Contemporary Reviews in Cardiovascular Medicine

Effect of Altitude on the Heart and the Lungs

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This review focuses on the effects of altitude exposure from 1 to several days or weeks as occurs in tourists, trekkers, and mountaineers who visit high altitude and normally reside near sea level. We briefly review the acute physiological adjustments and early acclimatization that occur in the cardiovascular system and the lungs of healthy individuals. These ensure life-sustaining oxygen delivery to the tissues despite a reduction in the partial pressure of inspired oxygen between 20% and 60% at 2500 and 8000 m, respectively. One of the acute adjustments, hypoxic pulmonary vasoconstriction (HPV), may be disadvantageous in those with a vigorous response and lead to 2 potentially lethal illnesses, high-altitude pulmonary edema (HAPE) and subacute mountain sickness (SAMS), which we present in more detail. Finally, on the basis of knowledge about the acute physiological adjustments and acclimatization and, when available, a review of the literature, we discuss the high-altitude tolerance of patients with coronary artery disease, congestive heart failure, arrhythmias, systemic hypertension, and pulmonary hypertension.

Effects of Exposure to High Altitude on the Normal Cardiovascular System

Circulation

The major effects of acute hypoxia on the heart and lung are shown in Figure 1. Hypoxia directly affects the vascular tone of the pulmonary and systemic resistance vessels and increases ventilation and sympathetic activity via stimulation of the peripheral chemoreceptors.[1] Interactions occur between the direct effects of hypoxia on blood vessels and the chemoreceptor-mediated responses in the systemic and pulmonary circulation.

Unraveling the underlying mechanisms of the hypoxic vasodilatation of systemic arterioles is an active area of research. Several mechanisms appear to regulate local oxygen delivery according to the needs of the tissues[2,3]; for instance, the release of ATP from red blood cells and the generation of NO by various ways appear to regulate local oxygen delivery according to the needs of the tissue. These mechanisms may decrease with prolonged stay at high altitude when oxygen content of the blood increases because of ventilatory acclimatization, an increase in hematocrit associated with plasma volume reduction, and an increase in red blood cell mass due to erythropoiesis.

Peripheral chemoreceptor afferent activity rises hyperbolically as hypoxia increases.[4] Ventilation and sympathetic activity are augmented, as demonstrated by increased urinary and plasma concentration of catecholamines[5] and skeletal muscle sympathetic activity.[6] With exposure over days to weeks, the sensitivity of the peripheral chemoreceptors to hypoxia increases, leading to further enhancement of ventilation (ventilatory acclimatization). This presumably also accounts for the further increase of sympathetic activity documented by microneurography after 3 weeks at 5200 m[6] and elevated catecholamines in urine and plasma.[5]

As shown in Figure 1, there is antagonism between the direct effects of hypoxia on the resistance vessels and those mediated by the chemoreceptors in both the systemic and pulmonary circulation. During the first few hours of exposure, hypoxic vasodilatation tends to override sympathetic vasoconstriction in the systemic circulation, resulting in an unchanged or slightly decreased systemic blood pressure. Blood pressure and systemic vascular resistance then rise over at least 3 to 4 weeks because of increasing sympathetic activity and reduced tissue hypoxia associated with acclimatization. The rise in blood pressure is not fully reversed by oxygen administration,[7] α-blockers, or β-blockers,[8] suggesting that additional mechanisms may be involved. The interindividual variation in blood pressure response to hypoxia may be explained in part by the finding that individuals with a brisk acute hypoxic ventilatory response also have a high blood pressure response to hypoxia.[9] In the pulmonary circulation, increased ventilation may modulate HPV to some extent by reducing alveolar hypoxia and because of respiratory alkalosis.

Heart

The consequences of acute hypoxia are an increase in heart rate (both at rest and on exercise), myocardial contractility, and cardiac output for the first few days. With acclimatization, cardiac output falls at rest and on exercise in association with a decrease in left ventricular work but an increase in right ventricular work.
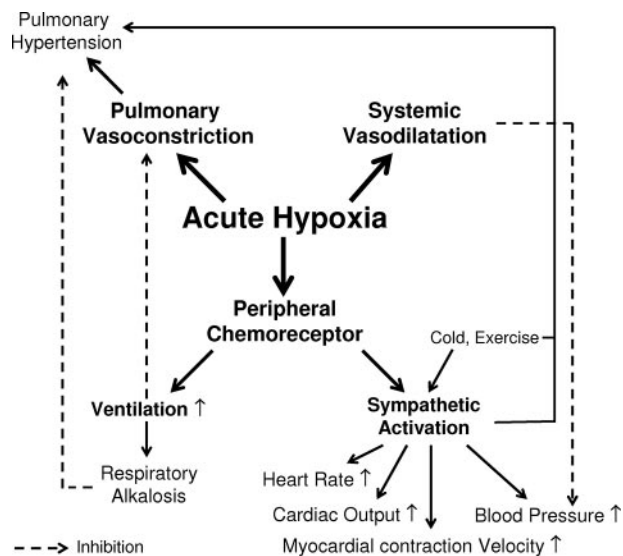
Figure 1. Effects of hypoxia on systemic and pulmonary circulation.

Heart Rate

The increase in heart rate is related to increased sympathetic activity and vagal withdrawal.[10] For a given level of exercise, heart rate is greater at altitude[11] (Figure 2), although the heart rate that can be achieved at maximal exercise is reduced compared with at sea level and in parallel with maximum oxygen consumption.[11] At 5260 m, vagal blockade by glycopyrrolate completely restored maximal heart rate to sea level values, whereas cardiac output did not increase. Acutely raising inspiratory Po_2 to sea level values increased work output and restored cardiac output.[12] These data indicate that enhanced parasympathetic neural activity accounts for the lowering of heart rate during exercise, whereas the reduction in cardiac output in hypoxia may be linked to the decreased maximum work capacity, ie, decreased signals from the skeletal muscle.

Coronary Circulation

On acute exposure to hypoxia, the epicardial coronary arteries dilate. An increase in resting myocardial blood flow compensates for the reduced oxygen content of the blood and contributes to the maintenance of cardiac function,[13] whereas exercise-induced coronary flow reserve is preserved at least to 4500 m.[14] In healthy young men, no myocardial ischemia on exercise was demonstrated during a simulated ascent to the summit of Mount Everest (8840 m) over 40 days.[15]

After 10 days at 3100 m,[16] coronary blood flow is decreased compared with at sea level and in proportion to the fall in left ventricular work because of the increased oxygen content of arterial blood with acclimatization. Thus, myocardial oxygen extraction per volume of blood increases to maintain myocardial oxygenation.

Cardiac Function

Cardiac contractility increases acutely, and submaximal cardiac output for a given oxygen uptake is increased during the first few days at altitude, although maximal cardiac output is unchanged[11,17] and maximum oxygen consumption (Vo_2 max) declines by $\approx 1\%$ per 100 m above 1500 m. This acute increase
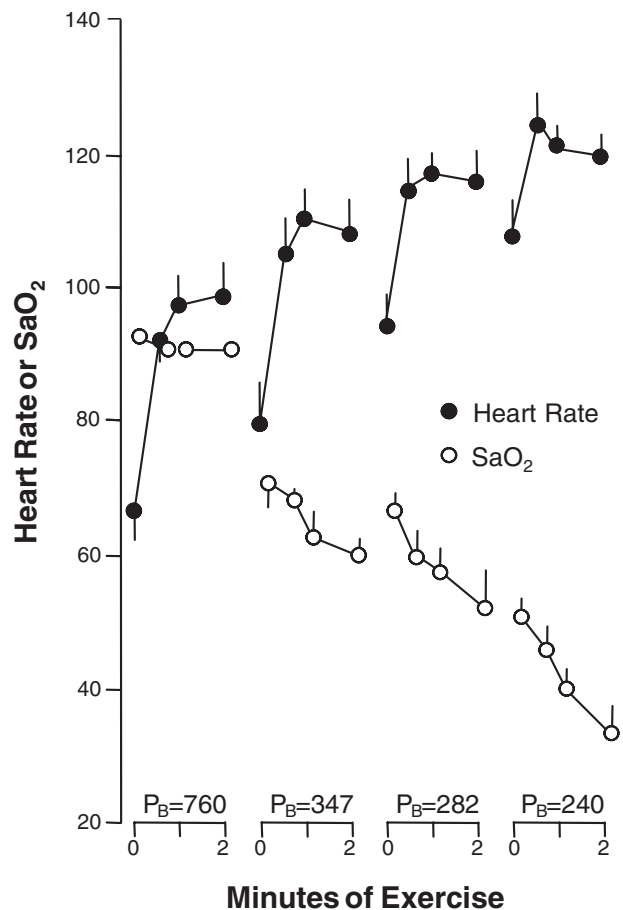

Figure 2. Time course of 5 subjects at various barometric pressures of heart rate (filled circles) and O_2 saturation (SaO_2) by ear oximeter (open circles) during exercise. Exercise intensities were 120 W for 3 subjects and 60 W for 2 subjects. Exercise intensity was reduced in 1 subject from 120 to 90 W at the highest altitude. Measurements are shown for barometric pressure (P_B) 760 (sea level), 347 (6100 m), 282 (7620 m), and 240 Torr (8840 m, summit of Mount Everest). Figure adapted from Reeves et al[11] with permission of the American Physiological Society. Copyright 1987, The American Physiological Society.

in cardiac output at submaximal workloads, largely explained by the increased heart rate, may be offset by reduced stroke volume, which is detectable on the first day.[18] Stroke volume falls during the first week at altitude and then tends to stabilize.[19,20] During more chronic altitude exposure, maximal cardiac output falls, and the maximum rate of oxygen consumption remains reduced.[21] For example, the stroke volume and cardiac output after 5 days at 2380 m were 15% to 20% lower than at sea level,[22] after 10 days at 3100 m were 16% lower, and after 21 days at 4300 m were 25% lower.

The fall in stroke volume is associated with reduction in left ventricular dimensions and filling pressure[11] and in part may be a consequence of diuresis and reduction of plasma volume, which decreases over the first weeks at high altitude by as much as 20% at 3800 to 4500 m.[23] The initial reduction of plasma volume in part may be mediated by chemoreceptors, increased release of atrial natriuretic peptide, and decreased synthesis of aldosterone,[24] whereas the further reduction of plasma volume occurs without a net loss of body water
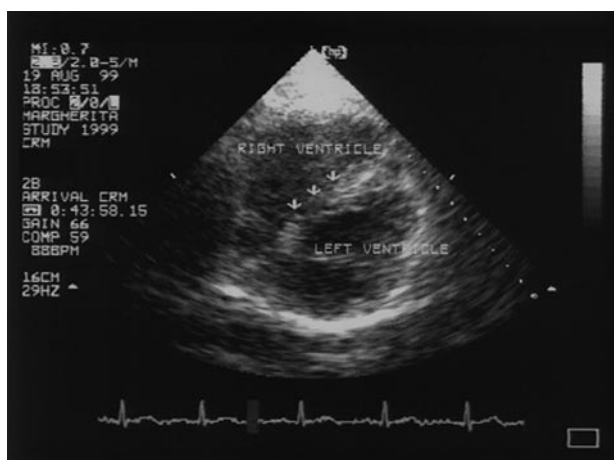
Figure 3. Transthoracic echocardiogram showing a parasternal short-axis view of the right and left ventricles. There is interventricular septal deviation toward the left as a consequence of hypoxic pulmonary hypertension.

by a fluid shift from the extracellular to the intracellular compartment.

Chronic right ventricular pressure overload may play a part in reducing left ventricular stroke volume. Pericardial constraint modulates the ventricular stroke volumes.[25] When the right ventricle dilates in response to increased pulmonary vascular resistance, the left ventricular diastolic volume is reduced. Pulmonary hypertension causes interventricular septal deviation toward the left ventricle, which alters left ventricular geometry and delays filling[26,27] (Figure 3). In pathological forms of pulmonary hypertension, this may cause diastolic dysfunction of the left ventricle,[28] whereas on acute hypoxic exposure diastolic dysfunction is overcome by enhanced atrial contraction.[29] Myocardial edema may also contribute to ventricular dysfunction.[30] Despite the fall in cardiac output, left ventricular function at rest is maintained even in a barochamber simulation of the summit of Mount Everest without a rise in left ventricular end-diastolic pressure.[11,31,32] Even severe exercise associated with an incremental test to exhaustion at 7625 m[31] or prolonged competitive running between 2350 and 4300 m in an ultramarathon[33] does not affect left ventricular systolic function, although pulmonary hypertension associated with transient right ventricular dysfunction was observed in the latter study. In summary, myocardial oxygen supply and left ventricular function are maintained in healthy individuals during maximal exercise at an altitude of 7625 m, at which maximal heart rate was reduced by 20% and cardiac output as well as exercise capacity was reduced by 40% to 50%.[34]

Pulmonary Circulation

Pulmonary Arterial Pressure at Various Altitudes
HPV was brought to wide attention by von Euler and Liljestrand in 1946.[35] The physiological significance of HPV at low altitude is obvious in the presence of localized hypoxia in the lungs, such as in pneumonia or atelectasis. When the whole lung is exposed to hypoxia, HPV may be disadvantageous because it results in a substantial increase in pulmonary vascular resistance and pulmonary arterial pressure (PAP).
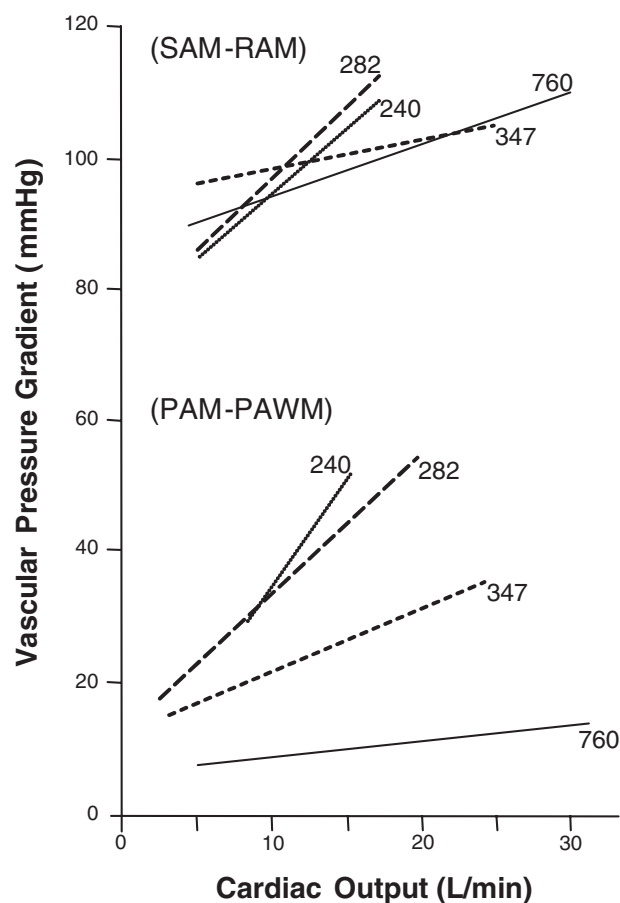

Figure 4. Relationship of mean systemic and pulmonary vascular pressure gradients to thermodilution cardiac output at various barometric pressures. Measurements are shown for barometric pressure (P_B) 760 (sea level), 347 (6100 m), 282 Torr (7620 m; filled circles), and 240 Torr (8840 m, summit of Mount Everest). SAM indicates systemic arterial mean pressure; RAM, right atrial mean pressure; PAM, pulmonary arterial mean pressure; and PAWM, pulmonary arterial wedge pressure. Figure adapted from Groves et al[36] with permission of the American Physiological Society. Copyright 1987, The American Physiological Society.

This has been documented by cardiac catheterization in various places and populations. A representative overview of studies performed at various altitudes is given in Table I in the online-only Data Supplement. Cardiac catheterization in a chamber study showed marked elevation of mean PAP at rest associated with an increase in pulmonary vascular resistance. The rise in pulmonary vascular resistance was greatest at the highest altitude and is in marked contrast to the systemic circulation (Figure 4). Pulmonary hypertension was only incompletely reversed by oxygen, suggesting that structural vessel remodeling had taken place.[36]

In Tibetans at 3658 m, mean PAP at rest and during exercise that results in a 3-fold increase of cardiac output is not different from the response observed in whites at low altitude.[36,37] These data are based on measurements in only 5 individuals. Recently, systolic PAP estimated by Doppler echocardiography at 4200 m in 57 Tibetans (mean age, 30 years) was 31 ± 7 mm Hg.[38] This is between values obtained in 21 healthy white (mean age, 33 years; range, 24 to 60 years) at 450 m (22 mm Hg) and after

rapid ascent to 4559 m (38±8 mm Hg).[39] Whether these differences in PAP reflect genetic adaptation of Tibetans to high altitude remains questionable.

PAP in Andeans living between 3700 and 4540 m is similar to that in healthy whites after acute exposure to a comparable altitude (Table I in the online-only Data Supplement). Autopsies from the Andes show greater muscularization of the distal pulmonary arterial branches and right ventricular hypertrophy.[40] These observations suggest that increased PAP persists not only in newcomers but also over many generations in high-altitude dwellers and that the right heart can sustain such an increased pressure load over a lifetime at 4500 m. Hemodynamic studies in Andean populations do not generally give sufficient information about the ancestry of the population studied. Considerable genetic admixture with whites may have occurred. Preliminary data on indigenous Aymara children report lower systolic PAP at 3600 m compared with white children, supporting the hypothesis that adaptation to high altitude decreases HPV.[41]

Mechanisms of HPV

HPV is intrinsic to the muscle cells of the pulmonary arteries and independent of the endothelium, as demonstrated in experiments with pulmonary vascular rings denuded of endothelium and with isolated smooth cells from pulmonary arteries.[42] Hypoxic contraction of smooth muscle cells is caused by an increase of Ca^{2+} within the cell. The majority of Ca^{2+} crosses the cell membrane from the extracellular compartment through L-type Ca^2 channels. A smaller part is released from intracellular stores in the cytoplasmic reticulum. Calcium entry into the smooth muscle cells is enhanced by mechanisms that are sensitive to changes in concentrations of radical oxygen species.

Although HPV is intrinsic to pulmonary smooth muscle cells, additional endothelium-dependent and -independent mechanisms modulate this response. Hypoxia also may increase PAP through endothelin and sympathetic activation, whereas HPV may be attenuated by increased synthesis of NO, hyperventilation improving alveolar P_{O_2}, and respiratory alkalosis.[43] For a more detailed discussion of mechanisms underlying HPV, the reader is referred to excellent reviews on this subject.[42,44]

Some studies report 2 phases of HPV in pulmonary arterial rings, the first of which is endothelium independent and peaks in ≈2 minutes. The second phase occurs only in preparations including endothelium and peaks after ≈40 minutes.[45] Studies in isocapnic hypoxia in humans demonstrate a rapid rise of PAP, reaching its maximum after 20 minutes, followed by a second more gradual rise starting 40 minutes after exposure to hypoxia,[46] whereas pressure remains constant between 2 and 8 hours into isocapnic hypoxia.[47] The time lag of ≈40 minutes between onset of hypoxia and the slow response are compatible with delayed release or de novo production of vasoactive substances.

Investigations analyzing lung perfusion by fluorescent microspheres demonstrate that HPV is inhomogeneous.[48] Magnetic resonance imaging in humans who have a normal PAP response to hypoxia has demonstrated that lung perfusion is inhomogeneous during hypoxia,[49] suggesting that HPV is normally inhomogeneous. Findings in HAPE-susceptible individuals[50] and in pigs[48] suggest that this inhomogeneity increases with the magnitude of HPV. Possible mechanisms that could account for inhomogeneity of HPV are baseline ventilation-perfusion ratio (V/Q) inhomogeneity with greater HPV in areas with low ventilation in relation to perfusion,[48] regional differences in endothelial release of NO,[51] and uneven distribution of smooth muscle cells in pulmonary arterioles. To our knowledge, the last hypothesis has not yet been examined properly.

Inhomogeneity of HPV may account for regional overperfusion of areas with weak vasoconstriction where capillary pressure increases because of higher flow, as has been shown in experimental lung models.[52] This mechanism may contribute to the interstitial edema postulated to occur especially with exercise at extreme altitude during Operation Everest II.[53] No measurements of indicators of lung water were made, however.

High-Altitude Pulmonary Edema

Clinical Aspects

HAPE is a noncardiogenic pulmonary edema that may occur in previously healthy individuals within the first 2 to 5 days after rapid ascent above 3000 to 4000 m. It was first described in South American high-altitude dwellers who returned from a sojourn at low altitude[54] and subsequently in unacclimatized lowlanders.[55] Altitude, rate of ascent, and, most importantly, individual susceptibility are the major determinants of HAPE in mountaineers and trekkers. At 4559 m, the last 2 factors account for variability in prevalence between <0.2% and 62%.

Early symptoms of HAPE include exertional dyspnea, cough, and reduced exercise performance. As edema progresses, cough worsens and is accompanied by breathlessness at rest and sometimes orthopnea. Gurgling in the chest
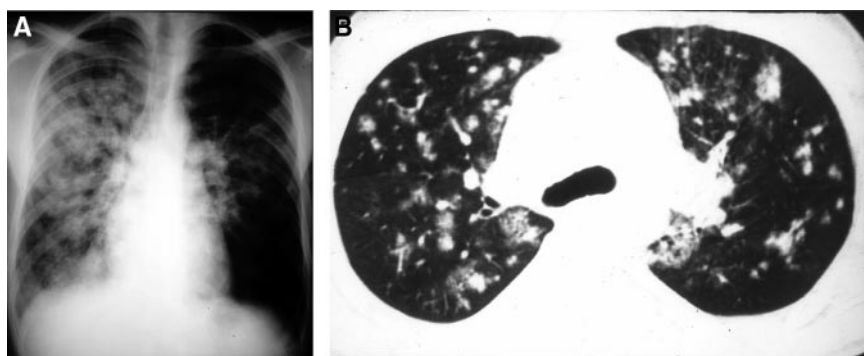
Figure 5. A, Radiograph of a 37-year-old male mountaineer with high-altitude pulmonary edema that shows a patchy to confluent distribution of edema, predominantly on the right side. Figure reprinted from Bärtsch et al[43] with permission of the American Physiological Society. Copyright 2005, The American Physiological Society. B, Computed tomographic scan of a 27-year-old mountaineer with recurrent HAPE showing patchy distribution of edema. Figure reprinted from Bärtsch et al[43] with permission of the American Physiological Society. Copyright 2005, The American Physiological Society.

and pink frothy sputum indicate advanced cases, which are often accompanied by ataxia and decreased levels of consciousness, which are early signs of early cerebral edema. Chest radiographs and computed tomographic scans of early HAPE cases show a patchy, peripheral distribution of edema,[56] as shown in Figure 5. Bronchoalveolar lavage performed within a day of ascent to 4559 m found elevated red cell count and protein concentration in the lavage fluid but no increase of inflammatory cells and proinflammatory mediators[39] (Figure 6 and Table II in the online-only Data Supplement).

Mean PAP is increased to 33 to 117 mm Hg before treatment between 3300 and 4600 m.[43] Pulmonary capillary pressure calculated from the pressure decay curve after occlusion is also elevated between 20 and 25 mm Hg[57] (Figure 7), exceeding threshold values of 17 to 24 mm Hg for edema formation.[43] Pulmonary capillary wedge pressure measured during complete occlusion remains normal.

The crucial role of a high PAP for HAPE is evidenced by placebo-controlled studies demonstrating a reduction in the incidence of HAPE from 60% to 70% to 10% when the excessive rise of PAP in HAPE-susceptible individuals is prevented by nifedipine (3×20 mg slow-release formulation daily)[58] or tadalafil (210 mg daily).[59] Dexamethasone (2×8 mg daily) surprisingly lowered PAP and prevented HAPE as effectively as tadalafil.[59] The high dose of dexamethasone precludes its use over more than a few days, particularly in individuals at risk of glucocorticosteroid-mediated side effects.

Prevention of HAPE by drugs is only necessary when rapid ascent is unavoidable. Slow ascent with an average daily ascent rate of 300 to 350 m above 2000 m prevented HAPE in susceptible individuals who climbed as high as 7000 m.[60] Lowering PAP is the primary goal of treatment. In principle, this can be achieved by descent or administration of supplemental oxygen or a pulmonary vasodilator, such as nifedipine slow-release formulation (20 mg every 6 hours).[61] Specific recommendations on how to obtain this goal depend on where HAPE occurs. The reader is referred to more extensive reviews for further details of the clinical aspects of HAPE.[43,60]

Pathophysiology

Pulmonary Hypertension

Several observations suggest that decreased NO bioavailability may account for the abnormal pulmonary vascular response in susceptible individuals. Decreased NO concentrations in exhaled air were found in HAPE-susceptible individuals during a 4-hour hypoxic exposure at low altitude[62] and during the development of HAPE at high altitude.[63] Furthermore, concentrations of nitrate and nitrite in bronchoalveolar lavage fluid were lower in mountaineers who developed HAPE compared with controls,[39] and HAPE-susceptible persons had an impaired endothelium-dependent vasodilator response to acetylcholine in the systemic circulation.[64] The abnormal rise of PAP in response to exercise in normoxia[65] might be explained by an impaired endothelial NO release in response to increased pulmonary blood flow. In accordance with this hypothesis, inhalation of 15 to 40 ppm NO lowered PAP and improved gas exchange to control
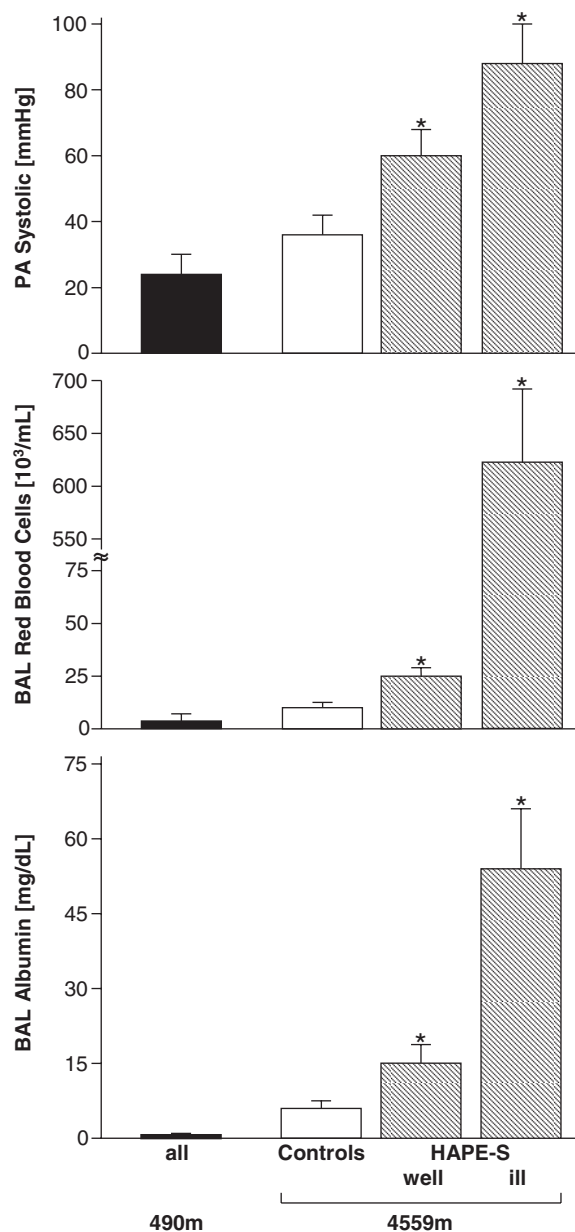

Figure 6. Pulmonary artery (PA) systolic pressure and bronchoalveolar lavage (BAL) fluid red blood cell and albumin concentrations in HAPE-resistant and HAPE-susceptible individuals at low and high altitude. "Well" denotes 6 individuals with a history of HAPE, of whom 4 developed HAPE within 18 hours after BAL; "ill" denotes 3 subjects with HAPE at the time of BAL. *$P < 0.05$ vs low altitude and vs controls. In addition, differences between "well" and "ill" were significant ($P < 0.05$). Error bars indicate SD. Figure adapted from Swenson et al[39] with permission from the American Medical Association. Copyright 2002, American Medical Association.

levels in subjects with HAPE.[66] The phosphodiesterase-5 inhibitor tadalafil, which increases cyclic GMP in lung tissue by inhibiting its degradation, lowered PAP and prevented HAPE.[59]

In a Japanese[67] and in an Indian[68] population, HAPE is associated with 2 endothelial NO synthase gene polymorphisms that are associated with vascular disease, such as hypertension and coronary heart disease. These findings are compatible with the concept of endothelium that is predis-
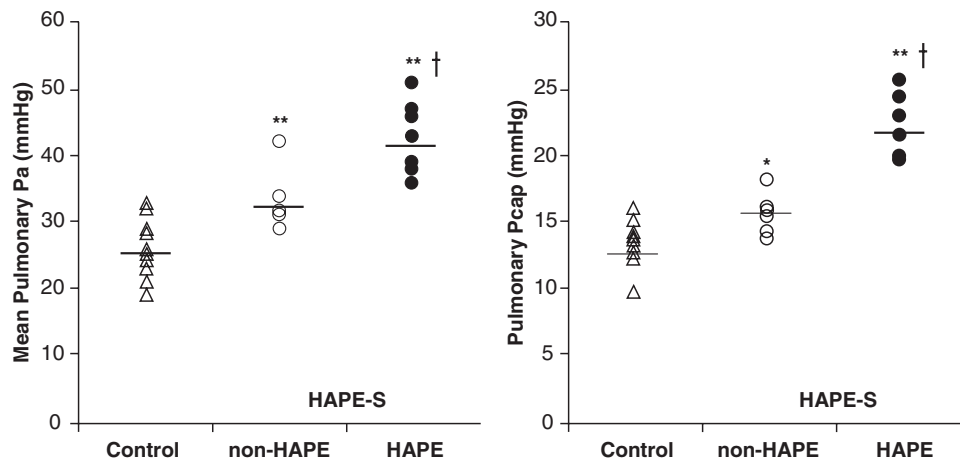
Figure 7. Mean pulmonary artery pressure (Pa) and pulmonary capillary pressure (Pcap) in 14 controls and 16 HAPE-susceptible (HAPE-S) subjects at high altitude. HAPE-S is further divided into those who developed HAPE and those who did not develop HAPE (non-HAPE). Bars indicate mean values in each group. *$P<0.05$, **$P<0.01$ vs control; †$P<0.01$ vs non-HAPE. Figure adapted from Maggiorini et al[57] with permission from Lippincott Williams and Wilkins. Copyright 2001, American Heart Association.

posed to greater vasoconstriction but could not be confirmed in whites.[69] Ethnic differences or different linkage disequilibrium in white and Japanese or Indian populations could account for the discrepant results.

It is likely that additional factors such as increased sympathetic activity or other vasoconstrictors such as angiotensin II,[70] endothelin,[71] or arachidonic acid metabolites[72] contribute to increased PAP in HAPE-susceptible subjects. Increased skeletal muscle sympathetic activity[73] and increased plasma and/or urinary levels of norepinephrine[70,74] compared with controls were found during hypoxia at low altitude and before and during[74] HAPE.

Hydrostatic Edema

Increased capillary pressure[57] and absence of markers of inflammation in bronchoalveolar lavage fluid containing high-molecular proteins and red cells[39] in early HAPE indicate that increased intravascular pressure can lead to a permeability-type edema with high protein concentration in the absence of inflammation. This concept was first advanced in left-sided congestive heart failure[75] and extended to HAPE by West et al,[76] who coined the term stress failure. Whether ruptures of basement membranes, as suggested by West et al, or nontraumatic, dynamic, pressure-sensitive stretching of pores or opening of fenestrae[77] accounts for the leak is debated.[43]

Inhomogeneous HPV[78] was suggested to explain how high PAP can account for high capillary pressure in HAPE. This widely favored hypothesis has received experimental support from animal studies using fluorescent microbeads[48] and from human lung perfusion analysis by magnetic resonance imaging.[49,50] In addition, hypoxic venoconstriction[79] could account for increased capillary pressure in HAPE, but this mechanism would not explain the often patchy radiographic appearance of early HAPE on lung imaging unless there is regional heterogeneity of hypoxic venoconstriction. Branching of capillaries directly from larger arterioles[80] or transarteriolar leakage[81] was suggested as an alternative or additional mechanism and might provide an explanation for the

less frequent cases of HAPE with early perihilar manifestations. The lack of similarity of the radiographic appearance between 2 separate episodes of HAPE in the same individual suggests that structural abnormalities do not account for edema location.[82]

Additional Contributory Factors

Enhancing Pulmonary Arterial and Capillary Pressure

The increase in cardiac output during exercise leads to a further rise in PAP and presumably capillary pressure. Very high pressures might also contribute to HAPE by ventricular interaction and explain the increased wedge pressure during intense exercise in hypoxia in HAPE-susceptible versus -nonsusceptible subjects.[65] In many cases, particularly at lower altitudes, exercise may be the decisive factor that leads to pulmonary edema.

Both a low hypoxic ventilatory drive leading to increased HPV and smaller lungs in relation to body size (decreased pulmonary vascular cross-sectional area) are known to increase PAP and hence susceptibility to HAPE.[43] The considerable overlap of both factors between HAPE-susceptible and -resistant individuals suggests that they are at best contributory but not essential for susceptibility to HAPE.

Any restriction or loss of pulmonary vasculature, such as hypoplasia, absence or occlusion of pulmonary arteries, or pneumonectomy, increases the risk of HAPE. Congenital anomalies of the large pulmonary arteries[83] are associated with an increased risk of developing HAPE at altitudes as low as 2000 m.

A patent foramen ovale has been found in ≈60% of HAPE-susceptible subjects at high and low altitudes.[84] Because PAP is also abnormally high in these individuals during normoxic exercise,[65] a patent foramen ovale may be a consequence of susceptibility to HAPE rather than a cause.

Increased Permeability

Any process enhancing the permeability of the alveolar-capillary barrier is likely to lower the pressure required for generating edema. Increased fluid accumulation during hy-

poxic exposure after priming by endotoxins or viruses in animals[85] and the association of preceding viral infections (predominantly of the upper respiratory tract) with HAPE in children visiting Colorado[86] support this notion. Under conditions of increased permeability, HAPE may also occur in individuals with a normal HPV response.

Reduced Fluid Clearance From the Alveolar Space
Hypoxia impairs fluid clearance from alveoli by inhibiting activity and expression of various sodium transporters.[87] It has been suggested that decreased capacity of epithelial sodium reabsorption might predispose to HAPE. This hypothesis is compatible with the finding that inhalation of high-dose salmeterol, a β_2-agonist that enhances transepithelial sodium transport,[88] can prevent HAPE in some susceptible individuals. Salmeterol has other actions that might modify HAPE; these include lowering PAP, increasing ventilatory response to hypoxia, and tightening cell-to-cell contacts. Molecules that specifically target alveolar epithelial sodium reabsorption are needed to evaluate the role of alveolar fluid clearance from the alveoli in the pathophysiology of HAPE.

Subacute Mountain Sickness

This term is misleading because SAMS is not related to acute mountain sickness. The term right heart failure of high altitude has been suggested.[89] SAMS appears to be the human equivalent of Brisket disease, which presents as edema of the dependent region of the neck and chest in cattle and was recognized >100 years ago at ≈3000 m in the Rocky Mountains. It has been attributed to pulmonary hypertension and right ventricular enlargement.[90] Although SAMS affects humans only after an altitude exposure of several months, it is included in this review because of its important cardiovascular consequences and its potential link to HAPE susceptibility.

The infantile form that was originally described in the Chinese literature[91] is rarely reported outside Tibet.[92] It predominantly affects infants and small children of Chinese lowland dwellers who move to high altitude for a prolonged time. The prevalence was estimated to be 3.6% in Tibet, but mortality was 15% despite descent.[93] Autopsies of children in Lhasa (3658 m) revealed right ventricular hypertrophy and increased muscularization of the pulmonary arterioles without plexiform arteriopathy.[94]

In adults, the syndrome has been reported in 10% to 20% of soldiers who engaged in strenuous exercise at 5800 to 6700 m for several months.[95] Subjects developed edema, breathlessness, angina, cough, orthopnea, and severe congestion. After descent to 300 m, mean PAP was still elevated at 26 mm Hg, rising to 40 mm Hg with mild exercise, although no pulmonary edema was observed on chest radiography. All recovered at low altitude within 3 to 4 months. Excessive pulmonary hypertension with right ventricular pressure overload appears to be a central feature of this illness, although the pathophysiology is not fully understood. Hypoxia-induced neuroendocrine activation may also play a role.[96]

The question arises of whether the exaggerated HPV observed in HAPE-susceptible individuals persists during prolonged exposure to high altitude causing SAMS. Support-

ing this is the similar prevalence of both illnesses: 15% for HAPE in soldiers transported rapidly to 5500 m[97] and 10% to 20% for SAMS when transported more gradually to the same altitude. In cattle, a strong relationship is reported between acute HPV and the severity of pulmonary hypertension that develops at high altitude.[98] Markers of susceptibility for HAPE, such as an exaggerated HPV or a low hypoxic ventilatory response, were, however, not detectable in a small number of soldiers with a history of SAMS.[92] This observation needs to be confirmed in a larger sample.

High-Altitude Tolerance of Patients With Cardiovascular Disease

For patients with cardiovascular disease, the high-altitude environment poses some additional physiological challenges that were not shown in Figure 1 because they are of lesser concern to normal subjects. Low humidity promotes dehydration and further augments the sympathetic activation caused by hypoxia. Increased ventilation causes respiratory alkalosis, which is not fully compensated above 3000 to 4000 m and may be accompanied by a fall of serum potassium.[99] This may be of particular relevance to patients on diuretics. Cold requires heat production, and this places further demands on the heart and circulation. Most people who travel to high-altitude areas will be self-selecting and in good health, but increasing opportunities for tourism at high altitudes is attracting patients with borderline health. Such patients should consider that some locations at high altitude are geographically remote from medical assistance. Altitude tolerance depends on the severity of the disease, the altitude, and the physical activity associated with the exposure. The danger of adverse effects is greatest during the first days of acute exposure and may decrease within a few days as oxygen delivery increases, mainly because of ventilatory acclimatization and reduction in plasma volume.

Pathophysiology

Sympathetic nervous system activation caused by cold and exercise may cause platelet activation[100] and trigger acute coronary syndromes.[101] Patients with coronary atherosclerosis have increased sensitivity to the constrictor effect of catecholamines.[102] In response to sympathetic activation, they constrict epicardial coronary arteries and reduce myocardial perfusion.[103]

The risk of myocardial ischemia is elevated by the increase in cardiac work during the first few days at altitude but reduces as cardiac work subsequently falls. Exercise-induced coronary flow reserve has been found to be significantly decreased at 2500 m in patients with coronary artery disease and a positive exercise test for myocardial ischemia.[14] Coronary spasm may be induced by sympathetic activation and alkalosis.[104] The combination of hypoxia and cold may act synergistically, with exercise as a stressor.[105]

Patients with chronic heart failure experience acute worsening of breathlessness and exercise capacity on ascent to altitude. Neurohumoral activation, a feature of chronic heart failure, is worsened by further stimulation of the sympathetic nervous system by hypoxia. Pulmonary hypertension caused by pulmonary venous hypertension may worsen as a conse-

quence of HPV. Patients are more prone to develop exercise-induced pulmonary edema as a consequence of increased pulmonary capillary hydrostatic pressure.[106] Reduced ventilatory reserve occurs because of increased ventilation for a given level of work[107] due to greater dead space ventilation and abnormal control of ventilation.[108] Severe heart failure stiffens the lungs, which increases the work of breathing. Pulmonary function may also be impaired.[109] Treatment with β-blockers reduces exercise-induced hyperventilation in hypoxia[110] and is associated with a fall in Pao$_2$.

Hypoxic pulmonary vasoconstriction may worsen any cause of pulmonary hypertension.[111] If the right ventricle is unable to compensate, deterioration and death may ensue.

Arrhythmias could be precipitated in susceptible patients at altitude as a consequence of sympathetic activation,[112] hypokalemia caused by respiratory alkalosis and diuretics, right ventricular pressure overload as a consequence of pulmonary hypertension, worsening myocardial ischemia, and heart failure.

The increase in systemic blood pressure in hypertensive patients may be more marked than in normal subjects. This may be a consequence of increased sympathetic activity in hypertensive and borderline hypertensive patients.[113] The increase in blood pressure is often mild but variable, with significant changes detectable at 1200 to 3000 m, and may be exaggerated with exercise.[114–116]

Small pericardial effusions without hemodynamic embarrassment have been observed in 47% of lowlanders ascending to 5200 m.[117]

Clinical Studies

There are several anecdotal reports of instability of coronary disease, often associated with exercise, at high altitude,[118] as well as the attainment of very high altitudes (>5000 m) without deterioration of known coronary disease. There have been a limited number of systematic studies of coronary artery disease performed in mostly unacclimatized patients at altitudes between 2500 and 3454 m (Table III in the online-only Data Supplement). The most common findings are that symptoms and ECG signs of myocardial ischemia did not develop at rest; that on symptom-limited maximal exercise testing exercise endurance, maximal oxygen consumption and workload were reduced to a level similar to that observed in healthy individuals; but that rate-pressure product on exercise was the same at low and high altitudes, suggesting that the main effect of hypoxia is on exercise heart rate and blood pressure rather than a direct effect on myocardial ischemia.

Two studies showed evidence for worse myocardial ischemia at high altitude. Acute exposure to 2500 m after an ascent from sea level depressed the ischemic threshold by 5% on day 1 but not on day 5[119] (Figure 8). One patient sustained myocardial infarction after an exercise test at altitude. Another study showed that exercise-induced coronary flow reserve decreased by 18% from normoxia to hypoxia in patients with angiographically proven obstructive coronary disease.[14] Furthermore, oxygen delivery to myocardium served by stenotic vessels decreased in hypoxia despite unchanged flow to remote nonstenotic arterial territories.
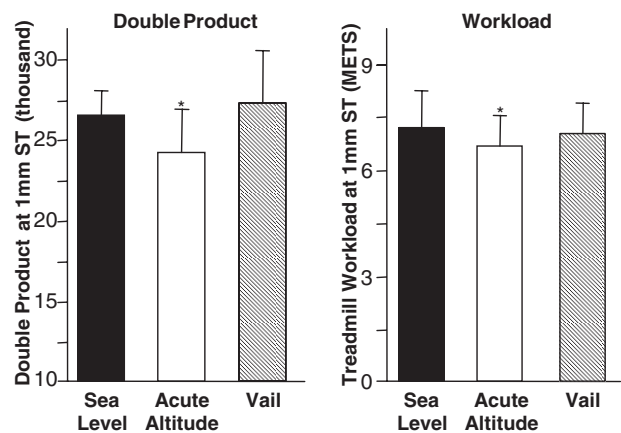

Figure 8. Effect of immediate exposure in a low-pressure chamber to a simulated altitude of 2500 m (acute) and effect of exposure over 5 days in Vail, Colo, to an altitude of 2500 m (Vail) on exercise, workload, and rate-pressure product in 20 subjects (mean age, 68±3 years); for details on subjects, see Table III in the online-only Data Supplement. Values represent mean±SEM for the ischemic threshold of the double product (heart rate×systolic blood pressure) and treadmill workload (in metabolic equivalents [METS]) at which 1 mm flat, downsloping, or slowly upsloping ST depression was first identified. Solid bars indicate sea level; open bars, acute simulated altitude to 2500 m; and hatched bars, 5 days of acclimatization to 2500 m in the field. Figure adapted from Levine et al[119] with permission from Lippincott Williams and Wilkins. Copyright 1997, American Heart Association.

There are no field studies of heart failure at high altitude. In a study using acute exposure to normobaric hypoxia, patients with chronic heart failure (mean ejection fraction 32% to 35%, left ventricular end-diastolic dimension >65 mm) experienced decline in their maximum exercise capacity with increasing altitude. Maximum work rate fell by 3% per 1000 m in normal subjects and 11% per 1000 m in subjects with severe heart failure at altitudes up to 3000 m (Figure 9).[109] Such a difference between patients and controls was not observed with minor heart failure (ejection fraction 39±6%) at 2500 m, where maximum power decreased by 3% to 4%.[120] There are no clinical studies of patients with idiopathic pulmonary arterial hypertension being taken to altitude, but there is evidence that it improves on descent.[121]

There are numerous reports of increased supraventricular and ventricular premature beats in healthy subjects on ascent to altitude, often but not exclusively associated with exertion. It has not been shown whether these findings predispose to sustained life-threatening arrhythmias. Although several studies have reported no life-threatening arrhythmias on exposure of patients with heart disease to altitude (Table III in the online-only Data Supplement), the numbers of patients are small. Arrhythmias were more common on exercise, but there were no changes in the signal-averaged ECG compared with at sea level.[119]

Sudden death or severe cardiovascular events were rarely reported from trekking in Nepal between 1984 and 1991,[122] although underreporting was likely. Sudden death during hiking in the Alps between 1100 and 2100 m[123] was not more frequent than sudden death with vigorous exercise at low altitude.
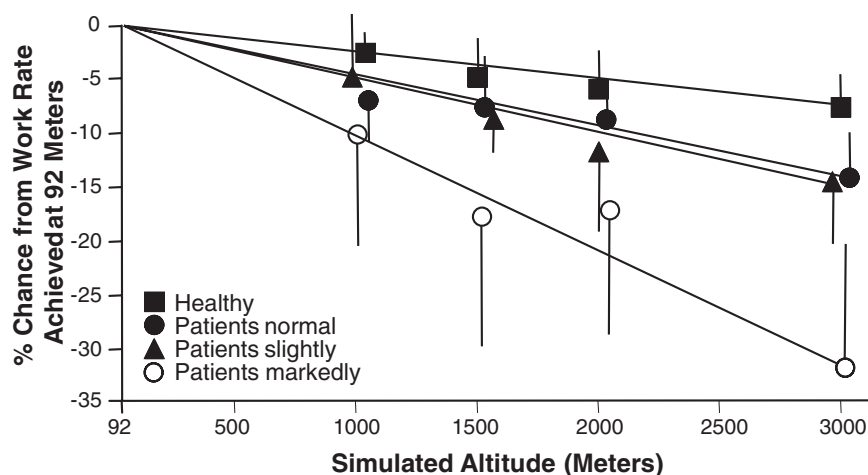
Figure 9. Reduction of work rate at simulated altitudes in heart failure patients and normal subjects. Patients were grouped according to the workload they had previously achieved on cycle ergometry. Mean (±95% CIs) reduction in maximum work rate with simulated altitude, as a percent decrease from maximum work rate at 92 m, is shown. Slopes differed ($P<0.05$) in healthy subjects (−2±1% per 1000 m; filled squares) compared with patients and between patients with normal (−4±2%; filled circles) or slightly diminished workload (−4±2%; filled triangles) compared with patients with markedly diminished workload (−10±3%; open circles). Figure adapted from Agostoni et al[109] with permission from Elsevier. Copyright 2000, Elsevier, Inc.

Recommendations

Despite the sparse evidence, patients with cardiovascular disease seek advice from their physician about journeying to high altitude. We have attempted to make some reasonable recommendations on the basis of published evidence and pathophysiology. High-altitude exposure may unpredictably precipitate an acute coronary syndrome or death. Not only will sea level exercise capacity be reduced on account of physiological changes, but angina may worsen at least for the first few days in association with increased heart rate and systolic blood pressure. In addition, the symptoms of high-altitude illnesses may be confused with those of cardiopulmonary disease such as myocardial infarction, acute pulmonary embolism, and heart failure. Exposure to high altitude may unmask coronary artery disease, left ventricular dysfunction, or pulmonary hypertension that was asymptomatic at sea level.

Nevertheless, at 2000 to 2500 m, mild hypoxemia is induced, alkalosis is minor, pH is back to normal within a day, and the reduction in exercise performance is small. This altitude corresponds to the ambient pressure maintained in commercial aircraft. Thus, patients with coronary disease considered eligible for long-haul flights without supplemental oxygen should tolerate visits to such altitudes by passive ascent. Exercise tolerance at this altitude will be almost the same as at low altitude provided that there are no concomitant illnesses that enhance hypoxemia or significant heart failure that may increase the altitude-induced loss of performance.[109]

The studies summarized in Table III in the online-only Data Supplement suggest that most patients with stable coronary disease that allows a sufficiently high exercise capacity at sea level can go to 3000 to 3500 m with minimal increased risk. These patients should be asymptomatic or be in Canadian Cardiovascular Society functional class I or II with mild stable symptoms at the levels of exercise they expect to pursue at altitude. In addition, they should have well-controlled blood pressure, have a negative exercise test at sea level or an ischemic threshold >6 metabolic equivalents, have no significant arrhythmia or heart failure, and be free of concomitant disease that affects ventilation or gas exchange. If coronary revascularization is planned, this should be performed before ascent. Patients should ascend

slowly (average ascent rate of 300 to 350 m/d above 2000 m) or stay for some days at 2000 to 2500 m. Activity may need to be restricted during the first 3 to 4 days of altitude exposure. If angina worsens on ascent, bed rest, oxygen, and descent may be required. Patients in whom ascent is contraindicated are those who have unstable or severe angina, objective evidence of myocardial ischemia at low workload, or a recent acute coronary syndrome.

Heart failure patients with severe or unstable symptoms or fluid retention should avoid ascent to altitude. Although hypokalemia is not significant in normal subjects below 4500 m, the use of diuretics may increase this risk at lower altitudes. Heart failure patients must be conversant with diuretic management, which may need alteration at altitude.

Patients with preexisting pulmonary hypertension should not exceed 1500 to 2000 m. Supplemental oxygen should be considered on commercial aircraft. Current drug therapies for pulmonary arterial hypertension improve hemodynamics incompletely and may not protect against the effects of hypoxic pulmonary vasoconstriction. HAPE has been reported in a patient with mild idiopathic pulmonary arterial hypertension.[124] Altitude may unmask pulmonary vascular disease in patients with significant septal defects and some patients with mitral stenosis, the latter also worsening because of impaired left ventricular filling due to tachycardia.

Clinical studies of arrhythmias are not adequate to draw any firm conclusions. Patients with unstable arrhythmias or high-grade ventricular ectopy such as Lown 4b should not ascend to altitude. In our experience, paroxysmal atrial fibrillation does not necessarily worsen on altitude exposure.

Overall, there is a paucity of data on which to make any recommendations about hypertensive patients going to altitude. The existing data cannot exclude the possibility that blood pressure might acutely become dangerously high in individuals whose pressure is not controlled at sea level. Patients with uncontrolled hypertension should therefore not venture to altitude until their blood pressure is controlled. Checking blood pressure in hypertensive patients during exposure to high altitude should be considered.

Disclosures

Dr Bärtsch reports no conflicts. Dr Gibbs reports having received speakers' fees for Actelion Pharmaceuticals and Schering Company and being an advisory board member for Actelion Pharmaceuticals, Encysive, Pfizer, and GlaxoSmithKline.

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