart disease – disease of the blood vessels supplying the heart muscle
- cerebro-vascular disease - disease of the blood vessels supplying the brain
- valvular heart disease – damage to the heart valves from rheumatic fever, bacterial infection or degenerative processes (ischaemia, sclerosis, myxomatosis)
- congenital heart disease - malformations of heart structure existing at birth
- congestive heart failure - inability of the heart to supply sufficient blood flow to meet the body's needs by different causes

Heart attacks and strokes are usually acute events and are mainly caused by a blockage that prevents blood from flowing to the heart or brain. The most common reason for this is a build-up of fatty deposits on the inner walls of the blood vessels that supply the heart or brain. Strokes can also be caused by bleeding from a blood vessel in the brain or from blood clots [4, 5].

Because of the development of modern transportation systems, ascent to high altitude has become very easy. Since mountain activities are very popular, it is speculated that a high percentage of people travelling to high altitude may have CVDs, with the same prevalence as in the general population.

Therefore, not only those who are fit and healthy but ever-increasing numbers of patients with CVDs are exposing themselves to high altitude.

A study on hikers and skiers in the Austrian Alps was performed to provide data on the prevalence of CVDs (coronary artery disease with and without myocardial infarction, systemic blood hypertension and cardiac arrhythmias) and showed that 12.7% of the hikers and 11.2% of the skiers were afflicted with at least one type of CVDs. Hypertension was the most frequent type: 70.9% in skiers and 68.1% in hikers. The frequency of CVDs was age dependent and more pronounced in men [6].

If it can be assumed that 4 to 5 million people with known CVDs are active in the Alps annually then approximately half will have significant risk factors for CVD. It is therefore inevitable that a significant number of cardiac events will occur in the mountains [2].

2 Effects of altitude environment on cardiovascular system

2.1 Altitude environment characteristics

An increase in altitude is associated with a decrease in barometric pressure. As a consequence, the partial pressure of oxygen availability progressively decreases with increasing elevation. There are many definitions for “high altitude”. According with Rimoldi and co-workers high altitude can be defined as the terrestrial elevation at which the oxygen haemoglobin saturation decreases below 90% [7]. At moderate latitude this corresponds to an altitude of about 2500m. Starting at his altitude, hypoxemia triggers a series of pulmonary and cardiovascular adjustments intended to maintain an adequate oxygenation of the different systems [7].

2.2 Physiological adaptation of the cardiovascular system

In the heart the major adjustments are an increase in heart rate, cardiac contractility and cardiac output [8]. As a direct consequence of these adjustments, myocardial workload and oxygen demand increase. To respond to this increased demand, the myocardium has to rely almost exclusively on coronary vasodilatation and enhancement of coronary blood flow because the coronary oxygen extraction is already very high at low altitude [8]. At the vascular level, the main initial adaptive mechanisms to altitude-induced hypoxemia are pulmonary artery vasoconstriction and peripheral and cerebral artery vasodilatation [7]. The pulmonary vascular pattern remains essentially unchanged with prolonged or lifelong altitude sojourn [8].

Very rapidly, however, for yet unknown reasons, the direct hypoxia-induced vasodilatation decreases and the adrenal medullary response increases causing an increase in systemic vascular resistance and systemic blood pressure [9].

The stimulation of the cardiovascular system reaches its maximum effects during the first few days of exposure; thereafter, probably related to the beneficial effects of subsequent respiratory, hematologic and muscular adaptation mechanisms, a new steady state is established [7].

After several days of acclimatization, cardiac output returns to normal, but the heart rate remains increased, so that stroke volume is decreased. Ventricular function is

maintained, with initially preserved or slightly depressed indices of systolic function, and an altered diastolic filling pattern [8, 9]. Exercise in acute as well as in chronic high-altitude exposure is associated with a brisk increase in pulmonary artery pressure above that seen in normoxia [8]. The relationships between workload, cardiac output and oxygen uptake are preserved, but there is a decrease in maximal oxygen consumption, which is accompanied by a decrease in maximal cardiac output, minimal in acute hypoxia but more pronounced with acclimatization [8].

With environmental changes in oxygen levels at high altitude to maintain oxygen homeostasis the human body is also able to respond to hypoxia switching on activation of numerous genes to increase oxygen delivery.

The Hypoxia-Inducible Factors (HIFs) are oxygen regulated transcription factors that are central to this hypoxic response and act as master switches to directly turn on these and other essential genes in response to hypoxia. The HIFs consist of a dimer of HIF-alpha and HIF-beta subunits, where the HIF-alpha subunits are regulated by oxygen levels, whereas the HIF-beta subunit is not.

For example, genes such as *erythropoietin* (*Epo*) increases red blood cell production, *vascular endothelial growth factor* (*VEGF*) stimulates vascular development, and other genes increase glucose transport and glycolysis to produce energy in the absence of oxidative phosphorylation.

Under normoxia the HIFs proteins are transcriptionally repressed, rendering them essentially inactive (X4).

Although there is a little intra-individual variability of the magnitude of the cardiovascular response during repeated high-altitude exposure, there is a large inter-individual variability of this response, which has important consequences since the absence of a history of exposure, the prediction of well-being at high altitude is very difficult. The enormous inter-individual variability in these adaptive responses may be further amplified by environmental and physical factors such as cold temperature, low humidity, exercise and psychological stress.

Altitude exposure carries no identified risk of myocardial ischemia in healthy subjects but it does have to be considered as a potential consequence in patients with previous cardiovascular conditions [8].

2.3 Risk of cardiovascular events at altitude

Whilst deaths in the mountains are most commonly due to trauma, high altitude illness, cold injury and avalanche burial, significant numbers of sudden deaths do occur [1]. Sudden death is the most common fatal manifestation of cardiac disease.

Sudden cardiac death (SCD) is responsible for a considerable number of fatalities in the mountain environment. [10]. Any strategy intent on reducing the risk of cardiac death will need to focus upon developing recommendations for those subjects with cardiac diseases as well as for those with risk factors for the coronary artery disease.

3 Cardiovascular conditions

3.1 Sudden cardiac death

3.1.1 General considerations

Sudden cardiac death (SCD) is defined as an “unexpected natural death from a cardiac cause within a short time period, generally < 1 hour from the onset of symptoms, in a person without any prior condition that would appear fatal” Up to 30 years of age, SCD is caused by coronary anomalies, primary electrophysiological abnormalities, hypertrophic and arrhythmogenic cardiomyopathy. In older persons SCD is mostly caused by coronary artery disease. In addition there is a third group of diagnoses which may cause SCD for both, young and older persons. These include unknown aortic stenosis and acute myocarditis.

SCD accounts for up to 52% of deaths during downhill skiing and 30% of mountain hiking fatalities [10]. In studies undertaken in the European Alps between 90-95% of SCD’s occur in males, while the frequency of SCD’s has been shown to increase dramatically in those aged over 34 years [1, 2].

Compared to the overall risk of SCD, the incidence of SCD during mountain activities is significantly greater: it has been shown to increase by a factor of 4.3 during mountain hiking and 2.1 during downhill skiing but only in men and not increased in women especially in those who were not regularly exercising [10, X]. The unaccustomed exercise together with altitude stress was suggested to increase the risk of SCD, but it is unclear to what degree hypoxia itself contributed to this risk [X].

3.1.2 Risk factors for SCD

In epidemiological studies conducted in the mountain environment the risk of SCD was found to be greatest:

- On the first day at altitude,
- In the late morning,
- During or immediately after unusual physical exercise,
- In people with cardiac risk factors,
- Following physiological stress triggered by factors such as anxiety, poor sleep, inter-current infection, inadequate food intake, depletion of carbohydrates stores and dehydration [2, 10].

People who suffered SCD had a much greater incidence of prior myocardial infarction, systemic hypertension, known coronary artery disease without prior myocardial infarction and were physically ingit [11, 12].

Importantly, only those who undertake regular exercise are afforded significant protection from the risk of SCD during vigorous activity. The relative risk of a life threatening cardiac event during exercise has been shown to be 150 in sedentary individuals and just 5 in those individuals who undertake regular aerobic exercise [1].

3.1.3 The psycho-physiology of SCD

Possible mechanisms of SCD include:

Myocardial ischemia, coronary artery spasm and the rupture or erosion of an atherosclerotic plaque have all been cited as potential causes for SCD in the mountain environment [10]. Vigorous exercise has a profound effect upon the autonomic nervous system, prompting changes in myocardial electrical stability and increases in an individual's susceptibility to fatal ventricular arrhythmias [1, 2]. Also, additional stressor such as altitude and extreme temperatures might contribute to the risk of SCD [2].

3.1.4 Recommendations for reducing or preventing SCD

Certain behavioural aspects such as rest on the first day at altitude followed by a gradual increase in activity on the following days and regular energy and fluid intake

should contribute to the SCD prevention. A relatively high level of fitness is a prerequisite for safe mountaineering [2].

Regular exercise not only increases basal vagal tone and enhances electrical stability, but also prevents the development of coronary artery disease and the formation of vulnerable plaques that are prone to rupture during surges in sympathetic activity [1]. Unfortunately, many heading to the mountains are sedentary and prone to coronary disease [6]. Exercise testing and an individual program of endurance training before participation in mountain activities may be advisable for physically inactive men over 40 [12].

Other preventive measures include a good acclimatization to higher altitude and planning mountain tours according to one's level of fitness [12].

Particular recommendations have to focus on persons with known coronary problems (see below – 3.2) as well as the larger population who have risk factors for the disease, on the therapy for treatable risk factors, on the preparation by individual physical training and on behavioural aspects.

Unfortunately, guidance for those with only risk factors for coronary disease is far less clear. For those undergoing physical activities the American College of Cardiology and the American College of Sports Medicine recommend that "those individuals who appear to be at greater risk of having underlying coronary artery disease (unfavourable levels of blood cholesterol and blood pressure, smoking, diabetes and adverse dietary habits) should be considered for exercise training program" [10, 13].

3.2 Coronary artery disease.

3.2.1 General considerations.

For recreational climbers and skiers, a common question is whether pre-existing coronary artery disease (CAD) precludes individuals from going to high altitude. Since very little evidence exists, the extent of the risk is not easily quantifiable and depends largely on the altitude reached, the acclimatization status, comorbid diseases and the leisure time activity planned [14].

However, it is important to make reasonable decisions on an individual basis answering questions like who can go how high, what type of pre-travel evaluation is neces-

sary, what kind of precautions or additional measures need to be taken during the trip and how does exercise capacity change at altitude is vital [X].

As stated above, the primary goal of the physiologic adaptation of the cardiovascular system to high-altitude exposure is to ensure maximal oxygen transport to the tissues.

The coronary oxygen extraction is normally very high. Therefore, in normal subjects the hypoxic myocardium must rely on an increase in oxygen delivery. This is achieved by the dilatation of epicardial arteries and an increase in myocardial blood flow [8].

3.2.2 Risk factors for CAD

When CAD patients go to high altitude, the question is whether the myocardium is adequately supplied with oxygen to avoid severe cardiac events, particularly during exercise.

In theory, an ascent to altitude has the potential to increase the risk of ischaemia in these patients since an imbalance develops between oxygen supply and demand. This is largely due because arteries that have undergone atheromatous changes are unable to dilate in the face of hypoxia [7].

Factors as acute hypoxia, physical activity and dehydration cause sympathetic nervous system activation at altitude that results in a widespread vasoconstriction and an increase in heart rate, blood pressure and cardiac output. The resulting increase in cardiac workload and oxygen demand is greatest in the first days of altitude exposure [8, 15] when the risk of myocardial ischemia is more elevated [9]. People with CAD have significant reduced capacity to compensate for increased demands on the heart. Diseased vessels have impaired endothelial vasomotor control, and thus alkalosis caused by increased ventilation and sympathetic activity may cause constriction of the coronary arteries and reduced myocardial perfusion [7, 15, 16, 17, 18]. Cold requires heat production and this places further demands on the heart and circulation [9].

There have been a limited number of systematic studies of CAD performed in mostly unacclimatized patients at altitudes between 2500 and 3454m [9,17, 18, X]. They show that travel to 3500m should be avoided unless patients have stable disease,

preserved left ventricular function and above-normal exercise capacity. CAD patients should avoid travel to elevations above 4500m owing to severe hypoxia at these altitudes.

CAD patients should consider that some locations at high altitude are geographically remote for medical assistance. It is also important to consider the danger that rescuers may be exposed to if evacuation should be necessary.

3.2.2.1 Thrombosis risk at altitude

Acute exposure to altitudes below 4000m is not associated with an increased risk for thromboembolic disease in individuals without thrombophilia [X1]. No data are available on the combined effects of hypoxia and thrombophilia at higher altitudes [X]. While some tests show that hypoxia enhances platelets activation at 4559m [X2], there are controversial results regarding platelet adhesion and aggregation at lower altitudes [X]. Since patients with CAD usually take inhibitors of platelet aggregation, the problem of possible platelet activation is probably of minor importance [X].

3.2.3 General recommendations

CAD patients can gain benefit from planned and individualized physical activity. The Bethesda Conference (2005) confirms the importance of initiating and continuing physical activity and, in some cases, competitive sports events in CAD patients [19]. Physical activities, especially those outdoors as mountain activity, are beneficial for CAD patients not only in terms of physical adaptation but also by providing an improvement in their quality of life. The traditional prohibitive attitudes that limited those with CAD to sea level activities has now been overcome, making it possible to guide these patients towards altitudes similar to those of the normal population. The feasibility of those with CAD undertaking physical activities in the mountains depends upon two factors: cardiovascular status and the nature of the activity to be undertaken. It is important that the cardiologist understands the physiological characteristics of the physical activities to be undertaken and the psychopathological mechanisms that can limit physical capacity in CAD individuals.

Moreover, in CAD patients it must be considered three factors: intensity, duration and frequency of the physical activity [19]. Climate conditions, particularly cold, may also contribute to increase cardiac stress.

The following factors: inducible ischemia by provocative tests, left ventricular contractile function, presence of arrhythmic events, aerobic capacity of the subject and morphological data of the coronary anatomy are all important indicators that permit to evaluate the clinical and functional requirements for CAD patients at moderate risk to perform physical activity at altitude [19].

In addition the patients should have well-controlled blood pressure, have a negative exercise test at sea level, have no significant arrhythmias and be free of concomitant disease that affect ventilation and gas exchange [9].

Patients stable, with well controlled CAD without residual ischemia who participate in unrestricted physical activity at sea level are probably safe to travel up to 3000-3500m with minimal increased risk [9, 14, 17, 18, X]. Information on the risks to those who with CAD ascend to altitudes above 5000m is lacking, although there are plenty of anecdotal examples of individuals with stable CAD performing well at these altitudes.

CAD patients have an increased risk for adverse cardiac events, requiring medical care and descent. So, they must bear in mind that in the case of an emergency, rescue may not be available immediately, since altitude regions are often remote areas.

3.2.3.1 Pre-travel evaluation

In individuals at risk of CAD (family history, diabetes mellitus, systemic hypertension, hypercholesterolaemia, obesity and smoking) and in all elderly men (>50 yrs) and women (>60 yrs) an assessment with their family doctor is recommended. Whilst some recommend an exercise test in elderly men and women with pre-existing cardiovascular factors, evidence for this approach is limited [X].

The CAD patient must have sufficient exercise capacity for the intended activities in the mountain. Therefore, a symptom-limited exercise test is mandatory mandatory is a strong recommendation is it right? in these patients. In case of a positive result, further proof of myocardial ischemia is recommended [X]. For now, there are no indications to perform hypoxic exercise testing prior to travel [X].

Patients with exertional angina are likely to experience a worsening of their symptoms at higher altitude. In these subjects, travel to high altitude is not recommended but, where necessary, a cautious ascent is needed and exercise severely limited [15, 17].

Ascent is contraindicated in patients who have unstable or severe angina, objective evidence of myocardial ischemia at low workload or a recent acute coronary syndrome [7, 9, 15].

Ascent is also contraindicated for 6 months after MI. After this period, a normal exercise stress test should be a pre-requisite to travel [15].

3.2.3.2 In-travel precautions

It is recommended that a slow ascent is advised. Patients should take time for an acclimatization period of several days and physical exertion should be limited [7, 14, 15, X]. Where possible direct transportation to an altitude above 3000m should be avoided [X]. Above 2000m, sleeping altitude should be increased by not more than 300 to 350m per night on average [X].

CAD patients who do not engage in exercise at sea level on a regular basis should not begin to exercise at high altitude [X].

If angina is worsened on ascent, bed rest, oxygen and anti-anginal therapy is required. Immediate descent should occur if symptoms persist or worsen. Those with a history of hypertension should check their blood pressure regularly and be prepared to adjust doses of antihypertensive drugs if required [X].

Adequate nutrition and hydration should be maintained at all times to minimize the risk of adverse events.

3.2.4 Operated CAD patients

In CAD patients who have successfully undergone coronary artery bypass surgery or coronary angioplasty, ascent to 3000m or beyond may be possible provided they are asymptomatic for at least 6 months and a negative pre-exposure assessment [18, X]. This should consist of a transthoracic echocardiography and a symptom-limited exercise test. Spiroergometry and Holter-ECG should be considered in individual cases.

There is no evidence to suggest that altitude exposure increases the risk of graft closure or stent restenosis [14, 15].

3.2.5 Medications and CAD

Medication at altitude should be taken as prescribed at sea level.

Patients on two or more anti-platelet agents or oral anticoagulation have a markedly increase in their risk of uncontrolled bleeding and should not be involved in activities with increased risk of injury. They should be discouraged from seeking high altitudes for prolonged periods, particularly in remote areas [7, X].

Acetazolamide (Diamox®) may be avoided in patients receiving long-term doses of Aspirin. By decreasing protein binding and renal secretion of Acetazolamide, concurrent Aspirin use can impair Acetazolamide elimination, leading to a greater degree of metabolic acidosis, thereby increasing the risk of Aspirin toxicity [20].

Several trials have demonstrated that long-acting Ca-channel-blockers (Nifedipine) used in the treatment of HAPE are safe in stable CAD patients [20]. If already on Ca-channel blockers patient cannot use Nifedipine for treatment of HAPE whilst awaiting descent.

Patients with CAD whose medication regimen includes nitrates should not receive Sildenafil or Tadalafil for HAPE prophylaxis because this combination of drug classes may cause profound hypotension. In patients with stable CAD who do not receive nitrates, Tadalafil appears to be safe since it does not increase the risk of serious cardiovascular events at sea level [20].

Patients receiving ß-blockers such as Metoprolol or Atenolol may experience limitations in their performance at high altitude. This is not only due to a reduction in maximum heart rate but also a blunting of the ventilator response to hypoxia [7, X3]. Vasoconstriction may also increase the risk of cold injury. Nevibilol should be considered since it increases oxygen delivery of the myocardium and the symptom-limited workload of the patient.

ß-agonists such as Salmeterol are used to prevent HAPE. These should be avoided in those already taking ß-blockers [20].

3.3 Congestive heart failure

3.3.1 General considerations

There are very few field studies of congestive heart failure (CHF) at high altitude [9, 21, 22].

However, some studies have been done using hypoxic exposure to simulate altitude (normobaric hypoxia) [15, 23]. In these patients maximum work rate fell by 3% per 1000m in normal subjects and 11% per 1000m in subjects with severe CHF at altitude up to 3000m [9]. However, these studies were limited to only a few hours of observation and therefore the effect of acclimatisation is not known [15].

In those with mild left ventricular dysfunction, a slow ascent up to 3000 m can be safely considered provided physical activity is limited, particularly during the first days of exposure [7, 21, 23]. However it has been observed those with CHF may deteriorate further if they develop AMS or HAPE [14, 15].

In cases of CHF, the pre-exposure assessment should include a transthoracic echocardiography and a symptom-limited exercise test. For better stratification, spiroergometry and Holter-ECG should be considered [7]. Rarely, the patient may benefit from exposure to the level of hypoxia that correspond to the expected altitude [X] under the direct supervision of a physician.

Patients with severe functional limitations (EF < 40% evaluated by echocardiography), clinical or biochemical signs of fluid retention or who are clinically unstable at their resident altitude should not go to high altitude [7].

3.3.2 Prevention and treatment

Patients with CHF should closely follow low altitude recommendations. These should include: restricting salt intake, close monitoring of body weight, recognition of signs of fluid retention (peripheral oedema, nocturia, orthopnea) and be prepared to adjust the dose of diuretic themselves [7, 15]. Dehydration due to exertion, low humidity, diuretics or diarrhoea needs to be avoided. If this does occur, the diuretic dose should be halved or stopped and fluid losses replaced. Electrolyte disturbances, particularly hypokalemia, may develop and predispose patients to arrhythmias and SCD [7]. Rehydration salts and dried fruit (especially apricots and bananas) may help to resolve this problem.

Since Acetazolamide (Diamox®) is a diuretic with kaliuretic effects, this should be avoided in those already receiving other diuretics [20].

3.4 Systemic arterial hypertension

3.4.1 General considerations

With prevalence rates of between 28% and 44% among adults in North America and Europe, systemic hypertension (SHT) is a common medical condition that predisposes individuals to a wide range of vascular disease [24]. Precise data on the prevalence of SHT amongst high altitude travellers is lacking, but survey studies suggest that between 6% and 14% of travellers to elevations between 1900 to 2900m have SHT [24]. Despite this high prevalence, little information exists to guide clinicians in counselling these patients.

3.4.2 Physiopathology of SHT

There is a significant amount of individual variability in the effects of altitude on blood pressure. These effects may not be clinically significant below 3000m [15]. However, in some people there is a pathological reaction to high altitude which results in a large increase in blood pressure [15, 24]. Unfortunately, we currently lack the ability to identify these individuals before exposure [24].

The principal determinants of blood pressure at high altitude are the same as those at low altitude. These include: cardiac output, which is dependent on heart rate and stroke volume, systemic peripheral resistance and central venous pressure [7]. Ambient hypoxia induces peripheral vasodilatation but also markedly activates the sympathetic nervous system, triggering an increase in cardiac output and systemic vasoconstriction that within a few hours overcomes the hypoxia-induced vasodilatation that is often seen on first arrival [7, 8]. The extent of this pressure increase may also depend upon other factors such as the level of altitude, cold, diet, exercise and genetics [15].

In hypertensive patients, this mechanism may be accentuated because hypertension-associated endothelial dysfunction may impair hypoxic vasodilatation and therefore facilitate further sympathetic vasoconstriction [7].

3.4.3 Risk assessment

At present the risk of major complications (stroke, myocardial infarction, intracranial bleeding) in patients with SHT exposed to high altitude is not known [7, 24]. Only a single study suggests an increasing risk for SCD in those with SHT during mountain hiking and skiing (50% vs 17% in male skiers older than 34 years who had SCD when compared with controls) [2].

No complications were reported in the studies that examined blood pressure responses during exercise at high altitude [24]. In addition, there is no evidence to support an association between SHT and an increase in the risk of high-altitude illness [24].

3.4.4 Practical recommendations

Since little data exists, it is impossible to predict who will experience significant increases in blood pressure at altitude. However, patients with uncontrolled SHT should not ascent to high altitude until their blood pressure is well managed [9].

Despite the possibility of a significant increase, a well-controlled SHT is not a contraindication to high altitude travel [15]. The patients should, of course, continue their normal medication [14] and during prolonged stays at altitude check their blood pressure in order to monitor their risk of complications. Aneroid sphygmomanometers have been validated for use at high altitude (4370m) [15].

A plan for medication adjustments should be prepared in advance. As a first line strategy, this should involve increasing the dose of the patient's own drugs before introducing new agents. At present there is no evidence to support specific recommendations to do this [24].

It is vital to treat symptomatic hypertension. Signs of headache, visual disturbance, shortness of breath, chest pain and altered mental status may all be symptoms of uncontrolled hypertension. Even in the absence of symptoms, a systolic blood pressure greater than 200 mmHg or a diastolic pressure greater than 120 mmHg warrants treatment [24]. In both of these cases, evacuation should be considered.

Any patient who makes medication adjustments should be instructed to return to their original regimen upon descent to lower elevation.

Nifedipine is a useful drug in uncontrolled SHT (slow release only) since it is not only an effective anti-hypertensive but also a pulmonary vasodilator and therefore prevents HAPE [24]. Caution should be exercised when administering Nifedipine to patients receiving other antihypertensive agents such as ß-blockers or α-blockers, since the combination may precipitate hypotension [20].

Evidence is lacking regarding another commonly used class of antihypertensive drugs, the ACE inhibitors [24], although anecdotally they seem to work well.

In young hypertensive patients ß-blockers drugs may limit maximal workload, limiting the heart rate response to increased activity and interfere with thermoregulation in response to heat or cold [15]. In contrast the older patients will have significant benefit from ß-blocker therapy since their maximal workload will increase O_2 utilization. The best effect was shown with Nivebilol which also dilates vessels

Some α-blockers (Clonidine) may reduce breathing and therefore they may reduce performance [14, 15, 24]. For other Authors drugs with some combined α/β blocking by a reduction of the myocardial properties (Carvedilol, Labetalol) or central effects (Clonidine) may be especially helpful for blood-pressure regulation at altitude because of reducing the increased sympathetic activity [X].

The development of hypotension may necessitate a later medication reduction with acclimatization to altitude [15].

At 4000m diuretics may cause a loss of 10% of plasma volume in 24 hrs. Patients receiving diuretics may reduce the dosage or stop the medication.

3.5 Cardiac arrhythmias

3.5.1 General considerations

At present, little is known about the effect that altitude has upon the heart's ability to conduct electricity. However episodes of atrial and ventricular tachyarrhythmias have been observed in the high altitude environment and been shown to lead to life threatening cardiac events.

3.5.2 Risk assessment.

A number of studies have documented ECG changes in healthy subjects at real and simulated altitudes up to 8.848m, however there is very little evidence to determine how those with cardiac arrhythmias cope [15].

High altitude may favour the development of supraventricular and ventricular arrhythmias via the activation of the sympathetic nervous system [7]. In addition, arrhythmias could be precipitated in susceptible patients as a consequence of right ventricular overload due to pulmonary hypertension [9].

There are numerous reports of increased supraventricular and ventricular premature beats in healthy subjects on ascent to altitude. However, it has been showed that the increased number of extra beats at altitude is benign and not associated with life-threatening arrhythmias [X].

Unfortunately, patients with pre-existing higher grade arrhythmia have never been studied at high altitude; therefore, no information exists as to whether altitude exposure leads to an exacerbation of these arrhythmias [X]. However, altitude-induced arrhythmias have been claimed to be responsible for a significant number of sudden cardiac deaths [2].

A rapid ascent to altitude may result in faster heart rates in patients with AF or atrial flutter [25, 27]. In these patients, the increased heart rate may critically increase the risk for arterial embolism in presence of a left atrial thrombus. Echocardiographic assessment and the oral anticoagulant therapy (necessary in these patients) may avoid this problem.

Pacemaker (PM) function remained unchanged in hypobaric chamber study simulating altitudes up to 4000m [7, 14], so patients with PM can be safely exposed to high altitude with no impact on ventricular stimulation thresholds [25]. In patients with a stable PM function, there is no need for additional PM testing before altitude exposure. Patients with a rate response PM may benefit from higher PM rates during exertion at high altitude [7].

There no data on patients with implantable cardioverter-defibrillators (ICD) at high altitude [7, 25].

PMs and ICDs are both constructed for altitudes (pressures) up to 4000m only. Contact manufacturer before going higher. Take care for balanced electrolytes, otherwise the device may fail.

If a patient with pacemaker dies on an expedition, cremation is not recommended.

3.5.3 Practical recommendations

Given the paucity of evidence, it is recommended that patients with cardiac arrhythmias should consult their cardiologist for individualized risk assessment and ad hoc adaptation of the treatment prior to pursuing high altitude travel.

For patients with paroxysmal and persistent AF, rate control (especially during exercise) should be ascertained by exercise testing or Holter-ECG prior to exposure. Because the ventricular rate response may accelerate at high altitude, patients should be instructed to check their heart rate and adapt their rate-limiting drugs in case rate control becomes inadequate [7]. A pulse monitoring watch with alarm threshold set at 70-80% of the individual's hypoxic threshold may be a useful guide.

High altitude exposure is strictly contraindicated in patients with uncontrolled ventricular arrhythmias. Those with a recent ICD implantation (< 6 months) or recurrent ICD interventions (discharge or overpacing) for ventricular arrhythmias, should not travel to remote geographic areas nor ascend to high altitude [7].

In patients with paroxysmal supraventricular tachycardia and atrial flutter, particularly in those considering long high altitude sojourns in remote areas, radiofrequency catheter ablation is recommended. At high altitude, the heart rate during these tachyarrhythmias may cause hemodynamic instability and result in life threatening symptoms [7].

In the mountain environment the presence of life threatening symptoms warrants an immediate evacuation and urgent medical care. Lesser symptoms may respond to a day spent resting, rehydrating and eating a series of small meals. Any increase in medication or the introduction of a new drug should be discussed in advance with the patient's cardiologist.

Avoid alcohol, caffeine and nicotine should all be avoided. Unfortunately all can trigger arrhythmias.

3.6 Valvular heart diseases

3.6.1 General considerations

There are no reports on the effects of high altitude exposure in patients with primary valvular heart disease. It is unnecessary in this review to describe in detail the physiopathology of the different valvular lesions (mitral or aortic, stenosis or insufficiency) and the potential risks associated with high altitude exposure.

3.6.2 Risk assessment

In general, most of the risks in these patients at high altitude are the same as described for heart failure and pulmonary artery hypertension. The potential problems in such patients are those related to the worsening of the pressure or volume overload associated with a particular valvular dysfunction [7].

The altitude-induced increase of heart rate and cardiac output may worsen the consequences of a valvular stenosis. The increased systemic vascular resistance and arterial blood pressure might adversely affect a pre-existing aortic or mitral valve regurgitation, whilst an increased pulmonary vascular pressure might aggravate pulmonary and tricuspid insufficiency. The right ventricular pressure overload may shift the interventricular septum to the left and alter the left ventricular geometry and filling, with consequent diastolic dysfunction [7].

Unsuspected aortic stenosis is relatively common. If a patient does not show an adequate increase (or – even worse – a decrease) of systolic blood pressure during stress test or if dyspnoea occurs at low workload this may indicate a significant stenosis. In this case, echocardiography must be performed and altitude avoided until assessed and treated. Surgery mat be needed and then the patient reassessed prior to altitude travel.

A valvular stenosis can be worsened by a fall in circulating volume. Therefore dehydration must be avoided and conditions that cause diarrhoea and vomiting will need to be treated aggressively.

In those patients with prosthetic heart valves (mechanical more than biological ones) a fall in circulating volume may increase the risk of thrombosis [7].

This risk may be exacerbated by changes in the efficacy of oral anticoagulation that is sometimes seen in altitude. Some papers have demonstrated that the coagulation

parameters may be altered during high altitude exposure [28, 29]. There are a few potential mechanisms by which Warfarin efficacy may be altered in response to increasing altitude [29]. In consequence, increasing altitude is a risk factor for subtherapeutic INR in Warfarin patients with increased risk of valvular thrombosis. This risk is doubled in AF patients [29].

3.6.3 Particular recommendations

High altitude exposure is contraindicated in patients with symptomatic and/or severe valvular heart disease. For patients with milder forms of valvular heart disease exercise testing and trans-thoracic echocardiography at rest are recommended before travelling.

Once at altitude, the patient should be advised not to take hard physical exercise [14]. Fluid balance should be equilibrated and blood pressure well controlled, at least during the first days at altitude [7]. New-onset arrhythmia, particularly AF is a concern and would merit descent. If there should be some doubt whether the patient is safe at the planned altitude, he should be exposed to isobaric hypoxia under supervision of a physician prior to travel.

In patients with prosthetic heart valves on Warfarin therapy, the increased risk of hemorrhage must be considered. Activities where there is risk of severe traumatic injury should be avoided. The use of a helmet is recommended in these patients when climbing [14].

Instructions and equipment for self-monitoring of INR and doses adaptation are recommended and the patient should be able to monitor and manage their own oral anticoagulation if far from help [7, 29]. Carry spare batteries and test equipment!

3.7 Pulmonary artery hypertension

3.7.1 General considerations

Pulmonary artery hypertension (PHT) is defined at sea level as a mean pulmonary artery pressure $\geq$ 25 mmHg at rest or $\geq$ 30 mmHg with exercise [30]. PHT develops as a result of a variety of processes (idiopathic, cardiac disease, lung disease, thromboembolic events, others) that lead to increased pulmonary vascular resistance.

Patients may have a diagnosis of pulmonary hypertension at the time of their pre-trip evaluation but some may be asymptomatic. The problem may lead to severe complications during exposure to high altitude. Undiagnosed PHT may explain poor performance in the mountain environment. When the diagnosis is suspected on the basis of patient's medical history, echocardiography is used to noninvasively measure pulmonary artery pressure [30].

PHT is a normal physiological response to altitude. It is the result of hypoxic pulmonary vasoconstriction and can be reproduced at sea level following exposure to hypoxic mixtures.

3.7.2 Risk assessment

PHT may be an important risk for developing HAPE, a non-cardiogenic form of pulmonary edema that develops after 2-5 days at elevations above 2500 m [31].

Others potential complications faced by these patients at high altitude include: worsening right ventricular function that develops into acute cor pulmonale as well as significant impaired gas exchange, that predisposes individuals to myocardial ischemia [7].

In patients with PFO the rise in pulmonary pressure may also create a right-to-left shunt with possible cerebral consequences (see 3.8.4) [7,30]. If there should be some doubt whether the patient is safe at the planned altitude, he should be exposed to isobaric hypoxia under supervision of a physician.

Most patients with metabolic syndrome or significant amounts of abdominal fat should be checked in a sleep-lab before they go to altitude.

3.7.3 Particular recommendations

Given the limited data, it is impossible to give evidence-based guidelines for managing those with PHT. The following recommendations represent a pragmatic approach to the problem [30].

Patients with known PHT need pre-travel evaluation by echocardiography.

In severe cases (mean pulmonary pressure >35mmHg or systolic pressure >50 mmHg at sea level) a sojourn to even modest altitude should be avoided [14, 30].

Patients with moderate PHT (mean <35 mmHg or systolic value < 50 mmHg) may travel safely to altitudes <3000 m. These individuals should consider prophylactic use of Nifedipine (30 mg twice daily) or Tadalafil (10 mg twice daily) for the duration of their sojourn. Supplemental oxygen should be available in the event of deterioration [30].

Travel into remote areas that are away from medical care should be avoided. They should take plenty of time to acclimatise, even for low altitudes. Any rapid ascent by cable-car or motorised vehicle may cause acute decompensation [14]. Since physical activity can increase pulmonary artery pressure, this should be limited at altitude.

Strong consideration should be given to monitoring oxygen saturation with a portable hand-held oximeter. Carefully monitoring of symptoms is warranted and all patients should be prepared to descend if worsening symptoms or excessive desaturation occurs [30].

At sea level, hypoxic chambers may help identify those with PHT who are particularly vulnerable to hypoxia [30]. However at present a protocol describing testing and management has yet to be devised.

3.8 Congenital heart diseases

3.8.1 General considerations

In general, congenital heart disease (CHD) can be divided into two main categories: “simple” and “complex” CHD. “Simple” CHD can be cured by surgical or transcatheter treatment whilst “complex” ones can only be treated palliatively and cure is rarely possible. The first category includes, with some exceptions, atrial (ASD) and ventricular (VSD) septal defects, patent ductus arteriosus (PDA) and pulmonary valve stenosis. Curative surgery tends to be possible if completed in early infancy and complete normalization of cardiovascular function is achieved. Coarctation of the aorta (AoCo) may often be included in this group if a significant residual pressure gradient is absent. The group of “complex” CHD’s includes lesions with anatomical abnormalities such as the tetralogy of Fallot (ToF) or transposition of the great arteries. In these cases a definitive anatomical repair is impossible and repair only restores a near-normal physiology. Even if a good functional result is achieved, the anatomical le-

sions (ventricular hypertrophy, valvular stenosis, pulmonary arteries' pathological changes) reduce the physical capacity of the subject [32].

Exercise training is nowadays considered as an integral part of rehabilitation in patients with CHD. However, in this particular population the level of exercise depends upon the individual functional condition and on the arrhythmogenic risk [32].

3.8.2 Risk assessment

Exposure to hypobaric hypoxia results in hypoxic pulmonary vasoconstriction. In some, this response can be exaggerated and lead to the development of HAPE [8, 9, 15].

Patients with CHD have an exaggerated pulmonary arteriolar vasoconstrictor response to hypoxia which may consequently make them more susceptible to HAPE.

In CHD's such as ASD, VSD and PDA, there is usually a net shunting of blood from the high pressure left side to the low pressure right side of the heart. On exposure to hypobaric hypoxia, right-sided pressure may increase resulting in a shunt reversal, from right-to-left. This may lead to intra arterial oxygen desaturation since a greater amount of deoxygenated blood bypasses the lungs [25]. This risk is not well understood or easily predicted. Some individuals have demonstrated the ability to function well whereas others have developed HAPE or right heart failure at moderate altitude. Symptoms may include dyspnoea, weakness on exertion and syncope [15].

Unfortunately, data does not exist on patients with CHD who have been operatively treated and later go to high altitude.

Pre-exposure assessment of patients with CHD may include transthoracic echocardiography, possibly during simulated high altitude (FiO_2 12%) and exercise testing. Specific cases may also need cardiac magnetic resonance and Holter-ECG. For patients with operated aortic coarctation 24-hour ambulatory blood pressure monitoring may be useful [7, 15, 34].

3.8.3 Particular recommendations

High altitude exposure for patients with cyanotic, complex CHD is contraindicated [7, 15, 25].

In patients with less severe forms of CHD, counselling must be tailored to the individual and based on the underlying defect, its severity and the type of high-altitude exposure planned [7].

If very strongly desired by the patient, a short-term trip with passive ascent up to 2000-2500 m may be considered, however with pre-exposure assessment and planning of prophylactic and emergency measures including oxygen supplement and possibly pulmonary vasodilators such as Nifedipine or Tadalafil [7]. Patients with CHD who plan to sleep in mountain huts should be screened by sleeping at least one night in isobaric hypoxia under the supervision of a physician.

3.9 Patent Foramen Ovale at altitude.

During foetal life, a small hole situated in the inter-atrial septum enables blood to flow between the right and left atria. This is known as the foramen ovale (FO). After birth, the pressure in the pulmonary circulatory system drops causing the FO to close. In 10-35% of normal individuals the FO remains open anatomically. This is known as a patent FO (PFO). An elevation in the right atrial pressure can cause the PFO to act as a passage for blood to pass to the left atrium. It is a known risk factor for embolic cerebral events (stroke) and migraine in hyperbaric and hypobaric settings [35, 36].

In healthy humans, studies in HAPE-prone subjects have demonstrated that a higher frequency of PFO's than in the normal population. This may represent trigger HAPE since deoxygenated blood will pass to the left atrium worsening altitude-induced hypoxemia and, in turn, the hypoxic pulmonary vasoconstrictor response [37, 38, 39]. In a recent study, PFO was found to be 4 to 5 times more frequent in HAPE-prone subjects than in mountaineers resistant to this condition. In addition, the arterial hypoxemia was more pronounced in patients with large PFO than in those with small defects [37, 38]. This suggests that the size and not simply its presence may be clinically relevant in the HAPE-prone subjects [39].

The presence of a PFO may be determined by trans-esophageal echocardiography, but it is possible that its presence appears only at altitude because of the dynamic changes in cardio-pulmonary blood flow. A hypoxic echocardiographic examination at sea level may, therefore, be a more useful screening tool for determining the presence of a PFO [36].

Despite these findings, there is no evidence that the presence of an asymptomatic PFO should be a contraindication to travel to high altitude [36].

4 ECG at high altitude

4.1 General considerations

The high altitude environment has a profound effect on the ECG of all persons who ascent to altitude. In normal people, the changes in rate, rhythm and morphology are consequences of the physiological processes of acclimatisation at the altitude.

4.2 Rate

At altitude, the heart rate during rest and submaximal exercise increases as a result of increased sympathetic activity. Above 5000 m a more significant increase is observed. Heart rate at rest and during submaximal exercise remains elevated for several weeks at altitude.

At the highest levels of physical exertion, heart rate is reduced. This is due to an increase in parasympathetic activity and may be a protective mechanism since it increases the duration of diastole and therefore the filling time of the ventricles and the perfusion time of the coronary arteries [40].

4.3 Rhythm

The most common rhythm disturbances at altitude take place during sleep, when episodes of periodic breathing disrupt the normal sleep pattern with cycles of apnoea and hyperpnoea. Fluctuations in heart rate show high rates during hyperpnea and slow ones during the apnea phase. Holter ECG recordings performed during sleep showed many kinds of arrhythmias: sinus arrest, marked bradycardia with junctional or ventricular escape rhythm, atrioventricular dissociation and idioventricular rhythm. These may be an attempt by the parasympathetic nervous system to improve myocardial perfusion in face of worsening hypoxia seen during the apnoea phase of the breathing cycle.

Premature atrial ectopics are the most commonly reported supraventricuar arrhythmia at altitude. Ventricular arrhythmias have also been widely reported at altitude, particularly ectopic beats and short runs of ventricular bigeminy [40].

4.4 Morphology

Changes in ECG morphology tend to be consistent with an increase in pulmonary artery pressure and the resulting changes to electrophysiology in the right atrium end ventricle. These findings present quickly, persist with prolonged exposure and return to normal once the subject has returned to sea level.

Right axis deviation, right bundle branch block and changes in the amplitude of P and T waves are seen on ascent to altitude. These may be explained by pressure overload that occurs in the right heart at altitude.

Ischaemic changes are rarely seen in healthy individuals at altitude.

ECG rapidly returns to normal following descent [40].

5 Heart transplanted patients

5.1 General considerations

Heart transplantation is a procedure performed on patients with end-stage heart failure or severe coronary artery disease. This consists of taking a working heart from a brain dead organ donor and implanting it into the patient. Post-operative survival periods now average 15 years.

Worldwide there are 3500 heart transplants performed every year in more than 200 Centres, and the total number of heart transplants reported in 2009 was more than 88,000.

5.2 Physiology of the transplanted heart

The intact heart is innervated by sympathetic and parasympathetic fibres from the autonomic nervous system. Transplantation necessitates transection of these fibres, hence yielding a denervated heart.

Following recovery of donor sinus node function, the denervated donor heart exhibits a faster resting rate, caused by the intrinsic tachycardia of the sinus node and absence of the counter-regulatory effects of the parasympathetic system. The donor heart relies on adrenal glands for its source of catecholamines. Thus, its response to

stress (hypovolemia, hypoxia, anemia, exercise) is delayed until circulating catecholamines can exert their positive chronotropic effect on the heart.

Cardiac denervation has several important clinical manifestations. The donor heart is slower to alter its heart rate during rest and exercise. Without sympathetic innervations, the transplanted heart needs an increase in venous return during exercise before the heart rate can increase. Eventually circulating peripheral catecholamines provide additional chronotropic support.

Coronary vasoregulation is altered.

The absence of a normal reflex tachycardia in response to venous pooling accounts for the high frequency of orthostatic hypotension in transplant patients.

Natriuretic peptide, which concentration is very high in these patients, play a key role in volume overload response of the donor heart, with its diuretic and vasodilating properties.

In heart transplant patients, pulmonary artery pressure may be elevated because of the previous long acting cardiac disease.

Because of all these problems, cardiac function and cardiac work capacity in these patients is reduced.

Moreover, cardiac drugs that act primarily through the autonomic nervous system (for example atropine) will have little or no effect on a denervated donor heart.

5.3 General recommendations

At present there is little evidence to develop guidelines for those with cardiac transplants who wish to ascend to altitude.

During the first post-transplant year there is a high risk of rejection. The patient is immunocompromised due to the anti rejection therapy and this may make them more prone to potentially serious infections when travelling to remote areas.

After 1 year, advice must be tailored to the individual and be based upon cardiovascular status and other physical (renal function, dismetabolic status) and psychological factors.

A pre-exposure assessment should include resting and stress transthoracic echocardiography to establish cardiac function and, importantly, pulmonary artery pressure.

An elevated pulmonary artery pressure (> 40mmHg) is a contraindication to altitude exposure. An exercise-ECG and Holter-ECG are important for identification of arrhythmias and evaluation of systemic arterial pressure stress behaviour.

Patient who are medically stable, physically fit and with well-controlled blood pressure and renal function are probably safe to travel up to moderate altitude (< 3000m). A passive ascent respecting acclimatization rules and avoiding heavy physical exertion may be recommended first. Adequate nutrition and hydration should be maintained. Patients should continue their normal medication, especially if a traveller's diarrhoea should occur.

5.4 Immunosuppression

Since the transplanted heart originates from another organism, the recipient's immune system may attempt to reject it. Immunosupressive drugs reduce that risk, but may have some unwanted side effects, such as increased likelihood of infections. With improving survival, the heart transplant recipient faces an increasing number of medical problems caused by both aging and the cumulative complications of immunosuppressive drugs.

Steroids are associated with the largest number of long-term adverse effects. Hypertension, emotional lability, cataracts, gastric ulcer, poor wound healing, and proximal myopathy are all associated with steroid therapy. Cosmetic effects (particularly troubling to many patients) include hirsutism, acne, easy bruising, skin fragility, moon face, buffalo hump, weight gain, and truncal obesity. Important metabolic effects are hyperlipidemia, salt and water retention, diabetes mellitus, osteopenia, and growth retardation in children. Long-term administration of steroids may result in chronic adrenal suppression, and adrenal insufficiency can follow a steroid taper or "stress" (illness, surgical procedures, infections).

The major side effect of **Azathioprine** is myelosuppression, including leukopenia, anemia, and thrombocytopenia. These side effects are generally dose dependent and resolve in 7 to 10 days with dose reduction. Pancreatitis, hepatitis, and hepatic veno-occlusive disease can occur but are rare. Skin cancers, once thought to be related primarily to AZA, are now thought to be related to the overall level of immunosuppression but altitude exposure to high UV levels may make this risk worse.

Mycophenolate Mofetil is usually well tolerated. Major side effects include nausea, vomiting, and diarrhea, which usually are responsive to a decrease in dosage. The risk of opportunistic infections appears to be high in patients treated with MMF.

Cyclosporine causes nephrotoxicity that can be acute, dose related or chronic with arteriolar sclerosis and tubulo-interstitial fibrosis. Rarely, CSA nephrotoxicity may be manifested as a hemolytic-uremic syndrome. Hypertension and hyperlipidemia occur in most patients. De novo diabetes mellitus at 1 year is present as many as 10% of patients. Neurological toxicity includes tremor, paresthesias, headache, seizures, mental status changes, visual symptoms, and insomnia. CSA can cause nausea, vomiting, cholestasis, and cholelithiasis and can contribute to the development of osteoporosis. Hypertrichosis, which occurs in at least 50% of patients, and gingival hyperplasia are side effects seen with CSA.

The side effects of **Tacrolimus** are similar to those of CSA although the incidence of hypertension and hyperlipidemia are somewhat lower. Hyperglycemia and neurological toxicity are more common with TAC than with CSA. Hyperglycemia is especially problematic at high doses and in some subgroups such as women and blacks. Diabetes may be more common when TAC is given with AZA than with MMF. Indeed, alopecia may be a side effect of TAC.

The major adverse affects of **Sirolimus** (or **Rapamycin**) include hyperlipidemia with hypertriglyceridemia and increased LDL cholesterol, thrombocytopenia, neutropenia, and anemia. Hypercholesterolemia and hypertriglyceridemia are at least partially responsive to dose reduction. The long-term consequences of these lipids are not yet well established. Thrombocytopenia seems to be dose related and is reversible, severe thrombocytopenia is rare, neutropenia may also occur. SIR does not appear to result in renal dysfunction or diabetes.

The availability of new drugs to treat infections, obesity, hypertension, hyperlipidemia, renal insufficiency, diabetes, osteoporosis, gout and malignancies has resulted in the heart transplant recipient and their physicians facing an almost overwhelming number of important drug–drug interactions. Predicting drug–drug interactions in a transplant recipient is often difficult. These patients are taking a large number of immunosuppressive and nonimmunosuppressive drugs with substantial potential for clinically significant adverse events as a result of drug–drug interactions.

A full discussion of the possible interactions is beyond the scope of this article. The subject should discuss the problem with his physician before leaving.

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Kommentar: Do you want to include this reference somewhere or what was the intention to put it here?

6 Summary of recommendations.

6.1 Pre-acclimatization in hypoxic chambers

Acclimatization is of vital importance for any lowlander who plans to ascent to an altitude >2.500m.

In some situations, a slow acclimatization process is impossible. Pre-acclimatization, when carefully planned, can decrease the risk of altitude diseases significantly. Since hypoxic chambers are more and more available, they can be used for pre-acclimatization to prepare for sojourns at high altitude. The special advantage of hypoxic chambers is the well-controlled environment and the safety for persons with individual risks or pre-existing conditions [41]. However, in those with pre-existing CVD nothing is better than spent acclimatising slowly in the mountain environment.

6.2 Medications used for the prophylaxis of AMS in cardiovascular patients

6.2.1 Acetazolamide (Diamox®)

The carbonic anhydrase inhibitor Acetazolamide is the gold standard drug in the prevention and treatment of AMS and HACE. Research studies in animals and a single study in humans have shown that this drug may play also a role preventing HAPE [20].

Acetazolamide should be avoided in CAD patients receiving long-term low dose Aspirin. By decreasing protein binding and renal tubular secretion of Acetazolamide, Aspirin can impair its elimination. This has the potential to cause a greater degree of metabolic acidosis that results in an, increase in CNS penetration of aspirin and therefore toxicity [20].

Because this drug is a diuretic with kaliuretic effects, care is necessary when administering acetazolamide to people already receiving other diuretic drugs, since this may increase the risk of electrolyte abnormalities and dehydration [20].

The kaliuretic effects mandate caution when administering Acetazolamide to people receiving digoxin for atrial fibrillation or cardiomyopathy since hypokalemia increases

the risk for junctional bradycardia, ventricular arrhythmias and other forms of digoxin toxicity [20].

6.2.2 Nifedipine

Nifedipine is a calcium-channel blocker that plays a primary role in the prevention and treatment of HAPE [20].

In the 1990s there was a debate about the safety of calcium channel blockers in patients with SHT and CAD after several studies had demonstrated an increased risk of myocardial infarction and even death following their administration. This concern has since dissipated since subsequent large several studies have demonstrated that calcium-channel blockers are safe in stable CAD patients [20].

Because of its effects on blood pressure, caution should also be exercised when administering Nifedipine to patients receiving other antihypertensive agents, such as ß-blockers or α-blockers, since in combination they may precipitate hypotension [20], the same in dehydrated patients. Avoid short release Nifedipine! Patients at altitude are in a status of maximal sympathetic stimulation and cannot balance the pressure reducing affect of Nifedipine.

6.2.3 Sildenafil (Viagra®) and Tadalafil (Cialis®)

Phosphodiesterase inhibitors such as Sildenafil and Tadalafil are beginning to be used to prevent HAPE since they are able to increase nitric oxide concentrations in the pulmonary vasculature and reduce pulmonary artery pressure. As yet there is no evidence to support the use of these drugs in the treatment of HAPE [20].

Those with CAD who take nitrates should not receive these drugs since in combination they may cause profound hypotension. In patients with stable CAD not receiving nitrates, these drugs appear to be safe from a cardiovascular standpoint because they don’t increase the risk of serious cardiovascular events [20].

6.2.4 Salmeterol

Salmeterol is a long-acting inhaled ß-agonist that has been shown to be effective at preventing HAPE in individuals susceptible to this condition [20].

Patients receiving ß-blockers may experience a decrease in the effectiveness of either the ß-blocker or Salmeterol if they are taken together [20].

*6.3 **Pre-requisites, general recommendations and contraindications** (modified from [7])*

General pre-requisites at low altitude
Stable clinical condition
Asymptomatic at rest
NYHA functional class I- II

General recommendations at high altitude
Ascent at a slow rate >2000 m
Increasing sleeping altitude by <300 m/d
Avoid over-exertion
Avoid direct transportation to an altitude >3000 m

Absolute contraindications to high-altitude exposure
Unstable angina
Symptoms or signs of ischemia during exercise test at low or moderate workload
Decompensated heart failure
Coronary revascularization, episodes of myocardial infarction or decompensated heart failure in the previous 6 months
Uncontrolled atrial or ventricular tachyarrhythmias
Poorly controlled arterial hypertension
Marked pulmonary hypertension
Severe valvular heart disease, even if asymptomatic
Cyanotic or severe acyanotic congenital heart disease
ICD implantation or ICD intervention for ventricular arrhythmias in the previous 6 months

6.4 Specific CV problems (modified from [15])

Arterial hypertension: ascend with caution
self-monitoring of blood pressure
therapy adjustment if necessary

Heart failure: contraindicated if symptomatic at resident altitude
ascend with caution if asymptomatic at resident altitude
instructions for treatment adjustment if heart failure develops

CAD: unstable angina = contraindicated
stable angina = ascend with caution after careful assessment of patient and itinerary

myocardial infarction = contraindicate for 6 months after MI
by-pass or angioplasty = non contraindications if asymptomatic at resident altitude 6 months after the event

Cardiac arrhythmias: individual cardiology risk assessment needed
instructions for heart rate self-monitoring and therapy adjustments

Congenital/valvular heart disease: ascend with caution
Instructions for self-monitoring of INR and doses adaptation
contraindicated if severe pulmonary hypertension

6.5 Pre-exposure assessment according to CVD (modified from [7])

CAD
Exercise testing.
If not conclusive, exercise testing with imaging modality
Transthoracic echocardiography at rest

CHF
Exercise testing
Spiroergometry
Transthoracic echocardiography at rest
Holter ECG

Arterial hypertension
If not well controlled → ambulatory blood pressure recording

Arrhythmias
Exercise testing
Holter ECG
Pacemaker testing if VVIR, DDDR or AAIR mode to adapt PM rates
If SVT or atrial flutter, consider catheter ablation before high-altitude exposure

Valvular / congenital heart disease
Exercise testing
Transthoracic echocardiography at rest
Echocardiographic assessment of LV and RV function and PuAP under simulated high-altitude

6.6 Checklist of recommendations (modified from [15])

Seek medical advice from a doctor experienced in altitude medicine

Avoid travel if medical condition is not stable

Purchase travel insurance including coverage for remote evacuation

Ensure optimal physical fitness prior to travel

Understand airline restriction and requirements for travel with medication or medical devices, use MEDA sheet, if necessary

Continue with regular treatments unless otherwise instructed by a physician

Consult a physician in relation to potential interactions with medications used to treat high altitude illness

Bring extra doses of regular medications

Carry emergency supplies of medications separate from the main supply

Travel with a partner or group

Inform and educate team leader or travel companions about your medical conditions

Maintain good levels of nutrition and hydration, treat traveller's diarrhoea aggressively [X,Y]

Allow extra time for acclimatization and restrict activity during this period

Descend to lower altitude immediately with the onset of symptoms

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Kommentar: Reference list must be finalized

Members of UIAA MedCom (in alphabetical order) to be updated in Whistler!

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History of this recommendation paper

In summer 2009 UIAA MedCom decided to focus the complex field of mountaineering with preexisting medical conditions more in detail. The first of these recommendation papers focused neurological conditions in 2009, another one in 2010 eye problems. The actual paper was initiated by the Italian group and approved in its present form at the annual MedCom meeting at Whistler / Canada in July 2012.