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# High-Altitude Exposure in Patients with Cardiovascular Disease: Risk Assessment and Practical Recommendations

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**Abstract** Because of the development of modern transportation facilities, an ever rising number of individuals including many patients with preexisting diseases visit high-altitude locations (>2500 m). High-altitude exposure triggers a series of physiologic responses intended to maintain an adequate tissue oxygenation. Even in normal subjects, there is enormous interindividual variability in these responses that may be further amplified by environmental factors such as cold temperature, low humidity, exercise, and stress. These adaptive mechanisms, although generally tolerated by most healthy subjects, may induce major problems in patients with preexisting cardiovascular diseases in which the functional reserves are already limited. Preexposure assessment of patients helps to minimize risk and detect contraindications to high-altitude exposure. Moreover, the great variability and nonpredictability of the adaptive response should encourage physicians counseling such patients to adapt a cautionary approach. Here, we will briefly review how high-altitude adjustments may interfere with and aggravate/decompensate preexisting cardiovascular diseases. Moreover, we will provide practical recommendations on how to investigate and counsel patients with cardiovascular disease desiring to travel to high-altitude locations. (Prog Cardiovasc Dis 2010;52:512-524)


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An increase in altitude is associated with a decrease in barometric pressure. As a consequence, partial pressure of oxygen is also reduced and oxygen availability progressively decreases with increasing elevation. High altitude is defined as the terrestrial elevation at which the oxygen hemoglobin saturation decreases below 90%. At moderate latitude this corresponds to an altitude of about 2500 m. Starting at this altitude, mainly via chemoreflexes involving the sympathoadrenal system,[1-3] hypoxemia triggers a series of pulmonary and cardiovascular adjustments intended to maintain an adequate oxygenation of the different organ systems (Table 1).

In the heart, as presented in more detail elsewhere in this special issue (Naeije, R. p 286-289), the major adjustments are an increase in heart rate, cardiac contractility and cardiac output.[4-7] 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 vasodilation and enhancement of coronary blood flow[8] because the coronary oxygen extraction is already submaximal at low altitude.

At the vascular level, the main initial adaptive mechanisms to altitude-induced hypoxemia are pulmonary

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**Abbreviations and Acronyms**

**CAD** = coronary artery disease

**CHF** = congestive heart failure

**ECG** = electrocardiographic

**HAPE** = high altitude pulmonary edema

**ICD** = implantable cardioverter-defibrillator

**LVEF** = left ventricular ejection fraction

**PFO** = patent foramen ovale

**PM** = pacemaker

**RV** = right ventricular

**RA** = right atrial

**SCD** = sudden cardiac death

artery vasoconstriction and peripheral and cerebral artery vasodilation. Very rapidly however, for yet unknown reasons, the direct hypoxia-induced vasodilation and the adrenal medullary response decrease, and systemic vascular resistance and blood pressure tend to increase.[9,16]

The hypoxia-mediated stimulation of the cardiovascular system reaches its maximum effects during the first few days of high-altitude exposure (Fig 1). Thereafter, probably related to the beneficial effects of subsequent vascular, respiratory, hematologic, and muscular adaptation mechanisms, a new steady state is established.

During the initial phase of high-altitude adaptation, several additional phenomena may have important pathophysiologic and clinical consequences. First, although there is little intraindividual variability of the magnitude of the cardiovascular response during repeated high-altitude exposure, there is a large interindividual variability of this response (Fig 2). Second, progressive stimulation of high-altitude adaptation mechanisms is not invariably associated with increasing benefits. Indeed, once these adjustments have reached their optimal effect, any further stimulation may have detrimental effects and induce specific high altitude-related diseases such as high-altitude pulmonary edema (exaggerated pulmonary hypertension) and/or high-altitude cerebral edema (exaggerated cerebral vasodilation) (Fig 3).

Table 1
Altitude-induced autonomic and cardiovascular adjustments

| Parameter | Acute Exposure | Long-term Exposure |
|---|---|---|
| Heart rate | ⇑[4-6] | ↑[4,5] |
| Stroke volume | = or ↓[5] | ↓[5] |
| Cardiac output | ⇑ [4-6] | ↑[4,5] |
| LVEF | ⇑[4,7] | ↑[4] |
| Coronary blood flow | ⇑[8] | = |
| Systemic blood pressure | ↑[9-13] | ↑[9,13] |
| Pulmonary artery pressure | ⇑[1,4,14,15] | ↑[4] |
| Sympathetic activity | ⇑[1,2] | ↑[3] |
| Adrenoreceptor density | =[2] | ↓[2] |
| Parasympathetic drive | =[2] | ⇑[2] |
| Muscarinic receptor density | =[2] | ⇑[2] |

⇑, clearly increasing; ↑, slightly increasing; ↓, slightly decreasing; =, equally to low altitude (references in text).

This large interindividual variability in the cardiovascular response to hypoxia has important consequences for the counseling because in the absence of a history of exposure, the prediction of well-being at high altitude is very difficult. This difficulty may be of particular importance for patients having cardiovascular diseases generally associated with impaired functional reserve.

## High altitude and cardiovascular diseases, (patho)physiology

### *Coronary artery disease*

Increased myocardial oxygen demand due to elevated heart rate, myocardial contractility, and ventricular afterload are the major determinants of myocardial ischemia in patients with coronary artery disease (CAD) exposed to high altitude. The mismatch between $O_2$ demand and supply may further be aggravated by inappropriate paradoxical hypoxia-induced coronary vasoconstriction[19] triggered by high altitude-induced respiratory alkalosis or coronary spasms.[20] In these patients, the capacity of the coronary circulation to augment perfusion distal to a coronary stenosis is limited already at sea level because coronary autoregulation induces microcirculatory dilatation downstream of a stenotic lesion (low perfusion pressure) to maintain normal myocardial perfusion at rest. At high altitude, the only way to increase blood flow to a myocardial region supplied by a stenotic artery is by sympathetic stimulation of collateral supply.[21]

The sympathoadrenergic augmentation of collateral supply to ischemic myocardium appears quite efficient because the available data suggest that in patients with stable CAD high-altitude exposure is relatively safe.[22-28] In patients with stable CAD, 5 studies assessed the incidence of electrocardiographic (ECG) signs of acute ischemia at altitudes between 2500 and 3500 m, either at rest (n = 20)[28] or during exercise (n = 85).[24-27] None of the patients developed symptoms or signs of ischemia. Only one study reports on high-altitude exposure of patients with CAD and impaired left ventricular ejection fraction (LVEF).[22] In this study, 23 patients (mean age, 51years) with CAD and a LVEF of 39% ± 6% underwent maximal symptom-limited exercise testing after rapid transport to 2500 m. None of the patients developed angina, ECG signs of ischemia, arrhythmia, or other complications, suggesting that acute exposure to 2500 m of stable asymptomatic patients with moderately impaired LVEF is safe. In line with these observations, there is no evidence for an increased incidence of acute myocardial ischemic events during commercial flights where cabin pressure is kept lower than 2500 m.[29]

Recent epidemiologic data suggest that long-term exposure at moderate altitude (1000-1960 m) has

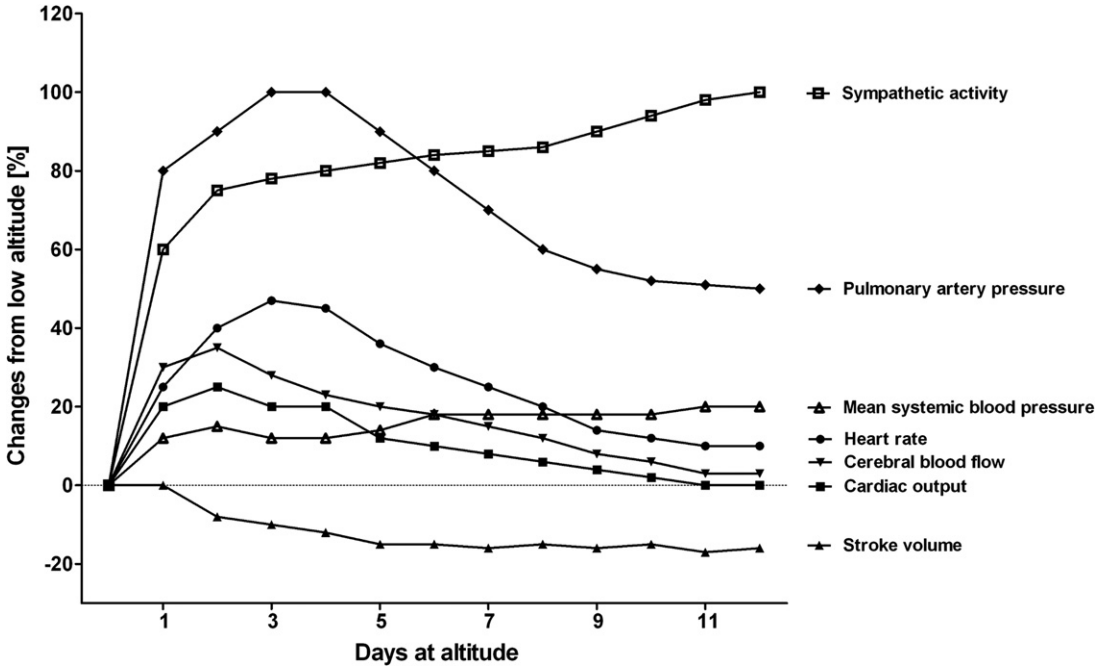


Fig 1. Average cardiovascular and autonomic changes during the first 10 days of acute high-altitude exposure between 3800 and 4559 m in healthy subjects. The hypoxia-mediated stimulation of the cardiovascular system reaches its maximum effects during the first few days of high-altitude exposure.[1,3,5,15,17]

favorable effects on mortality from CAD and stroke. This favorable effect was not restricted to those who were born at this altitude but also seen in those who moved to high altitude later in their life.[30] It is not known whether in patients with CAD, long-time high-altitude exposure may have similar favorable effects.

### *Congestive heart failure*

Adaptive mechanisms to high-altitude exposure that may represent risk factors in patients with congestive heart failure (CHF) include further stimulation of the already activated sympathetic nervous system, increased heart rate and myocardial oxygen demand, increased ventricular afterload, and enhanced interdependence between the right and left ventricle due to the increased pulmonary artery pressure (see later).

There are no field studies on the effect of high-altitude exposure in patients with CHF. An Italian chamber study assessed the effects of simulated altitude on exercise capacity in 38 patients (mean age, 61 years) with stable heart failure of various etiologies and an average LVEF of 35%.[31] Compared to sea level, simulated high-altitude exposure up to 3000 m was not associated with an increased incidence of exercise-induced arrhythmias or myocardial ischemia, and none of the patients developed acute heart failure. However, high-altitude exposure decreased the (maximal) exercise capacity in these patients. This decrease was greatest in patients with the lowest exercise capacity at sea level.

Several factors may limit exercise capacity in heart failure patients at altitude. For example, the acute pressure overload due to increased pulmonary artery pressure may deteriorate right ventricular (RV) function, adversely affecting left ventricular filling, and thereby limit exercise capacity. Moreover, the interdependence between the right and left ventricle rises as pulmonary artery pressure increases. Right ventricular pressure overload shifts the interventricular septum to the left and alters the left ventricular geometry and filling. Although in healthy subjects, increased left atrial contraction compensates for left ventricular geometry and filling alterations and prevents diastolic dysfunction, this compensatory mechanism may not be operational in patients with chronic heart failure.[7,32]

There is only one field study that examined the effects of high-altitude exposure in patients with CAD and moderately diminished systolic left ventricular function (ejection fraction around 40%) who were fully compensated and free of symptoms and signs of ischemia during exercise testing at low altitude. None of these patients experienced ischemia or other complications during acute exposure to 2500 m and symptom-limited exercise testing at this altitude.[22]

Taken together, available data suggest that high-altitude exposure up to 3000 m is not associated with a

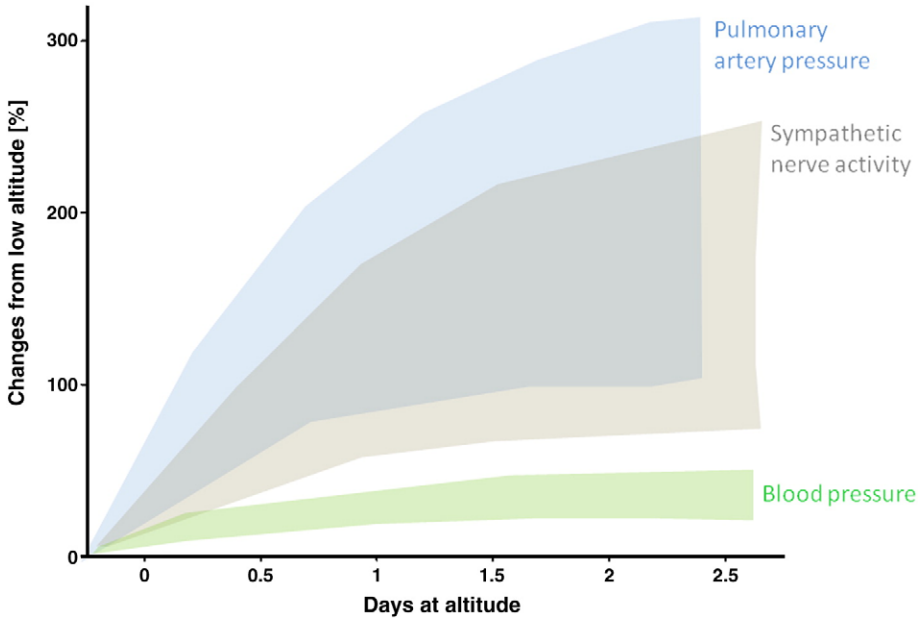


Fig 2. Range of systolic pulmonary artery pressure, sympathetic nerve activity, and systolic blood pressure during the first 2 and half days of high-altitude exposure (4500 m) in normal subjects.[1,4,7,10-13,15,18] Note that there is enormous interindividual variability of these responses.

substantially increased risk of cardiovascular complications in patients with stable, compensated heart failure.[22,31]

### *Arterial hypertension*

The principal determinants of blood pressure at high altitude are the same as those at low altitude and include cardiac output, which is dependent on heart rate and stroke volume, systemic peripheral resistance, and central venous pressure, an index of volume status. Ambient hypoxia induces peripheral vasodilation but also markedly activates the sympathetic nervous system. The latter triggers an increase in cardiac output and systemic vasoconstriction

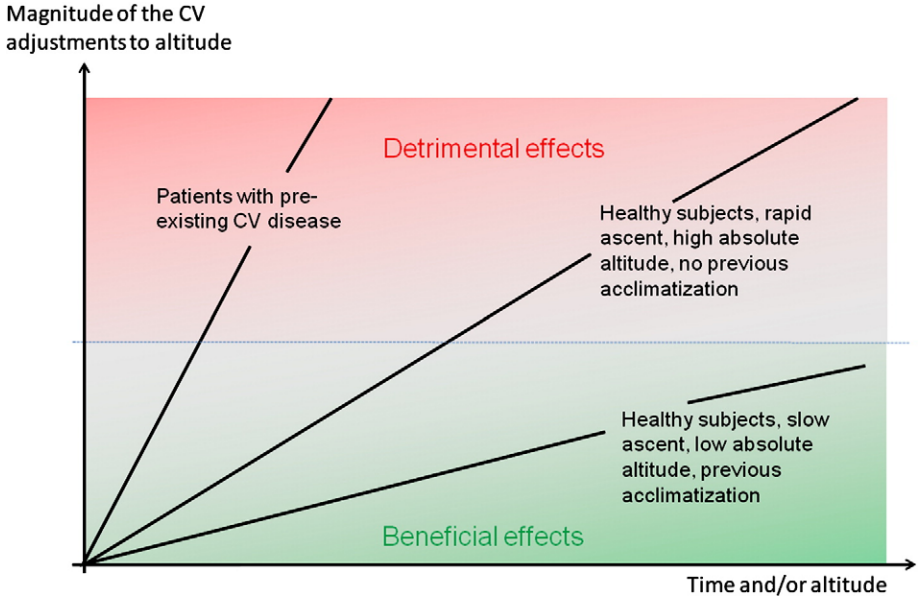


Fig 3. Beneficial/detrimental effects of high-altitude adjustments in healthy subjects and in patients with cardiovascular disease. Appearance of detrimental effects depends on absolute reached altitude, rapidity of ascent, and preexposure clinical condition. In healthy subjects, lack of acclimatization, rapid ascent to very high altitude, particularly if associated with increased susceptibility to high-altitude diseases, may precipitate life-threatening problems. In patients with preexisting cardiovascular disease, this susceptibility may be even greater and life-threatening problems may occur already at moderate absolute altitude and slow ascent rate.

that within a few hours overcomes the hypoxia-induced vasodilation and promotes an increase in blood pressure. In hypertensive patients, this mechanism may be accentuated because hypertension-associated endothelial dysfunction may impair hypoxic vasodilation and facilitate sympathetic vasoconstriction. On the other hand, the ambient low humidity, increased ventilation, and physical effort may lead to dehydration, a state that may contribute to lower blood pressure. In hypertensive patients, the use of diuretics or other drugs may worsen this effect. In healthy subjects, the net effect of these altitude-induced changes is usually a modest increase of arterial blood pressure,[10,33,34] but this individual response may be quite variable.[10,11] In untreated patients with mild to moderate arterial hypertension, the altitude-induced increase of systolic blood pressure may exceed 20 mm Hg,[11] whereas in well-controlled hypertensive patients, this increase was modest both at rest and during exercise.[22,24,27]

There are no reports of major complications (retinopathy, intracranial bleeding, myocardial infarction, stroke) in patients with hypertension exposed to high altitude,[12,13] except for a single study suggesting an increased odd ratio (1.5) for sudden cardiac death during mountain hiking or skiing.[35] Finally, there is no evidence for an altered prevalence of high altitude-related illness in patients with arterial hypertension.

### *Anomalies of the pulmonary circulation*

High-altitude exposure is associated with hypoxic pulmonary vasoconstriction. This pulmonary vasoconstriction may be further aggravated by sympathetic activation, cold, physical exercise, and increased cardiac output.[36] Preexisting pulmonary hypertension at sea level of any origin may deteriorate at altitudes greater than 2000 m, particularly during exercise.[31] Because of the increased afterload, these patients are also at risk for developing acute cor pulmonale, particularly if RV function is already impaired at low altitude.[37] Moreover, patients with a congenitally (absent or abnormal pulmonary arteries) or acquired (obstructed vessels) restricted pulmonary vascular bed or pulmonary vascular dysfunction (Trisomy 21)[38] are at increased risk to develop exaggerated pulmonary hypertension and high altitude pulmonary edema (HAPE) at considerably lower altitudes than those typically associated with a risk of HAPE.[39,40] Whether this is also the case for patients having other forms of pulmonary hypertension is not known.

Finally, patients in whom pulmonary hypertension has caused a right-to-left shunt may develop more significant hypoxemia at high altitude. In conjunction with a decreased tissue blood flow, this exaggerated hypoxemia may facilitate myocardial ischemia and chest pain particularly during exercise.

#### *Valvular heart disease*

There are no reports on the effects of high-altitude exposure in patients with primary valvular heart disease. It is beyond the scope of this review to describe in detail the pathophysiology of the various valvular pathologic conditions and individually relate them to the potential risks associated with high-altitude exposure. Most of the risks can be anticipated according to what has been described above for heart failure and pulmonary hypertension. The potential problems of high-altitude exposure in such patients are those related to the worsening of the pressure or volume overload associated with a particular valvular dysfunction. The altitude-induced increase of heart rate and cardiac output might worsen a valvular stenosis, the increased systemic vascular resistance and arterial blood pressure might adversely affect a preexisting aortic or mitral valve regurgitation, and an increased pulmonary vascular resistance might aggravate pulmonary and tricuspid regurgitation. Dehydration, which frequently occurs during the first days at high altitude, may worsen valvular stenosis. Dehydration, together with reduced plasma volume secondary to an increased release of atrial natriuretic peptide and decreased aldosterone synthesis,[41] altered blood viscosity,[42] and development of a procoagulatory state[43] may also increase the risk of valvular thrombosis in patients with prosthetic mechanical heart valves. This risk may increase further if oral anticoagulation is not optimal.

### *Patent foramen ovale*

As described elsewhere in this special issue, in HAPE-prone individuals,[38] acute high-altitude exposure is associated with exaggerated hypoxic pulmonary vasoconstriction and pulmonary hypertension. A right heart pressure overload may facilitate the shunting of deoxygenated blood from the right to the left atrium via a patent foramen ovale (PFO) and further aggravate hypoxemia at high altitude. In line with this hypothesis, in HAPE-prone subjects, PFO was 4 to 5 times more frequent than in mountaineers resistant to this condition and associated with lower arterial oxygen saturation and a higher systolic pulmonary artery pressure at high altitude.[18] Moreover, in HAPE-susceptible subjects, the size of the PFO was directly related with arterial hypoxemia, suggesting that the size of the PFO, rather than its mere presence, may be clinically relevant in this setting (Fig 4). Observations made in divers with decompression illness and patients with platypnea-orthodeoxia are in line with this hypothesis.[44,45] The significance of these results is 2-fold. First, the markedly greater frequency of PFO in HAPE-prone individuals could suggest that, together with exaggerated hypoxic pulmonary hypertension and defective alveolar fluid clearance,[14] PFO may represent an additional constitutional anomaly associated with HAPE

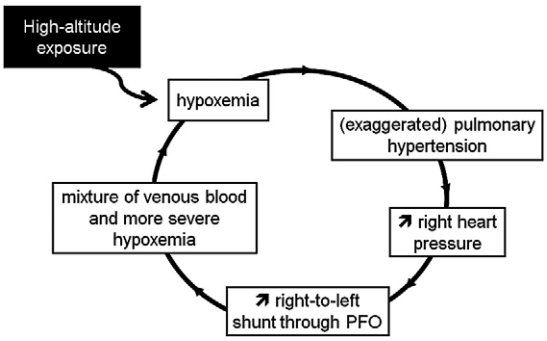


Fig 4. Altitude-induced hypoxia evokes pulmonary vasoconstriction. In the presence of a PFO. this initiates a vicious cycle by causing right-to-left shunting across the PFO that in turn aggravates hypoxemia, resulting in reduced mixed venous oxygen tension, more severe hypoxemia, and therefore greater pulmonary hypertension.

susceptibility.[38] Second, these findings could be consistent with the concept that in HAPE-prone individuals with a large PFO, the acute hypoxic pulmonary vasoconstriction initiates a vicious cycle by causing right-to-left shunting across a PFO that in turn aggravates hypoxemia, resulting in reduced mixed venous oxygen tension, greater alveolar hypoxia, and greater pulmonary hypertension[46] (Fig 4). Finally, an interesting issue raised by these findings in HAPE-prone subjects that deserves further study is whether in subjects with large PFOs but no history of previous high-altitude exposure, a PFO may represent a risk factor for HAPE.

### *Patients with congenital heart disease*

The most frequent acyanotic defects are bicuspid aortic valve, atrial septal defect, ventricular septal defect, and patent ductus arteriosus. The 3 latter defects, if uncomplicated, are associated with left-to-right shunt and may favor the development of pulmonary hypertension.[37] The pulmonary hypertension associated with high-altitude exposure may, therefore, augment the afterload of the subpulmonic ventricle. This problem may be further aggravated by exercise and, in extreme situations, result in a shunt reversal and further worsening of the high altitude-associated hypoxemia.[18,47]

Cyanotic patients are characterized by a right-to-left shunt or severely reduced pulmonary flow. In most cases, particularly in patients with the Eisenmenger syndrome, the right-to-left shunt is the consequence of severe pulmonary hypertension. Because hypoxia elicits pulmonary vasoconstriction, high-altitude exposure can only have detrimental effects in these patients and should, therefore, be strictly discouraged. Not surprisingly, data on high-altitude exposure of patients with congenital cyanotic heart disease are sparse. Harinck et al[48] studied 12 adults with cyanotic heart disease (7 with Eisenmenger syndrome and 5 with other complex cyanotic heart diseases) during simulated 1.5 to 7 hours of flights in a hypobaric chamber (simulated altitude: 2468 m). There were no significant cardiovascular complications despite an average decrease of arterial oxygen saturation from 86% ± 5.2% to 79% ± 5.4% during the longer simulated flight.

### *Arrhythmias*

High altitude may favor the development of arrhythmias via activation of the sympathetic nervous system and increased adrenaline spillover during exertion, aggravation of myocardial ischemia, acute RV pressure overload, and hypokalemia secondary to respiratory alkalosis, diuretics, vomiting related to acute mountain sickness, and diarrhea. Altitude-induced arrhythmias have been claimed to be responsible for a significant number of sudden cardiac deaths (SCDs). For example, for an 8-year period in the Austrian Alps, there were 642 SCDs, and in this registry, 30% of all deaths during mountain sports at altitude were attributed to SCD,[49,50] possibly related to sympathetically mediated ventricular arrhythmia. However, the relatively high incidence of SCD in these reports is surprising and suggests preexisting cardiac disease in many of these cases. In line with this speculation, the risk factor profiles of 68 males who died of SCD during downhill skiing at altitude, revealed prior myocardial infarction, hypertension, and known coronary heart disease in many of them.[51] By contrast, in patients with stable CAD[22,24,25] or compensated heart failure,[22,31] the incidence of malignant ventricular arrhythmias or SCD was not increased, in spite of an increase of premature supraventricular and ventricular beats.[52,53]

Pacemaker function remained unchanged in a hypobaric chamber study simulating altitudes up to 4000 m.[54] There are no data on patients with implantable cardioverter-defibrillators (ICDs) at high altitude.

### *Cerebrovascular disease*

Studies from India and Pakistan suggested that long-term stay at high altitude may increase stroke incidence,[55,56] whereas recent data from Switzerland suggest that long-term high-altitude stay between 1000 and 1960 m may decrease the incidence of stroke.[30] It is not known whether short-term sojourns at high altitude pose a risk for first-ever stroke. In persons with a history of stroke, high altitude might increase the risk for recurrence, particularly during the first weeks and months after the event. High altitude-induced dehydration and reduced plasma volume, increased hematocrit and polycythemia, endothelial dysfunction, altered coagulation, and thrombocyte aggregation are all potential factors that may facilitate thrombus formation and stroke.[43] Normally, cerebral blood flow increases at high altitude.[17] Stenoses and occlusions of extra- and intracranial arteries, whether symptomatic or asymptomatic, might compromise this

cerebral blood flow adjustment and expose these persons at enhanced stroke risk.[57] Furthermore, thrombus formation can also affect the venous side of the cerebral circulation. Cerebral venous thrombosis has been reported in mountaineers, and those having high-altitude cerebral edema appear to be at increased risk for this problem.[58] Patients with a history of cerebral hemorrhage are probably at increased risk for recurrence at high altitude because of blood pressure changes. This is also true for the rupture risk of cerebral aneurysms, cavernomas, and arteriovenous malformations because blood pressure changes at high altitude might increase the intraluminal pressure.

## High altitude and cardiovascular diseases, practical recommendations

Because of the paucity of existing studies, evidence-based recommendations for unacclimatized patients with cardiovascular disease who are considering high-altitude exposure are not possible. The following recommendations, summarized in Tables 2 and 3, are based on the available data and our own experience and should reasonably ensure the patients' safety.

Conditions that represent contraindications for high-altitude exposure are summarized in Table 2. Several factors other than the illness(es) itself have to be taken into account when assessing the risk of high-altitude exposure of cardiovascular patients. Among these factors are the altitude to be reached, the rapidity of the ascent, the geographic location, the planned activity, the medical environment and rescue possibilities, and the physical fitness at low altitude. As a general rule to keep the risk as low as possible, patients should be in a stable and compensated clinical condition at low altitude and have a functional class lower than II (Table 2).

When ascending above 2000 m, patients should limit the mean daily rate of ascent to 300 to 400 m, to allow for proper acclimatization.

### *Coronary artery disease*

High-altitude exposure is contraindicated in patients with unstable CAD and in those who experience ischemia already at low to moderate workload (<80 W or <5 metabolic equivalents; Table 2). Traveling to high altitude is also contraindicated for at least 3 months after an acute coronary syndrome, myocardial infarction, or percutaneous or surgical coronary revascularization (Table 2).

In individuals at risk for or with known CAD and in all elderly men (>50 years) and women (>60 years), we recommend symptom-limited exercise testing before a prolonged high-altitude sojourn (Table 3). If exercise testing is clinically and/or electrically negative, then high-altitude exposure can safely be considered. If positive, further imaging testing is recommended. In patients with stable angina and an ischemic threshold of more than 6 metabolic equivalents, altitude exposure up to 3500 m may be considered, in particular, if passive ascent is planned. These patients, as well as all others with asymptomatic CAD and a negative exercise test, need to respect acclimatization rules and limit their physical activity (<70% of maximal heart rate achieved during exercise testing) during the first 3 to 5 days of exposure. If angina occurs, patients should not ascend any further, limit their physical activity, and consider descent to lower altitudes. Antianginal drugs should be administered to relieve symptoms, but as will be mentioned later (section on arterial hypertension), $\beta$-blockers will limit physical performances.[59] Because of the markedly increased risk of uncontrolled bleeding, patients under dual platelet antiaggregation and concomitant oral anticoagulation should be strongly discouraged to seek high altitudes for prolonged periods, particularly in remote areas of the globe.

Table 2
Prerequisites, general recommendations, and contraindications to high-altitude exposure

General prerequisites at low altitude
- Stable clinical condition
- Asymptomatic at rest
- Functional class < II

General recommendations at high altitude
- Ascent at a slow rate > 2000 m (increasing sleeping altitude by < 300 m/d)
- Avoid overexertion
- Avoid direct transportation to an altitude > 3000 m

Absolute contraindications to high altitude exposure
- Unstable clinical condition, ie,
  - unstable angina
  - symptoms or signs of ischemia during exercise testing at low to moderate workload (<80 W or <5 metabolic equivalents)
  - decompensated heart failure
  - uncontrolled atrial or ventricular arrhythmia
- Myocardial infarction and/or coronary revascularization in the past 3-6 mo
- Decompensated heart failure during the past 3 mo
- Poorly controlled arterial hypertension (blood pressure ≥ 160/100 mm Hg at rest, > 220 mm Hg systolic blood pressure during exercise)
- Marked pulmonary hypertension (mean pulmonary artery pressure > 30 mm Hg, RV-RA gradient > 40 mm Hg) and/or any pulmonary hypertension associated with functional class ≥ II and/or presence of markers of poor prognosis[37]
- Severe valvular heart disease, even if asymptomatic
- Thromboembolic event during the past 3 mo
- Cyanotic or severe acyanotic congenital heart disease
- ICD implantation or ICD intervention for ventricular arrhythmias in the past 3-6 mo
- Stroke, transient ischemic attack, or cerebral hemorrhage during the past 3-6 mo

### *Congestive heart failure*

Patients with severe functional limitation, clinical or biochemical signs of fluid retention, or who are clinically

Table 3
Recommendations and preexposure assessment according to cardiovascular disease

| Clinical Condition | Proposed Preexposure Assessment and Recommendations for Patients |
|---|---|
| CAD | |
| Asymptomatic revascularization < 6 mo | Consider exercise testing according to coronary status |
| Asymptomatic revascularization > 6 mo | Exercise testing<br>If not conclusive → exercise testing with imaging modality |
| Asymptomatic reduced LVEF | Exercise testing<br>If not conclusive → exercise testing with imaging modality<br>Transthoracic echocardiography at rest |
| Reduced LVEF | |
| Any cause | Exercise testing<br>Transthoracic echocardiography at rest<br>Instructions for treatment adjustments if heart failure develops |
| Arterial hypertension | |
| | If not well controlled → ambulatory blood pressure recording<br>Instructions for self-monitoring of blood pressure and treatment adjustments if uncontrolled hypertension or hypotension develops |
| Pulmonary hypertension | |
| | Exposure contraindicated if marked pulmonary hypertension or if functional class > I (see Table 2)<br>Echocardiographic assessment of RV function and of pulmonary artery pressure under simulated high altitude ($FIO_2$: 12%; if RV-RA gradient N 40 mm Hg patients should be strongly discouraged) |
| Valvular heart disease | |
| Symptomatic and/or severe | Exposure contraindicated |
| Mild aortic or mitral regurgitation | Exercise testing, transthoracic echocardiography at rest<br>Instructions for self-monitoring of blood pressure and treatment adjustments if uncontrolled hypertension or hypotension develops<br>Instructions for self-monitoring of international normalized ratio and dosis adaptation |
| Congenital heart disease | |
| Acyanotic or cyanotic | Exposure contraindicated if functional class > I<br>Exercise testing and echocardiographic assessment of left and RV function and pulmonary pressure under simulated high altitude (FIO2, 12%; if RV-RA gradient > 40 mm Hg patients should be strongly discouraged) |
| Arrhythmia | |
| Associated with CAD/CHF | Exercise testing |
| Pacemaker | Testing only if VVIR, DDDR, or AAIR mode to adapt PM rates |
| Supraventricular tachycardia/atrial flutter | Consider catheter ablation before high-altitude exposure |
| Paroxysmal or persistent atrial fibrillation | Exercise testing and Holter-ECG<br>Instruction for heart rate self-monitoring and therapy adjustments in case of insufficient rate control (>90 beats per min at rest) |
| Cerebrovascular disease | |
| All conditions | Avoid trekking or climbing alone |
| Ischemic stroke or TIA < 90 d ago | Avoid traveling to higher altitudes (>2000-2500 m)<br>Avoid air travel |
| Ischemic stroke or TIA > 90 d ago, thorough workup of the stroke has been performed and risk factors are treated adequately | Avoid extreme altitude > 4500 m |
| Stenosis or occlusion of a major extra- or intracranial cerebral artery | Avoid traveling to altitude >2000-2500 m |
| Hypertensive hemorrhage | Travel to high altitude only if blood pressure is controlled and not before 90 d after the event |
| Hemorrhage as a result of amyloid angiopathy | Avoid high altitude |
| Known cerebral aneursym, arteriovenous malformation, or cerebral cavernoma | Check blood pressure. Avoid extreme altitude >4500 m |

*Abbreviations:* VVIR, ventricular pacing, ventricular sensing, inhibition response, and rate-adaptive; DDDR, atrial and ventricular pacing, atrial and ventricular sensing, dual response, and rate-adaptive; AAIR, atrium paced, atrium sensed, and pacemaker inhibited in response to sensed atrial beat and rate-adaptive; TIA, transient ischemic attack.

unstable should not travel to high altitude (Table 2). If a patient with stable compensated CHF considers a prolonged sojourn at high altitude, the preexposure assessment should at least include a transthoracic echocardiography and a symptom-limited exercise test (Table 3). For better risk stratification, spiroergometry and

Holter-ECG should be considered in individual cases. In compensated and stable patients, exposure up to 3000 m can safely be considered, provided acclimatization rules are respected and physical activity is limited, particularly during the first days of exposure. Patients should be informed that exercise performance will decline at altitude, particularly if functional capacity is already reduced at sea level.[31] Patients should know and strictly adhere to the usual recommendations that also apply to low altitude, including restriction of salt intake, self-monitoring of body weight (if possible) and signs of fluid retention (peripheral edema, nocturia, orthopnea, and others), and they should be familiar with self-adjustment of diuretic dosage. The appearance of signs and symptoms of pulmonary congestion represents a medical emergency and warrants descent to lower altitude and seeking medical advice. The distinction between pulmonary edema related to decompensated CHF or HAPE can be challenging in the field. In the absence of medical help, the patient should be instructed to take 1 or 2 supplemental doses of a loop diuretic and, if no improvement is achieved within 4 to 6 hours, to start a treatment with a calcium-channel blocker (slow-release nifedipine, 20 mg, every 6 hours) that should be beneficial if HAPE is responsible for the symptoms.

Dehydration due to exertion, low humidity, diuretics, or diarrhea needs to be avoided. If in patients with CHF such a situation occurs, particularly in the case of persistent and/or severe diarrhea, the diuretic dose should be halved or even stopped, and fluid loss should be compensated. Electrolyte disturbances, particularly hypokalemia, may develop and put the patient at risk for arrhythmia and SCD.

### *Arterial hypertension*

Blood pressure should be well controlled before seeking high altitude. If a patient is well controlled, antihypertensive therapy should not be modified before departure. In principle, all recommended classes of antihypertensive drugs can be used.[60] Calcium-channel blockers (and α-receptor blockers) may have additional beneficial effects for the prevention of HAPE by attenuating pulmonary hypertension. If a longer sojourn at high altitude is planned, diuretics should not be first-line therapy because they may increase the risk of hypokalemia and dehydration. β-Blockers may cause problems because they limit exercise capacity and exercise-induced hyperventilation at high altitude and may aggravate hypoxemia during exercise.[59] Although angiotensin-converting enzyme inhibitors may increase the hypoxic ventilatory response and improve short high-altitude tolerance,[61] they may impair renal erythropoietin synthesis, and in turn, long-term adaptation to high altitude.[62]

Because the blood pressure response to high-altitude exposure is unpredictable and variable, patients should be instructed to self-monitor blood pressure and to adapt antihypertensive therapy,[60] if hypertension worsens or symptomatic hypotension develops (especially during the first days at altitude).

### *Anomalies of the pulmonary circulation*

As a general rule, due to the increased risk of developing HAPE and/or acute cor pulmonale, traveling to altitudes higher than 2000 m is contraindicated for patients with pulmonary hypertension (Table 2). For patients with milder forms of pulmonary hypertension (RV to right atrial [RV-RA] gradient ≤35 mm Hg and functional class ≤II at low altitude), travel to high altitude (up to 3000 m) may be considered, provided careful preexposure assessment and prophylactic measures (Table 3). The assessment should include a transthoracic echocardiography (RV-RA gradient, RV function) and a symptom-limited exercise test including monitoring of arterial oxygen saturation. For patients considering remote locations with no rapid transport facilities to lower altitudes and/or prolonged sojourn at high altitude, we recommend high-altitude simulation at low altitude by breathing hypoxic air via a facial mask. During hypoxic breathing (partial pressure of $O_2$ in the inspired air adjusted to the simulated altitude), arterial oxygen saturation is constantly monitored, and after steady state has been reached (20 minutes), systolic pulmonary artery pressure and RV function are estimated by Doppler echocardiography. If for a simulated altitude of 4500 m ($F_{IO_2}$: 12%), one of the following criteria is fulfilled, patients should be strongly discouraged to travel to high altitude: RV-RA gradient greater than 40 mm Hg and/or deterioration of RV function. For those going to high altitude, nifedipine should be prescribed to be taken if symptoms of HAPE develop.

### *Valvular heart disease*

High-altitude exposure is contraindicated in patients with symptomatic and/or severe valvular heart disease (Table 2). For patients with milder forms of valvular heart disease considering traveling to altitude, the same pretrip assessment and recommendations as for patients with CHF apply (Table 3). Once at altitude, fluid balance should be equilibrated and blood pressure well controlled. Because of the highly variable blood pressure response at altitude, we recommend blood pressure self-monitoring in hypertensive patients with more than mild mitral or aortic regurgitation, at least during the first days at altitude. New-onset arrhythmia, particularly atrial fibrillation is a concern and may be difficult to manage by the patient himself (see paragraph on arrhythmias later). In patients with prosthetic mechanical heart valves, valvular thrombosis and hemorrhagic complications are potential problems. Hence, activities at risk for traumatic

injury should be avoided at high altitude, and if the sojourn location is remote from medical care, the patient should be able to monitor and manage oral anticoagulation. The latter is of particular importance if gastrointestinal problems such as vomiting or diarrhea occur, and tight international normalized ratio monitoring is indicated.

### *Patients with congenital heart disease*

Patients with cyanotic, complex, or severe congenital heart disease are too fragile to consider high-altitude exposure (Table 2). The aforementioned chamber study of Harinck et al[48] should not be taken as evidence that such patients may tolerate high altitude. Simulated altitude exposure or flying in a commercial airplane are not the same as true high-altitude exposure. Nevertheless, if very strongly desired by the patients, a short-term trip with passive ascent up to 2000 to 2500 m may be considered, however, not without preexposure assessment and planning of prophylactic and emergency measures including oxygen supplement and possibly pulmonary vasodilators. Preexposure assessment should include transthoracic echocardiography during simulated high altitude ($F_{IO_2}$: 12%) and exercise testing and, in individual cases, cardiac magnetic resonance imaging and Holter-ECG (Table 3). In patients with less severe forms of congenital heart disease, counseling must be individualized, and based on the underlying defect, its severity and the type of high-altitude exposure must be planned.

### *Arrhythmia*

Patients in whom arrhythmia is associated with an underlying heart disease should follow the disease-specific recommendations made previously to limit the risk of malignant arrhythmia. For patients in whom arrhythmia is associated with CAD or heart failure, we suggest a stress test before exposure (Table 3). This test should be free of ischemic ECG changes and ventricular arrhythmias. High-altitude exposure is strictly contraindicated in patients with uncontrolled ventricular arrhythmias and recent ICD implantation (<3 months if the ICD was implanted for primary prevention, <6 months if the ICD was implanted for secondary prevention of malignant ventricular arrhythmias) (Table 2). Patients with recurrent ICD interventions (discharge or overpacing) for ventricular arrhythmias should neither travel to remote geographic areas nor

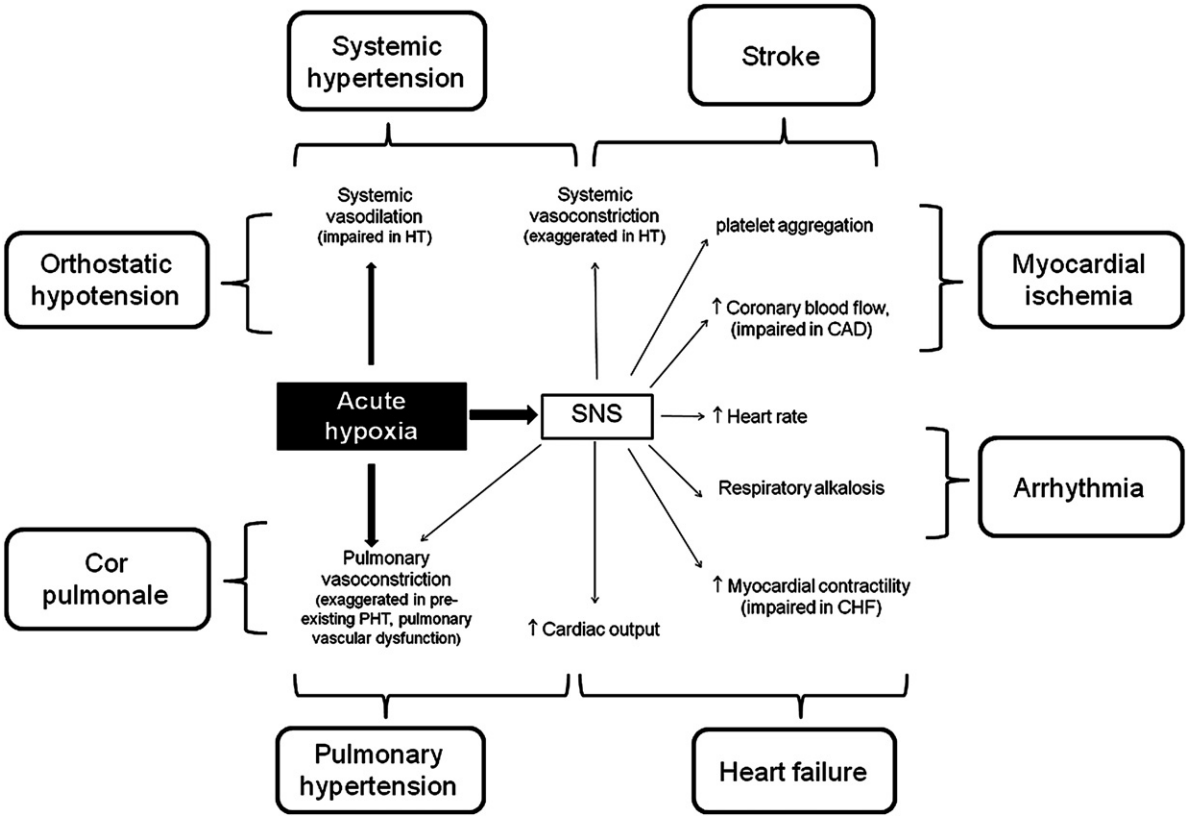


Fig 5. Main (patho)physiologic changes during high-altitude exposure and their associations with specific clinical conditions. *Abbreviations*: HT, arterial hypertension; SNS, sympathetic nerve activity; PHT, pulmonary hypertension.

engage in activity at high altitude. For ICD patients free of device therapy and without symptoms or signs of heart failure or myocardial ischemia, high-altitude exposure may be considered on an individual basis, taking into account the altitude to be reached, the rapidity of ascent, the geographic location, the physical activity planned, and the duration of exposure.

There is little safety concern in patients with pacemakers. In patients with stable pacemaker (PM) function, there is no need for additional PM testing before high-altitude exposure. Patients with a rate response pacemaker (ventricular pacing, ventricular sensing, inhibition response, and rate-adaptive; atrial and ventricular pacing, atrial and ventricular sensing, dual response, and rate-adaptive; or atrium-paced, atrium-sensed, and pacemaker-inhibited in response to sensed atrial beat and rate-adaptive mode) may represent an exception to this rule because they may benefit from higher PM rates during exertion at high altitude.

In patients with paroxysmal supraventricular tachycardias and atrial flutter, particularly in those considering high-altitude sojourns in remote areas of the globe, we recommend radiofrequency catheter ablation because at high altitude, heart rate during these arrhythmias may significantly increase and hemodynamic tolerance may decrease, with aggravation of symptoms including a risk of near-syncope and syncope. For those with paroxysmal and persistent atrial fibrillation, rhythm, or rate control, especially during exercise, should be ascertained by exercise testing or Holter-ECG before exposure. Because the ventricular rate response may accelerate at high altitude, patients should be instructed to check their heart rate and to adapt their rate-limiting drugs in case the rate control of atrial fibrillation becomes insufficient. Patients known for benign symptomatic ventricular or atrial premature beats or nonsustained tachycardias should be informed that the frequency and severity of their symptoms may increase at high altitude, and ad hoc adaptation of the treatment should be discussed (ie, increased doses in case of chronic prophylactic treatment, pill in the pocket in the others).

### *Cerebrovascular diseases*

Recommendations for patients with cerebrovascular disease contemplating traveling to high altitude are summarized in Table 3.

## Conclusions

High altitude has become a popular leisure time destination that is visited not only by healthy individuals but also by increasing numbers of patients with preexisting diseases. The low ambient oxygen triggers a series of physiologic adaptations intended to maintain adequate organ oxygen supply. There is enormous interindividual variability in these responses that may be further amplified by external factors such as cold temperature, low humidity, exercise, and stress. These adjustments, although generally tolerated by most healthy individuals, may induce major problems in patients with cardiovascular diseases, particularly those with already limited functional reserves at low altitude (Fig 5). Preexposure assessment helps to minimize risk and detect contraindications to high-altitude exposure. Moreover, the great variability and nonpredictability of the adaptive response should incite physicians counseling such patients to adapt a cautionary approach.

## Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

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