Altitude exposure is not a contraindication for patients with heart disease in general

Going to high altitude with heart disease

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Summary

As a result of ease of travel, a rising number of individuals, including many patients with pre-existing cardiovascular disease, visit high-altitude locations (>2500 m). Exposure to high altitude triggers a series of physiological responses intended to maintain adequate tissue oxygenation. Even in healthy subjects, there is enormous interindividual variability in these responses, which may be further amplified by environmental factors. These adaptive mechanisms may cause major problems in patients with pre-existing cardiovascular disease who are not able to compensate for such physiological changes. Pre-exposure assessment of patients helps to reduce risk and detect contraindications to high-altitude exposure. The great variability and unpredictability of the adaptive response should encourage physicians counselling such patients to adopt a cautious approach. Here, we briefly review how high-altitude adjustments may interfere with and aggravate/decompensate pre-existing cardiovascular diseases. Moreover, we provide practical recommendations on how to investigate and counsel patients with cardiovascular disease desiring to travel to high-altitude locations.

Key words: high-altitude exposure; cardiovascular disease; barometric pressure; altitude-induced hypoxaemia; cardiovascular risk assessment

Introduction

Ascent to altitude is associated with a decrease in barometric pressure and, in keeping with Dalton's law, with a consequent decrease of oxygen partial pressure and availability to tissues. High altitude is defined as the terrestrial elevation at which the oxygen haemoglobin saturation (SaO_2) decreases below 90%. At moderate latitudes this corresponds to an altitude of about 2500 m. Starting at this altitude, hypoxaemia triggers, mainly via chemoreflexes involving the sympathoadrenal system [1–3], a series of respiratory and cardiovascular adjustments intended to maintain adequate oxygenation of the different organ systems.

The acute and chronic cardiovascular changes for adaption to high altitude are described elsewhere in more detail [4]. The major adjustments are an increase in heart rate, cardiac contractility and cardiac output [5–8]. 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 [9], because coronary oxygen extraction at rest is already submaximal at low altitude.

At the vascular level, the main initial adaptive mechanisms to altitude-induced hypoxaemia are pulmonary artery vasoconstriction, and peripheral and cerebral artery vasodilation. Very rapidly, for as yet unknown reasons, this direct hypoxia-induced vasodilation decreases, and systemic vascular resistance and blood pressure tend to increase [10, 11]. The hypoxia-mediated stimulation of the cardiovascular system reaches its maximum effect during the first few days of high-altitude exposure (fig. 1).

Thereafter, probably related to the beneficial effects of subsequent vascular, respiratory, haematological and muscular adaptation mechanisms, a new steady state is established. Several additional phenomena may have important pathophysiological and clinical consequences during the initial phase of high-altitude adaption. Although there is little intraindividual variability in the magnitude of the cardiovascular response during repeated high-altitude exposure, there is a large interindividual variability in this response [1, 7, 8, 12–17]. Progressive stimulation of high-altitude adaptation mechanisms is not invariably associated with increasing benefits. Once these adjustments have reached their optimal effect, any further stimulation may have detrimental effects and may induce specific high-altitude-related diseases such as high-altitude pulmonary oedema (HAPE; exaggerated pulmonary hypertension) and/or high-altitude cerebral oedema (HACE; exaggerated cerebral vasodilation).

This large interindividual variability in the cardiovascular response to hypoxia has important consequences for counselling, particularly of patients with pre-existing cardiovascular diseases associated with impaired functional reserve. In the absence of a history of exposure, the prediction of wellbeing at high al-

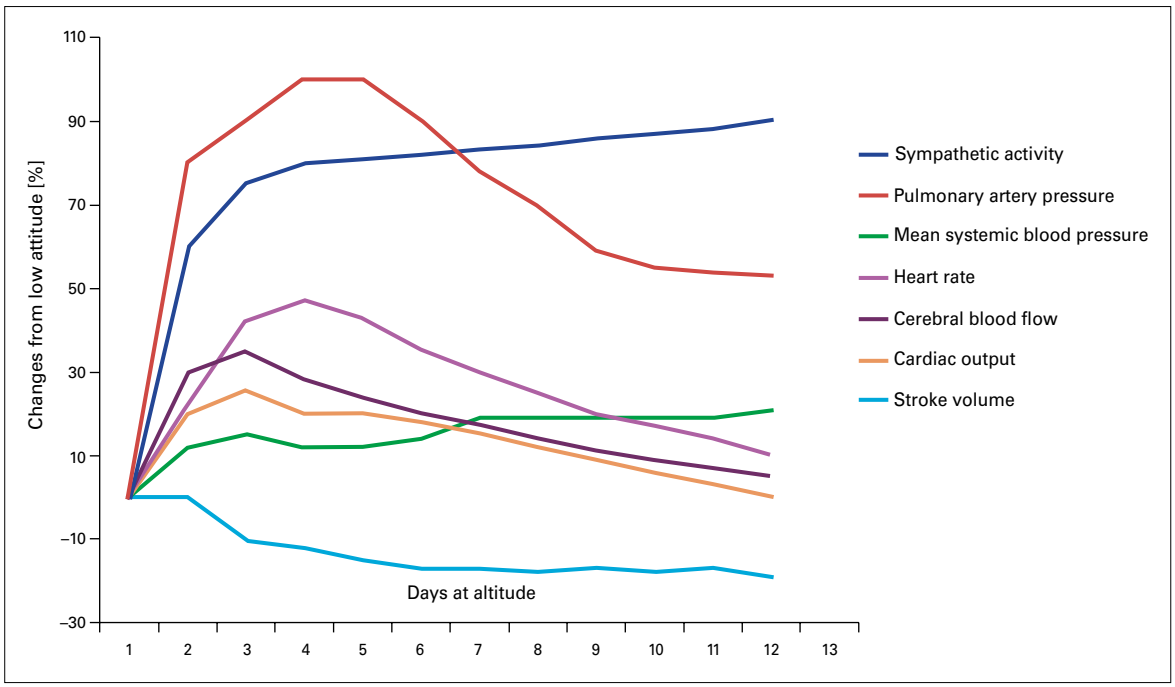

Figure 1: Average cardiovascular and autonomic changes in healthy subjects during the first 10 days of acute high altitude exposure between 3800 m and 4559 m. The hypoxia stimulation of the cardiovascular system reaches its maximum effect during the first few days of high-altitude exposure [1, 3, 5, 15, 59]. Modified from [64] with permission of Elsevier.

titude is very difficult. However, literature on whether people with pre-existing cardiovascular conditions should be allowed to go to high altitude is scarce.

Pathophysiological considerations in patients with pre-existing cardiovascular diseases

Coronary artery disease

The major determinants of myocardial ischemia in patients with coronary artery disease (CAD) exposed to high altitude are increased myocardial oxygen demand due to elevated heart rate, increased myocardial contractility and increased ventricular afterload. The mismatch between oxygen demand and supply may be further aggravated by inappropriate paradoxical hypoxia-induced coronary vasoconstriction [18] triggered by high-altitude-induced respiratory alkalosis or coronary spasm [19].

At sea level, the capacity of the coronary circulation to augment perfusion distal to a coronary stenosis is already limited, because coronary autoregulation induces microcirculatory dilatation downstream of a stenotic lesion (low perfusion pressure) to maintain normal myocardial perfusion at rest. Furthermore, coronary artery vasodilatation in patients with CAD is impaired during severe hypoxaemia [20]. Sympathetic stimulation of the collateral supply [21] is probably one of the major mechanisms that increases blood flow to a myocardial region supplied by a stenotic artery at high altitude.

The available data suggest that in patients with stable CAD high-altitude exposure is relatively safe [22–30]. Thus, the sympathoadrenergic augmentation of collateral supply to ischaemic myocardium seems to be quite efficient.

Several studies have assessed the incidence of electrocardiographic signs of acute ischaemia in patients with stable CAD at altitudes between 2500 and 3500 m, either at rest or during exercise (table 1) [22–30], and showed no increased risk for stable patients. Consistent with these results, there is no evidence for an increased incidence of acute myocardial ischaemic events during commercial flights where cabin pressure is kept lower than the pressure at 2500 m [29].

Long-term exposure at moderate altitude (1000–1960 m) was suggested to have favourable effects on mortality from CAD and stroke [31]. A favourable effect was found in patients born at this altitude as well as in patient who moved there later in their life. It is unknown if, in patients with CAD, long-time high-altitude exposure can have similar favourable effects.

Congestive heart failure

Several factors may limit exercise capacity at altitude in patients with congestive heart failure (CHF). An increase in sympathetic activity results in elevated pulmonary vascular resistance, blood pressure, ventricular afterload, heart rate and myocardial oxygen demand. The acute pressure overload due to increased pulmonary artery pressure may cause right ventricular function to deteriorate and may adversely affect left ventricular filling. Furthermore, the interdependence between the right and left ventricle increases with rising pulmonary artery pressure. In healthy subjects, increased left atrial contraction compensates for left ventricular geometry and filling alterations and prevents diastolic dysfunction. In patients with CHF (and therefore impaired diastolic function) this compensatory mechanism may be altered [8, 32].

Experimental evidence on high-altitude exposure in patients with CHF is scarce (table 1). However, available data suggest that there is no increased risk of cardiovascular complications in patients with stable, compensated heart failure at short-term high-altitude exposure up to 3500 m [22, 33, 34].

Arterial hypertension

The principal determinants of blood pressure at high altitude are the same as those at low altitude. The most important are cardiac output (heart rate x stroke vol-

Table 1: High-altitude exposure studies in patients with coronary artery disease, congestive heart failure and congenital heart disease.

	Disease	N	Mean age (years)	Exercise and altitude	Key findings
	CAD				
Morgan et al. [25] 1990	Stable CAD	9 males	50–75	Maximal treadmill stress testing at moderate (1590 m) and high (3081 m) altitude	Ischaemic endpoints during exercise occurred at a lower workload at 3100 m but at a similar rate-pressure product.
Erdmann et al. [22] 1998	Stable CAD/CHF and LVEF 35%	23 males vs 23 HC	51 (± 9)	Maximal symptom-limited bicycle stress test at 1000 m and 2500 m	In both groups, significant decrease in exercise capacity. No angina, ECG signs of ischaemia, arrhythmia or other complications occurred.
Schmid et al. [27] 2006	CAD (15 patients post STEMI, 7 post NSTEMI; 12 (± 4) mo after the event	20 males and 2 females	57 (± 7)	Symptom-limited bicycle ergometer stress test at 540 m and 3454 m	No ECG signs of myocardial ischaemia or significant arrhythmias after rapid ascent to high altitude. Decreased exercise capacity at high altitude.
De Vries et al. [30] 2010	CAD (mean 5.6 ± 3.6 years after acute myocardial infarction, LVEF 54 ± 6%)	7 males, 1 female vs 7 HC	53 (± 8)	Exercise test and echocardiography at sea level and 4200 m	No symptoms or echocardiographic signs of myocardial ischaemia (changes in global LV function and wall motion score index) during and after exercise up to an altitude of 4200 m. Patients and HC showed comparable changes at high altitude compared with sea level ,with an increase in RV diameter, a decrease in TAPSE, and decreased E'.
	CHF				
Agostoni et al. [33] 2000	Stable CHF (12: peak VO_2 >20 ml/min/kg, 14: 20–15 ml/min/kg, and 12: <15 ml/min/kg; LVEF<40%, LVEDD >65 mm)	38 (28 males, 10 females) vs 14 HC	61 (± 7)	CPX with inspired oxygen fractions equal to those at 92, 1000, 1500, 2000, and 3000 m	Decrease in maximal exercise capacity at simulated exposure up to 3000 m, greatest in patients with the lowest exercise capacity at sea level. No increase in exercise-induced arrhythmias, myocardial ischaemia and no heart failure.
Schmid et al. [34] 2015	Stable CHF (VO_2 >50% of the predicted, LVEF 28.8±5.4%)	29 (25 males, 4 females)	60.0 (±8.9)	CPX, haemodynamic response (inert gas rebreathing system), and Holter ECG recording at 540 and 3454 m	Decrease in mean peak VO_2 at 3454 m compared with lowland. One patient developed a self-limiting ventricular tachycardia during CPX at high altitude.
	CHD				
Harinck et al. [49] 199	Cyanotic heart disease (7 with Eisenmenger, 5 with other complex heart disease)	12 (6 females, 6 males vs 27 HC	16–26	Simulated commercial flight (altitude of 2468 m) for 1.5 to 7 hours	No significant cardiovascular complications despite a more pronounced decrease of arterial oxygen saturation during the longer simulated flight.
Staempfli et al. [50] 2016	Fontan	16 (56% female)	28 ± 7	CPX at 540 m and 3454 m	Short-term high altitude exposure was clinically well tolerated and showed no negative impact on pulmonary blood flow and exercise capacity in Fontan patients compared to HC.

Abbreviations: CAD: coronary artery disease; CHD: congenital heart disease; CHF: congestive heart failure; CPX: cardiopulmonary exercise testing; E': E-wave tissue Doppler velocity; ECG: electrocardiography; HC: healthy controls; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; NSTEMI: non ST-elevation myocardial infarction; RV: right ventricular; STEMI: ST-elevation myocardial infarction; TAPSE: tricuspid annular peak systolic excursions; VO_2: oxygen consumption (references in the text)

ume), systemic peripheral resistance and central venous pressure. Peripheral vasodilatation and activation of the sympathetic nervous system are triggered by hypoxia. Due to endothelial dysfunction in hypertensive patients, there might be impaired hypoxic vasodilatation and paradoxical sympathetic induced peripheral vasoconstriction. In healthy persons, these mechanisms usually result in a modest increase of blood pressure, but with high interindividual variability [12, 16, 35, 36]. In patients with mild to moderate arterial hypertension, systolic blood pressure at altitude may increase >20 mm Hg [16]. Only a modest increase at rest and during exercise was found in patients with controlled blood pressure [22, 24, 27].

To our knowledge, there are no reports of major complications (retinopathy, intracranial bleeding, myocardial infarction, stroke) in hypertensive patients exposed to high altitude [13, 14], but one study suggested an increased odd ratio (1.5) for sudden cardiac death during sports (mountain hiking or skiing) [37]. Furthermore, there is no evidence for an altered prevalence of high-altitude-related illness in this patient population.

Anomalies of the pulmonary circulation

At altitude, hypoxic pulmonary vasoconstriction and an increase of pulmonary vascular resistance can be observed in response to lower alveolar oxygen pressure, resulting in an increase of pulmonary artery pressure. This physiological mechanism is important at high altitude, diverting blood flow from hypoxic to nonhypoxic lung regions (i.e., improving ventilation-perfusion mismatch at high altitude). Sympathetic activation, cold temperature, physical exercise and an increased cardiac output may further increase pulmonary artery pressure [38]. Pre-existing pulmonary hypertension at sea level may worsen at altitudes greater than 2000 m, particularly during exercise [33]. Such patients, particularly those with impaired right ventricular function, are at risk for developing acute cor pulmonale due to an increased afterload [39]. In patients with a congenital (absent or abnormal pulmonary arteries) or acquired (obstructed vessels) restricted pulmonary vascular bed or with pulmonary vascular dysfunction (Down's syndrome), exaggerated pulmonary hypertension and high-altitude pulmonary oedema (HAPE) occur at a lower altitude than in other patients prone to HAPE [40, 41]. In patients with pulmonary hypertension and concomitant patent foramen ovale, hypoxaemia may be aggravated at high altitude by an increase of right-to-left shunt. This phenomenon, together with a concomitant decreased tissue blood flow, may exacerbate myocardial ischaemia, particularly during exercise.

Valvular heart disease

To the best of our knowledge, there are no clinical data on the effects of high-altitude exposure in patients with primary valvular heart disease. To describe in detail the pathophysiology of the different pathological valvular conditions and individually relate them to possible risks associated with high-altitude exposure is beyond the scope of this article. From a pathophysiological point of view, patients with valvular diseases show several similarities to patients with heart failure and/or pulmonary hypertension. Increase of heart rate and consequently cardiac output might worsen a valvular stenosis. Pre-existing aortic or mitral valve regurgitation might worsen owing to increased systemic vascular resistance and arterial blood pressure, whereas tricuspid and pulmonary regurgitation may worsen because of increased pulmonary vascular resistance. Volume loss, which frequently occurs during the first days at high altitude, may be particularly dangerous in patients with valvular stenosis. At high altitude, the risk of valvular thrombosis in patients with prosthetic mechanical heart valves, especially with sub-therapeutic prothrombin time International Normalised Ratio, may be increased by volume loss, reduced plasma volume secondary to an increase of atrial natriuretic peptide and decreased aldosterone synthesis [42], altered blood viscosity [43], and the development of a procoagulatory state [44].

Patent foramen ovale

Acute high-altitude exposure in HAPE-prone subjects is characterised by exaggerated hypoxic pulmonary vasoconstriction and pulmonary hypertension [45]. In patients with patent foramen ovale (PFO), the resulting right heart pressure overload may further aggravate hypoxaemia at high altitude because of right-left shunting. In line with this concept, PFO was four to five times more frequent in HAPE-prone subjects and associated with exaggerated hypoxaemia and higher systolic pulmonary artery pressure at high altitude than in subjects without PFO [17]. Therefore, PFO might represent an additional constitutional anomaly associated with HAPE susceptibility [45], together with pulmonary vascular dysfunction and impaired alveolar fluid clearance [46]. Furthermore, there might be a vicious cycle in HAPE-prone individuals with a large PFO, due to acute hypoxic pulmonary vasoconstriction causing right-to-left shunting, aggravating hypoxaemia and resulting in mixed venous oxygen tension, greater alveolar hypoxia and greater pulmonary hypertension [47].

Patients with congenital heart disease

Bicuspid aortic valve, atrial septal defect, ventricular septal defect and patent ductus arteriosus are the most frequent acyanotic defects. The three latter, if uncomplicated, are characterised by a left-to-right shunt, which may favour pulmonary artery hypertension [39]. This, together with the hypoxia-induced rises in pulmonary pressure at high altitude, may result in an overload of the subpulmonic ventricle. Exercise may further increase afterload and, in extreme situations, may lead to shunt reversal with resultant pronounced hypoxaemia [17, 48].

Cyanotic patients are characterised by a right-to-left shunt and/or severely reduced pulmonary flow. The right-to-left-shunt is, in most patients, particularly those with the Eisenmenger syndrome, the result of severe pulmonary hypertension. High-altitude exposure can only have harmful effects in these patients and should be strictly discouraged. Only scarce data on high-altitude exposure of patients with congenital heart disease are available [49, 50].

Arrhythmias and pacemakers

High altitude may favour arrhythmogenesis via activation of the sympathetic nervous system and increased adrenaline spillover during exertion, aggravation of myocardial ischaemia, acute right ventricular pressure overload and hypokalaemia secondary to respiratory alkalosis. A significant number of sudden cardiac deaths (SCDs) have been ascribed to altitude-induced arrhythmia. During an 8-year period in the Austrian Alps, there were 642 SCDs [51, 52], possibly related to sympathetically mediated ventricular arrhythmias. However, this surprisingly high incidence suggests underlying cardiac disease in many of these cases. Furthermore, one study revealed a matching risk profile (prior myocardial infarction, hypertension and CAD) in 68 males who died of SCD during downhill skiing at altitude [53]. In contrast, there is no increased incidence of malignant ventricular arrhythmias or SCD in patients with stable CAD [22, 24, 25, 27, 30] or in patients with compensated heart failure [22, 33, 34], despite an increase of premature supraventricular and ventricular contractions [54, 55].

In a hypobaric chamber study stimulating altitudes up to 4000 m, stimulation thresholds and the strength-duration curve of pacemakers remained unchanged [56]. No studies on patients' safety with implantable cardioverter-defibrillators (ICDs) at high altitude are available. EN 45502-1 standard (the European standard for general requirements for the basic safety of active implantable medical devices) requires low pressure testing for pulse generators to 70 kPa, equivalent to approximately 3000 m of altitude, for a minimum of 1 hour. However, during manufacturing devices are tested at much lower atmospheric pressures than those reached during mountaineering, suggesting that the risk of device failure at high altitude is probably low.

Cerebrovascular disease

An increase of stroke incidence during long-term stays at high altitude has been described [57, 58], whereas long-term stay at an altitude between 1000 and 1960 m may decrease the incidence of stroke [31]. No evidence for an increased stroke risk during short-term stays at high altitude was found. Dehydration and reduced plasma volume at high altitude, increased haematocrit and polycythaemia, endothelial dysfunction, altered coagulation and thrombocyte aggregation are potential factors that may promote thrombus formation and stroke, particularly in patients with a recent history of stroke [44]. A fall in PaO_2 at high altitude produces cerebral vasodilatation [59]. Patients with stenosis or occlusions of extra- and intracranial blood vessels (whether symptomatic or asymptomatic) are at increased risk of stroke as a result of a potential compromise of cerebral blood flow regulation [60]. Furthermore, patients with high-altitude cerebral oedema appear to be at risk for cerebral venous thrombosis [61].

Heart transplant patients

Because of transection of sympathetic and parasympathetic fibres during transplantation and, as a result, missing counterregulatory effects of the parasympathetic system on the sinus node, the denervated donor heart exhibits a faster resting heart rate. Moreover, the transplanted heart relies on the adrenal glands as source of catecholamines. Because of the time lag before circulating catecholamines exert their positive chronotropic effect, the response to stress at high altitude (hypovolaemia, hypoxia, exercise) is delayed. There is only scarce evidence on cardiac transplant patients going to high altitude [62, 63]. Most of the risk can be attributed to immunosuppression, especially when travelling to a remote area.

Practical recommendations before high-altitude exposure

Evidence-based recommendations for non-acclimatised patients with cardiovascular disease [64, 65] who are considering high-altitude exposure are not possible because of the limited number of studies. Our recommendations (see tables 2 and 3) are based on the available data and our own experience. They should

reasonably ensure the patients' safety. In table 2, conditions that preclude individuals from going to high altitude are listed. In figure 2, we suggest a pre-exposure assessment algorithm for patients with cardiovascular disease. When assessing the risk from high-altitude exposure in cardiovascular patients, factors (e.g., comorbidities, the altitude to be reached, the rapidity of ascent, the geographical location, the planned activity, the medical environment and rescue possibilities) other than the cardiovascular disease have to be considered. Moreover, the patient should be in a stable and compensated clinical condition at low altitude with a New York Heart Association class lower than II (table 2). A slow ascent to allow proper acclimatisation is advised when ascending above 2000 m. On average, sleeping altitude should be increased by not more than 300–400 m per 24 hours. In general, it seems that going to moderate altitude is safe in patients with stable disease who have good exercise tolerance at sea level. Even if adverse events are rare, there should be limits – not only for safety reasons, but also for the traveller to enjoy the sojourn. In the event of symptoms, patients should take their medication as instructed and if symptoms persist or worsen, immediate descent is crucial. Patients should strictly adhere to low altitude recommendations according to their respective cardiovascular disease. Furthermore, in patients with particular forms of cardiovascular disease, counselling must be individualised.

Table 2: Prerequisites, general recommendations and contraindications to high-altitude exposure. References in text. Modified from [64] with permission of Elsevier.

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, i.e., unstable angina, symptoms or signs of ischaemia 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 revascularisation in the past 3–6 mo Decompensated heart failure during the past 3 mo Poor blood pressure control (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 [39] Severe valvular heart disease, even if asymptomatic Thromboembolic event during the past 3 mo Cyanotic or severe acyanotic congenital heart disease ICD implantation in the past 3 months if primary prevention, in the past 6 months if secondary prevention or ICD intervention for ventricular arrhythmias Recurrent ICD-interventions Stroke, transient ischaemic attack, or cerebral haemorrhage during the past 3–6 mo

Table 3: Recommendations and pre-exposure assessments according to cardiovascular disease.

Clinical condition		Proposed pre-exposure assessment and recommendations for patients
CAD	Asymptomatic revascularisation <6 mo	Consider exercise testing according to coronary status
	Asymptomatic revascularisation >6 mo	Exercise testing If not conclusive → exercise testing with imaging modality
	Asymptomatic reduced LVEF	Exercise testing and transthoracic echocardiography at rest If not conclusive → exercise testing with imaging modality
	Stable angina and ischaemic threshold of more than 6 METs	Exposure up to 3500 m can be considered, in particular if passive ascent is planned. Limit physical activity (<70% of maximal heart rate achieved during exercise testing) If angina occurs, patients should not further ascend, limit physical activity, and take anti-anginal medication. Immediate descent if symptoms persist or worsen

Table 3 (continued).

Reduced LVEF (any cause)		Exercise testing Transthoracic echocardiography at rest Consider CPX and Holter-ECG in selected patients Adhere to low altitude recommendations such as restricting salt intake, as well as close monitoring of body weight, avoid dehydration and diarrhoea (loss of potassium) Instructions for adjustment of medication (diuretics) if signs of heart failure In the case of signs and symptoms of pulmonary congestion, immediate descent to lower altitude and seeking medical advice are mandatory. In the absence of medical help, take 1 or 2 supplemental doses of loop diuretic. If no improvement is achieved within 4 to 6 hours, initiate HAPE treatment with a CCB (slow-release nifedipine, 20 mg, every 6 hours)
Arterial hypertension		If not well controlled → ABPM Instructions for self-monitoring of BP and adjustment of medication if poor BP control or hypotension develop Favour CCB owing to a beneficial effect on HAPE
Pulmonary hypertension		Exposure contraindicated if marked pulmonary hypertension or if functional class >I (see table 2) Echocardiographic assessment of RV function and of pulmonary artery pressure under simulated high altitude (FIO_2: 12%; if RV-RA gradient >42 mm Hg at rest or >53 mmg Hg during exercise patients should be strongly discouraged) or TTE and symptom-limited exercise test including monitoring of arterial oxygen saturation Prophylaxis for HAPE with nifedipine 30 mg twice daily Travel up to 3000 m can be considered if normal test results
Valvular heart disease	Symptomatic and/or severe	Exposure contraindicated
	Mild aortic or mitral regurgitation	Exercise testing, transthoracic echocardiography at rest Instructions for self-monitoring of BP and adjustment of medication if uncontrolled hypertension or hypotension develop Instructions for self-monitoring of international normalised ratio and dose adjustment If anticoagulation, avoid activities at risk for traumatic injury at high altitude Avoid exaggerated physical activity and keep fluid balance equilibrated
Congenital heart disease	Acyanotic or cyanotic	Exposure contraindicated if functional class >I CPX and echocardiographic assessment of left and RV function, and pulmonary pressure under simulated high altitude (FIO_2, 12%; if RV-RA gradient >40 mm Hg patients should be strongly discouraged) Consider cardiac magnetic resonance imaging and Holter-ECG in selected patients Consider ABPM in patient with aortic coarctation A short-term trip with passive ascent up to 3400 m may be considered with a proper pre-exposure assessment and planning of prophylactic and emergency measures including oxygen supplement and pulmonary vasodilatators in selected patients.
Heart transplant	<1 year	Avoid high altitude in remote areas
	>1 year	Transthoracic echocardiography at rest and exercise test Echocardiographic assessment of RV function and of pulmonary artery pressure under simulated high altitude (FIO_2: 12%; if RV-RA gradient >42 mm Hg at rest or >53 mmg Hg during exercise patients should be strongly discouraged) Control blood pressure and renal function Consider exercise test and Holter-ECG to identify arrhythmia and to evaluate BP under stress.
Arrhythmia	Associated with CAD/CHF	Exercise testing (no ECG changes indicating myocardial ischaemia and no ventricular arrhythmia)
	Pacemaker	Testing only if VVIR, DDDR, or AAIR mode to adapt PM rates (in particular for exercise at high altitude)
	Supraventricular tachycardia/atrial flutter Atrial fibrillation	Consider catheter ablation before high-altitude exposure Exercise testing and Holter-ECG Instructions for heart rate self-monitoring and adjustment of medication in the event of insufficient rate control (>90 beats per min at rest)
	Symptomatic ventricular or atrial premature beats, or non-sustained tachycardia	Ad hoc adaptation of the treatment should be discussed (e.g. higher doses in cases of chronic prophylactic treatment or "Pill-in-the-Pocket" approach)
	ICD	ICD follow-up Contact the manufacturer or the device-treating physician prior to an expedition to extreme altitudes.

Table 3 (continued).

Cerebrovascular disease	All conditions	Avoid trekking or climbing alone
	Ischaemic stroke or TIA <90 d ago	Avoid traveling to higher altitudes (>2000–2500 m) Avoid air travel
	Ischaemic 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 haemorrhage	Travel to high altitude only if BP is controlled and not before 90 d after the event
Haemorrhage as a result of amyloid angiopathy		Avoid high altitude
Known cerebral aneurysm, arteriovenous malformation, or cerebral cavernoma		Check BP. Avoid extreme altitude >4500 m

Abbreviations: MET, metabolic equivalent of task; BP, blood pressure; CCB, calcium channel blocker; HAPE, high altitude pulmonary oedema; CPX, cardiopulmonary exercise testing; ABPM, 24-hour ambulatory blood pressure monitoring; RV, right ventricular; 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; min, minute; ICD, implantable cardioverter defibrillator; TIA, transient ischaemic attack, modified from [64] with permission of Elsevier.

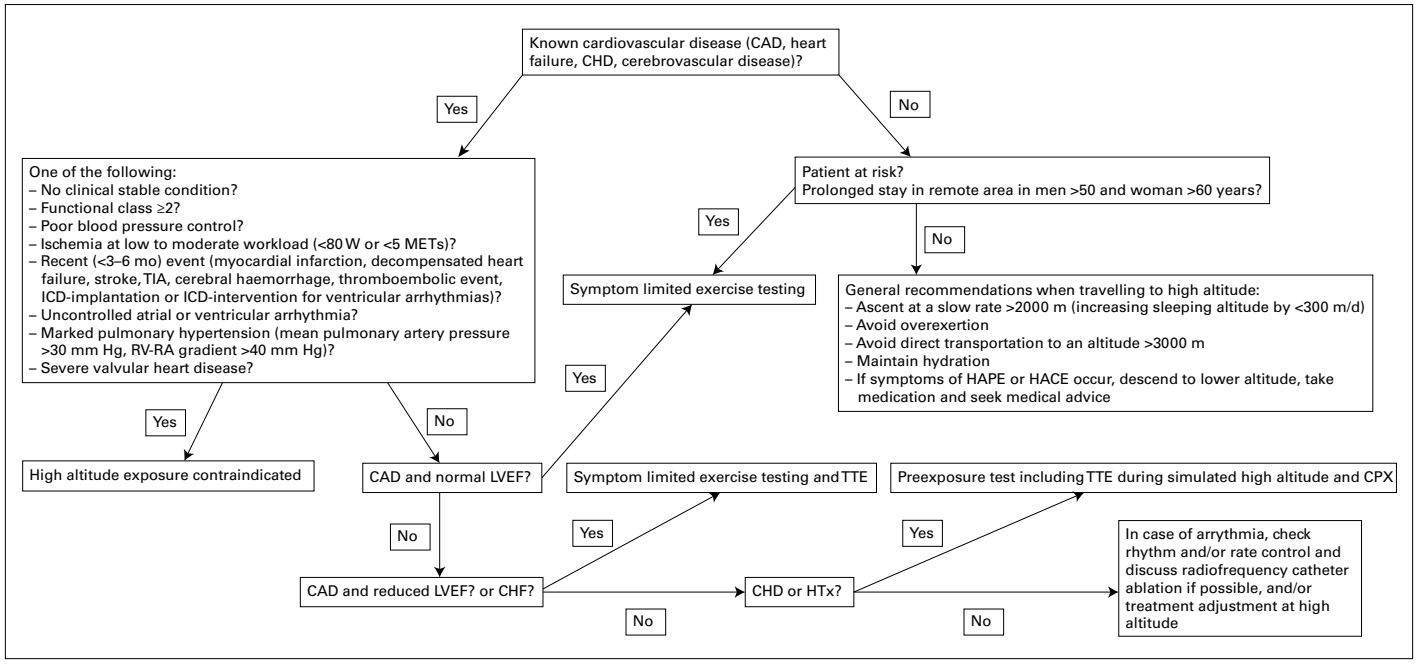

Figure 2: Possible algorithm for patients with cardiovascular disease travelling to high altitude. Prerequisites, general recommendations, and contraindications. Abbreviations: CAD coronary heart disease; CHD congenital heart disease; W Watt; METs metabolic equivalents, mo months; TIA transient ischaemic attack; ICD implantable cardioverter defibrillator; RV right ventricle; RA right atrium; LVEF left ventricular ejection fraction; CHF congestive heart failure; HTx heart transplant; TTE transthoracic echocardiography; CPX cardiopulmonary exercise testing; HAPE high altitude pulmonary oedema; HACE high altitude cerebral oedema.

Conclusions

Altitude exposure is not a contraindication for patients with heart disease in general. The low ambient oxygen triggers a series of physiological adaptations intended to maintain adequate organ oxygen supply. External factors such as cold temperature, low humidity, exercise and stress may further amplify these responses, which show high interindividual variability. In patients with cardiovascular disease, particularly in

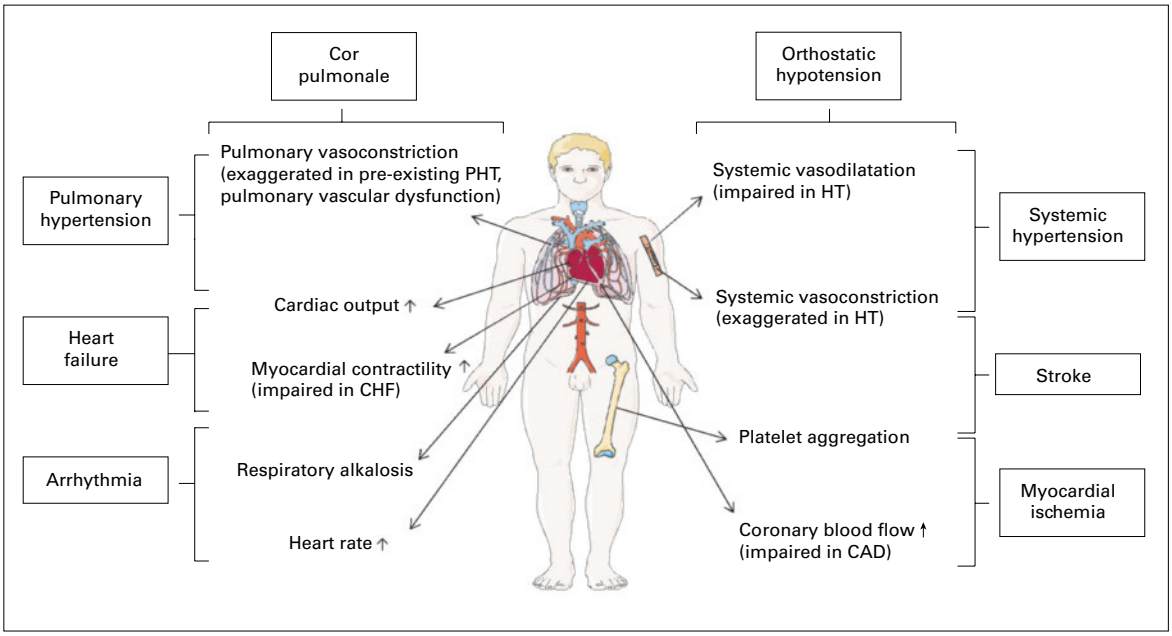

Figure 3: Main (patho)physiological changes during high-altitude exposure due to hypoxia and resulting sympathetic nerve activity and their associations with specific clinical conditions. Abbreviations: HT arterial hypertension; PHT pulmonary hypertension; CHF congestive heart failure; CAD coronary artery disease. Modified from [64] with permission of Elsevier.

those with already limited functional reserves at low altitude, these adjustments may induce major problems (fig. 3).

According to the patient's history and disease, a proper pre-exposure assessment helps to minimise risk and detect contraindications to high-altitude exposure. Furthermore, the great variability and unpredictability of the adaptive response, as well as the moderate evidence level, should encourage physicians to counsel such patients to adopt a cautious approach. Patients with cardiovascular disease need tailored advice based on their actual status and detailed instructions on how to act if they should become symptomatic at high altitude.

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References

The full list of references is included in the online version of the article on www.cardiovacmed.ch.