Peer reviewed article

High altitude pulmonary oedema

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Summary

Altitude, speed and mode of ascent and, above all, individual susceptibility are the most important determinants for the occurrence of high altitude pulmonary oedema (HAPE). This illness usually develops only within the first 2–5 days after acute exposure to altitudes above 2500–3000 m. An excessive rise in pulmonary artery pressure preceding oedema formation is the crucial pathophysiological factor. Recent investigations using right heart catheterisation and bronchoalveolar lavage (BAL) in incipient pulmonary oedema have shown that HAPE is a hydrostatic oedema in the presence of normal left atrial pressure with non-inflammatory high permeability leakage of the alveolocapillary barrier and mild alveolar haemorrhage. An inflammatory response may develop later in more advanced cases, as has been documented by BAL. Furthermore, decreased fluid clearance from the alveoli may contribute to such non-cardiogenic pulmonary oedema. Supplemental oxygen is the primary treatment in areas with medical facilities, while the treatment of choice in remote mountain areas is immediate descent. When this is impossible and supplemental oxygen is not available, treatment with nifedipine is recommended until descent is possible. Even susceptible individuals can avoid HAPE if they ascend slowly with an average gain of altitude not exceeding 300–350 m/day above an altitude of 2500 m.

Key words: pathophysiology; treatment, prevention; inflammation; pulmonary artery hypertension; alveolar fluid clearance

Epidemiology

There are two typical settings for HAPE, a pulmonary oedema which may occur in healthy individuals within a few days of arrival at high altitude. The first setting involves high-altitude dwellers returning from sojourns at low altitude, while the second involves rapid ascent by unacclimatised lowlanders. The first medical description of HAPE was published in Peru and recognised reentry HAPE as a pulmonary oedema associated with electrocardiographic signs of right-ventricular overload [1]. The first cases of HAPE in unacclimatised lowlanders climbing to high altitude were reported from the Rocky Mountains [2]. The two forms very probably share the same pathophysiology.

Altitude, rate of ascent and, most importantly, individual susceptibility are the major determinants of HAPE in mountaineers and trekkers. The prevalence of HAPE is <0.2% in a general alpine mountaineering population when ascent occurs in three or more days to an altitude of 4559 m. When the same altitude is reached within 22 hours, the incidence increases to 7% in mountaineers without, and to 62% in those with, a history of radiographically documented HAPE [3]. The incidence of HAPE also increases from 2.5 to 15.5% when an altitude of 5500 m is reached by airlift [4] as opposed to trekking over 4–6 days [5].

HAPE may also occur at lower altitudes between 2500 and 3000 m in the Japanese Alps and in North America [6]. The estimated incidence in visitors to ski resorts in the Rocky Mountains of Colorado is 0.01–0.1% [7]. Women may be less susceptible to HAPE than men [8, 9]. Re-entry HAPE has also been reported from the Rocky Mountains and appears to run in susceptible families and chiefly affect children, findings also reported from the Andes [10, 11].

Most recently HAPE has been reported in Alpine resorts located at altitudes between 1400 and 2400 m in an area with facilities for skiing up to 3200 m [12]. Susceptibility to HAPE may have been increased in these patients by previous or unrecognised underlying illness, as discussed later in this review, and some may have had diastolic heart failure rather than HAPE, due to hypertensive heart disease.

There were no financial relationships in connection with this article.

Signs and symptoms

HAPE presents within 2–5 days of arrival at high altitude [4]. It is rarely observed below altitudes of 2500–3000 m and after 1 week of acclimatisation at a particular altitude. In most cases it is preceded by symptoms of acute mountain sickness (AMS) [13]. Early symptoms of HAPE include exertional dyspnoea, cough and reduced exercise performance. As pulmonary oedema progresses, cough worsens and breathlessness at rest and sometimes orthopnoea occur. Gurgling in the chest and pink frothy sputum indicate advanced cases.

The clinical features are cyanosis, tachypnoea, tachycardia and elevated body temperature generally not exceeding 38.5 °C. Rales are discrete initially and typically located over the middle lung fields. There is often a discrepancy between the minor findings on auscultation compared with the degree of alveolar infiltration on chest x-ray. In advanced cases signs of concomitant cerebral oedema, such as ataxia and decreased levels of consciousness, are frequent findings.

Subclinical HAPE probably occurs and causes no or minimal symptoms which can be ignored or attributed to other factors. The true incidence is unknown, although two recent studies have suggested that upwards of 50% of persons may have subclinical fluid accumulation in the lung, consistent with occult oedema which resolves spontaneously even though subjects remain at high altitude [14, 15]. These studies employed very indirect measures of lung water changes, spirometry, closing volume and transthoracic impedance, all of which may vary for other reasons relating to the high altitude environment, such as increases in cardiac output, cold-induced mild bronchoconstriction, exercise and hypocapnia.

Further evaluation

Ordinarily there are no characteristic laboratory findings [6]. Abnormal results may be due to concomitant dehydration, stress and previous exercise. Inflammation markers and changes in blood coagulation are discussed in the section on pathophysiology. Arterial blood gas measurements in 4 cases of advanced HAPE at 4559 m demonstrate the severity of this illness; mean arterial PO_2 was 23 ± 3 (SD) mm Hg (controls: 40 ± 5) and arterial oxygen saturation was 48 ± 8% (controls 78 ± 7%) [16]. In early cases values around 30 mm Hg for PO_2 and 70% for SaO_2 are observed at this altitude.

Chest x-ray and CT-scans in early HAPE show patchy peripheral distribution of oedema, as shown in Figure 1. The radiographic appearance of HAPE is more homogeneous and diffuse in advanced cases and during recovery [17–19]. Moreover, in patients who had two episodes of HAPE the similarity of the radiographic appearance between the two episodes was random, suggesting that structural abnormalities do not account for oedema location [18].

Autopsies reveal distended pulmonary arteries and diffuse pulmonary oedema with bloody foamy fluid present in the airways but no evidence of left ventricular failure [20, 21]. Further, hyaline membranes were found in most cases and arteriolar thrombi, pulmonary haemorrhages or infarcts were often present.

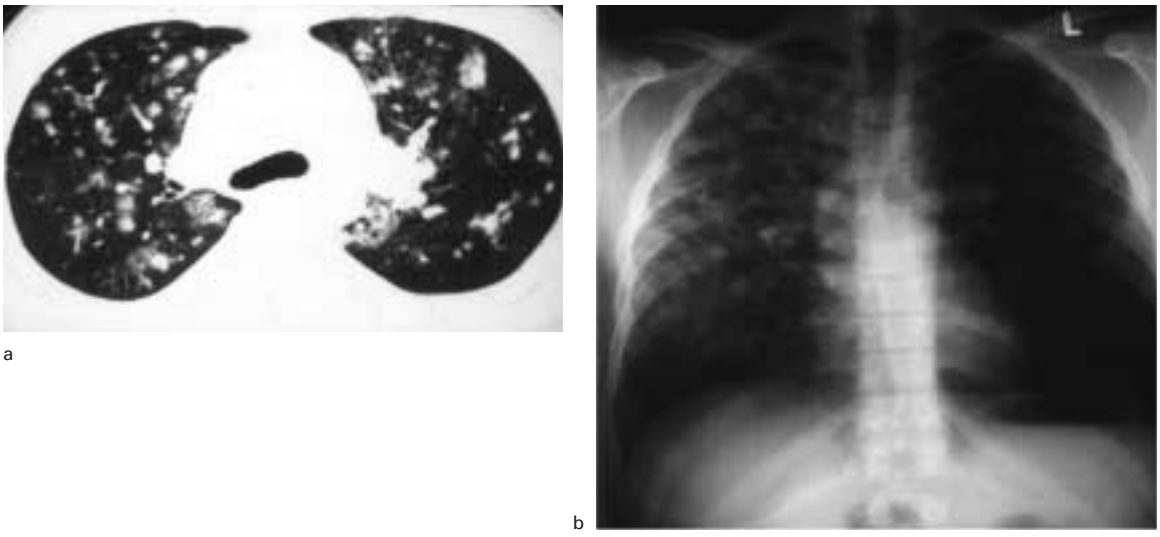

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Figure 1

Chest x-ray and CT of a male patient with recurrent HAPE showing patchy distribution of oedema, predominantly in the upper lung fields on the right side.

Pathophysiology

Haemodynamics

Exaggerated pulmonary artery pressure

Cardiac catheterisation of untreated cases of HAPE at high altitude reveals mean pulmonary artery pressures of 60 (range 33–117) mm Hg [22–24], while wedge pressures are normal. Estimations of systolic pulmonary artery pressure by echocardiography reveal values between 50 and 80 mmHg for subjects with HAPE and 30–50 mm Hg for healthy controls [25–27].

It is well established that an excessive rise in pulmonary artery pressure is crucial for the development of HAPE, since this pressure rise precedes HAPE [26] and drugs lowering pulmonary artery pressure improve gas exchange in HAPE [27, 28] and are effective in its treatment [29] and prevention [26]. Individuals susceptible to HAPE also exhibit an exaggerated pulmonary artery pressure rise under hypoxia and exercise [30–32].

At Capanna Margherita (4559 m) right heart catheterisation recently showed that the abnormal rise in pulmonary artery pressure in individuals susceptible to HAPE is accompanied, as shown in Figure 2, by capillary pressure increased to above 20 mm Hg in those who develop HAPE [33]. This threshold value is in keeping with previous experimental observations in dogs of a PO_2-independent critical capillary pressure of 17–24 mm Hg, above which the lungs continuously gain weight [34]. These results suggest that pulmonary capillary hypertension plays an important role in the pathophysiology of HAPE.

Mechanisms of exaggerated hypoxic pulmonary vascular response (HPVR)

The cause of exaggerated HPVR in HAPE-susceptible subjects is not known. Besides a possibly increased pulmonary hypoxic vasoconstrictor response, a lower hypoxic ventilatory response (HVR) [35–38] and slightly lower lung volumes [37, 39, 40] may contribute to increased PAP by causing greater alveolar hypoxia [41] and reducing the number of recruitable vessels. Furthermore, microneurography in HAPE subjects demonstrates increased muscular sympathetic activity during hypoxia at low altitudes and prior to HAPE at high altitudes [42]. In accordance with these findings, increased plasma and/or urinary levels of

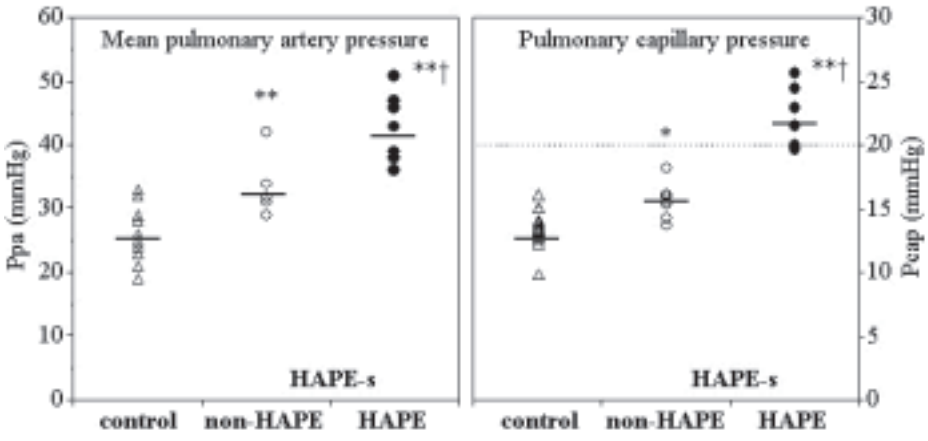


Figure 2

Mean pulmonary artery pressure (Ppa) and pulmonary capillary pressure (Pcap) in 14 controls and in 16 high altitude oedema-susceptible (HAPE-s) subjects at high altitude. HAPE-s is further divided into those who developed HAPE (HAPE) and those who did not (non-HAPE). Bars indicate the mean values in each group. * p<0.05, ** p<0.01 vs. control, † p<0.01 vs. non-HAPE

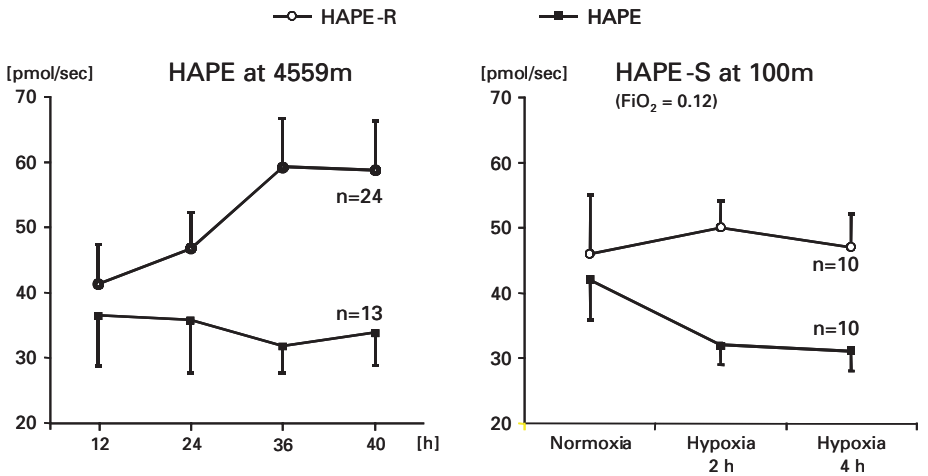


Figure 3

Left panel: Exhaled NO over 40 hours at 4559 m in individuals developing HAPE and not developing HAPE (HAPE-R) despite identical exposure to high altitude (data from [49]). Right panel: Exhaled NO in individuals with (HAPE-S) and without (HAPE-R) susceptibility to HAPE during 4 hours of exposure to hypoxia (FIO_2 = 0.12) at low altitude (data from [48]).

norepinephrine compared to controls were found to precede [43] and accompany [43, 44] HAPE. It is conceivable that increased sympathetic activity contributes to the brisk HPVR and that HAPE may bear some resemblance to neurogenic pulmonary oedema [45].

Several strands of evidence suggest that susceptibility to HAPE may be associated with endothelial alterations in the pulmonary circulation: higher concentrations of endothelin are found in the plasma of HAPE patients than in healthy controls at high altitude [46, 47]. There is also indirect evidence that NO production is reduced in HAPE-susceptible individuals since they have lower exhaled NO during acute [48] and prolonged [49] exposure to hypoxia (Figure 3) and lower concentrations of nitrate and nitrite in BAL fluid [50] than control subjects. The concept of an endothelium predisposed to greater vasoconstriction is also supported by the fact that in the Japanese population HAPE is positively associated with two endothelial nitric oxide synthase (eNOS) gene polymorphisms (G894T-variant and 27-base pair [BP] variable numbers of tandem repeats), which are associated with vascular diseases such as essential hypertension and coronary heart disease [51]. However, an investigation in Caucasians equivalent to the Japanese study did not find an association between susceptibility to HAPE and a number of eNOS polymorphisms including the G894T variant [52]. Ethnic or environmental differences or a different linkage disequilibrium in Japanese and Caucasians could account for the discrepant results. The observation that inhaled NO did not normalise pulmonary artery pressure in HAPE-susceptible individuals, but did so in those resistant to HAPE [53], indicates that impaired NO synthesis cannot fully account for the excessive pulmonary vascular reactivity in HAPE-prone subjects. It is likely that additional factors mentioned above, such as heightened sympathetic activity and other vasoconstrictors such as arachadonic acid metabolites, contribute to increased Ppa in HAPE-susceptible subjects.

Mechanism accounting for increased capillary pressure

There are at least two explanations for the occurrence of pulmonary capillary hypertension in individuals susceptible to HAPE. The first is inhomogeneous hypoxic vasoconstriction causing regional overperfusion of capillaries in areas of low arterial vasoconstriction, resulting in irregularly distributed pulmonary oedema rich in protein and red blood cells [54]. The observation of increased susceptibility to HAPE in individuals with an absent right pulmonary artery [55] accords well with the overperfusion hypothesis. Uneven distribution of arteriolar muscle cells could lead to uneven vasoconstriction. Rapid remodelling [56] resulting in more homogeneous perfusion could then account for the clinical observation that HAPE only occurs during the first few days of acute exposure to a particular altitude. Thus far increased inhomogeneous pulmonary perfusion during hypoxia has not been clearly demonstrated in subjects susceptible to HAPE, possibly because of inadequate spatial resolution of the methods applied.

The second hypothesis suggests that hypoxic constriction occurs either at the smallest, leaky arterioles and at the venules, or both. There is evidence from animal experiments using a double occlusion technique [57, 58] that the small arterioles are the site of transvascular leakage in the presence of markedly increased Ppa in hypoxia [59] and that pulmonary veins contract in response to hypoxia [60, 61] increasing the resistance downstream of the fluid filtration region. Inhomogeneous vasoconstriction may therefore not be necessary to explain alveolar flooding in subjects with HAPE. However, we may still need to retain some element of regional heterogeneity of HPV (either at arterial and venous sites or both) to explain the heterogeneity of regional oedema, at least as we observe it on chest x-ray or CT scans (Figure 1).

In addition to either mechanism, an increase in pulmonary blood flow on exercise will raise pulmonary capillary pressure [31] due to venous resistance, as suggested by Younes et al. [62].

Inflammation

BAL performed within a day of ascent to 4559 m reveals elevated red blood cell counts and serum-derived protein concentration in the BAL fluid (see table) both in subjects with HAPE and in those who developed HAPE within the next 24 h [50]. Although these findings are consistent with a possible inflammatory leak, there was no increase in alveolar macrophages and neutrophils or in the concentration of proinflammatory mediators (interleukin- [IL-] 1, TNF-alpha, IL-8, thromboxane, prostaglandin E2 and leukotriene B4) at high altitude, and there was no difference between individuals resistant and susceptible to HAPE. The fact that the alveolar protein concentration may exceed the plasma protein concentration in HAPE suggests that active salt and water reabsorption occurs and concentrates the protein leaked in the initial stages of HAPE (see discussion below on alveolar fluid clearance).

These data indicate that there is a partial disruption of the alveolar-capillary barrier that is not caused by an inflammatory process. The intriguing finding of a normal pulmonary leak index in early HAPE, as reported by one of the authors [33], can be explained by the definition of this index, which uses a labelled protein to mark the magnitude of alveolar leak and labelled red blood cells as an indicator of the intra-vascular compartment. Since, in HAPE, red cells also leak into the alveoli, the leak cannot be detected by this method.

However, analysis of bronchoalveolar lavage (BAL) fluid of mountaineers with more advanced HAPE on Mount McKinley [63] and in hospitalised HAPE patients in Japan [64] showed, in many but not all cases, not only high concentrations of proteins as measured in early HAPE,

Table 1

Bronchoalveolar lavage (BAL) at 550 m and on the second day at 4559 m in 8 control subjects (CONT) and in 9 HAPE-susceptible subjects (HAPE-S) of whom 3 had pulmonary oedema at the time of BAL. Of the 6 HAPE-S without pulmonary oedema at the time of BAL, 4 developed HAPE within 18 hours after BAL. * p <0.05 vs. 550 m ** This calculation is based on a dilution factor of 100 calculated for this lavage technique and an average plasma protein of 70 g/l.

	550 m		4559 m		
	CONT n = 8	HAPE-S n = 9	CONT n = 8	HAPE-S (well) n = 6	HAPE-S (ill) n = 3
White cell count ($\times 10^4$ ml)	8.1	6.3	9.5	8.1	9.8
Macrophages (%)	94	95	83	82	85
Neutrophils (%)	1	0	0	0	1
Red cells (% of total BAL cells)	1	4	6	51*	74*
Total protein (mg/dl)	1	2	14	34	163*
Total protein (% of plasma protein)**	1	3	20	48	232
PAP systolic (mm Hg)	22	26	37*	61*	81*

but also elevated proinflammatory cytokines, leukotriene B_4 and increased granulocytes. Furthermore, urinary leukotriene E_4 excretion was increased in patients with HAPE reporting to clinics in the Rocky Mountains [65]. These observations suggest that, in more advanced cases of HAPE, inflammation may occur and contribute to enhanced pulmonary capillary permeability. Evidence of in-vivo thrombin and fibrin formation in advanced [16] but not in early HAPE or preceding HAPE [66] indicates that activation of blood coagulation only occurs in advanced cases and may be a consequence of the inflammatory response.

In conclusion, the results of all these studies indicate that HAPE is a hydrostatic type of pulmonary oedema, the pathophysiological mechanism of which is excessive hypoxic pulmonary vasoconstriction of small arteries and veins, probably leading to overdistension of the vessel wall, which opens the cellular junctions and possibly causes stress failure of the alveolo-capillary membrane [67]. Thus, signs of inflammation found in BAL fluid of patients with advanced HAPE are a secondary event.

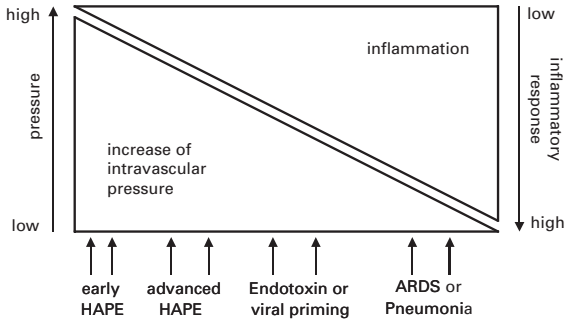
It is conceivable that any process enhancing the permeability of the alveolar-capillary barrier would lower the pressure required to generate oedema. Indeed, increased fluid accumulation during hypoxic exposure after priming by endotoxins or viruses in animals [68] and the association of previous viral infections (predominantly of the upper respiratory tract) with HAPE in children visiting Colorado [69] support this concept. Under conditions of increased permeability HAPE may also occur in individuals with normal hypoxic pulmonary vascular response (Figure 4). Thus, upper respiratory tract infections shortly before a sojourn in the French Alps and vigorous exercise at altitudes between 2000 and 3000 m may explain why in some cases HAPE develops at a surprisingly low altitude [12]. Other cases may be due to diastolic heart failure in hypertension and to undiagnosed pathology favouring the occurrence of HAPE, such as silent pulmonary embolism possibly triggered by prolonged road, rail or air travel [70].

Alveolar fluid clearance

A further mechanism which may contribute to the pathophysiology of HAPE has been pointed out recently. Results obtained in cell cultures and animal models suggest that impairment of fluid clearance from the alveoli may be involved in the pathophysiology of HAPE. The cell and membrane processes which mediate water and sodium transport across type II alveolar epithelial cells are shown in Figure 5. Hypoxia decreases transepithelial sodium transport [71] and accounts for decreased fluid clearance from the alveoli of hypoxic rats at an F_IO_2 of 0.08 [72]. Mice partially deficient in the apical (alveolar-facing) epithelial sodium channel show greater accumulation of lung water in hypoxia [73]. Transalveolar sodium transport may be stimulated by beta-2 receptors and a recent field study has shown successful prevention of HAPE with inhalation of salmeterol, a beta-2 agonist [74]. It should, however, be noted that the doses employed were 2.5 times higher than recommended for the treatment of obstructive lung disease. Furthermore, due to the multiple actions of this drug, such as lowering of pulmonary artery

Figure 4

Role of capillary pressure and inflammatory response in various forms of pulmonary leak. In early HAPE, increased intravascular pressure is the major factor accounting for oedema formation, while in advanced cases an inflammatory response contributes to oedema formation. In pneumonia or ARDS, intravascular pressure is, at least initially, normal in most cases and inflammation accounts for the leak. Increased permeability due to inflammation, such as an upper respiratory tract infection [69] or priming by endotoxins or viruses [68] prior to hypoxic exposure may facilitate the occurrence of pulmonary oedema in the presence of a normal increase in pulmonary artery pressure under hypoxia.



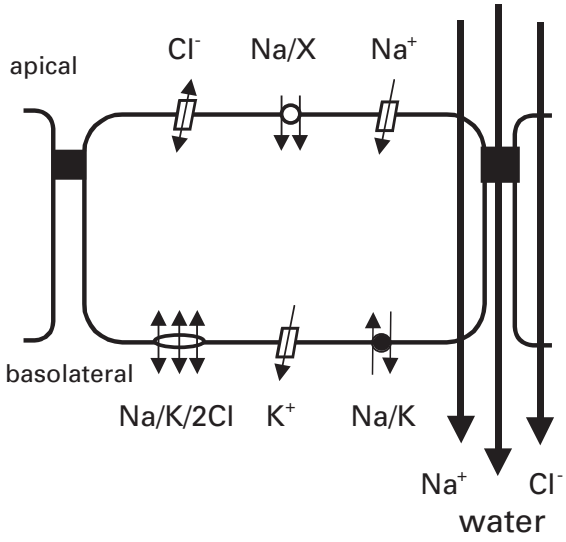


Figure 5

Removal of alveolar fluid is driven by the active reabsorption of Na^+ entering the cell via Na channels and Na-coupled transport (Na/X). Na/K-ATPases keep the intracellular Na-concentration low. Active Na reabsorption thus generates the osmotic gradient for the reabsorption of water. The contribution of Cl transport and the exact pathways by which Cl and water pass the cells are not known.

pressure, increasing of ventilatory response to hypoxia and tightening of cell-to-cell contacts, the contribution of stimulated alveolar fluid clearance to the positive study outcome is not clear [75]. With this consideration in mind, preliminary analysis of a subset of the patients of Sartori et al. [74] showed significant reduction of systolic pulmonary artery pressure by salmeterol [76]. Definitive evaluation of the role of depressed alveolar fluid clearance in the pathophysiology of HAPE will require more specific drugs.

Sartori et al. also found that HAPE-susceptible individuals had a lower transepithelial nasal potential in normoxia than non-susceptible controls [74], a reduction which could be ascribed to lower sodium transport by the epithelial sodium channel (ENaC). These findings may point to a constitutional, possibly genetically determined reduction of sodium transport across the respiratory epithelium. Although a recent investigation confirmed the difference in nasal potential between HAPE-susceptible individuals and controls in normoxia, this difference could not be attributed to the EnaC [77]. The study also showed that nasal epithelium may not adequately reflect ion transport across the alveolar epithelium. Hence the significance of a lower nasal potential in HAPE-susceptible individuals is unclear for the moment.

Prevention

Slow ascent is the most effective method of prevention, and one that is effective even in susceptible individuals. Personal observations of 9 ascents in 7 mountaineers (by P.B.), who had all developed HAPE more than once upon rapid ascent in the Alps, indicate that altitudes of up to 7000 m can be reached by these individuals without medical problems when the average daily ascent rate above 2000 m does not exceed 350–400 m per day or with a staged ascent [79].

To avoid life-threatening illness, mountaineers with symptoms of altitude sickness should be advised not to ascend further and to descend if the symptoms do not improve after a rest day. Since exercise-induced circulatory changes may worsen or cause pulmonary oedema [31], vigorous exercise should be avoided during the first days of altitude exposure by individuals with a history of HAPE and by those with symptoms of altitude sickness, or after a rapid ascent to altitudes above 3500–4000 m. As pointed out earlier, susceptibility to HAPE may be increased during and shortly after infections [69].

Prophylaxis with nifedipine (an inhibitor of hypoxic pulmonary vasoconstriction) can be recommended for individuals with a history of unquestionable HAPE if slow ascent is not possible [26]. 60 mg daily of a slow-release formulation should be given, starting with the ascent and ending on the third or fourth day after arrival at the final altitude, if the stay is to be prolonged, or after returning to an altitude below 3000 m or one to which the individual is acclimatised. It should be emphasised that nifedipine helps to avoid HAPE but is not effective for prevention of acute mountain sickness [80]. Interestingly, acetazolamide, which is often used for AMS prevention, blunts hypoxic vasoconstriction in animals [78, 81]. Whether it does so in humans, however, has not been tested and hence it cannot be recommended for this purpose.

Given the uncertainties mentioned above with regard to the preventive effect of inhaled beta-2-receptor agonists, we do not recommend using such drugs instead of nifedipine for the prevention of HAPE. Whether it makes sense to use such drugs (in the dose recommended for treatment of obstructive pulmonary disease) in addition to nifedipine needs to be investigated.

Treatment

Immediate improvement of oxygenation is the treatment of choice. Specific recommendations depend on where HAPE occurs. For the mountaineer in a remote area without medical care, descent has first priority while the tourist with HAPE in a resort in the Rocky Mountains may stay at altitude if arterial oxygen saturation can be maintained above 90% with low-flow oxygen (2–4 l/min) and monitoring by family or friends is guaranteed. Relief of symptoms is achieved within hours and complete clinical recovery usually occurs within 2–3 days. Severe, advanced cases need to be evacuated to low altitude, where they may require prolonged hospitalisation [6], especially if there is coexistent HACE.

In Himalayan mountaineers mortality has

been estimated at approximately 50% if neither descent nor any other form of treatment is possible. If descent is impossible and supplemental oxygen is not available, portable hyperbaric chambers [82] and treatment with nifedipine (20 mg slow-release formulation every 6 h) should be initiated until descent is possible. In mountaineers with HAPE at 4559 m, persistent relief of symptoms and improvement of gas exchange and radiographic appearance were documented over 34 h with 20 mg nifedipine every 6 h [29]. There were no significant side effects with nifedipine in this therapeutic trial or when administered as prophylaxis. The question whether inhalation of beta-2-receptor agonists might be used in addition to nifedipine requires investigation. It is likely that sildenafil, which attenuates hypoxic pulmonary vasoconstriction [83] is effective for the prevention and treatment of HAPE, but no clinical trials have yet been reported.

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References

1 Lizarraga L. Soroche agudo: Edema agudo del pulmón. An Fac Med (San Marco, Lima) 1955;38:244–74.
2 Houston CS. Acute pulmonary edema of high altitude. N Engl J Med 1960;263:478–80.
3 Bärtsch P, Maggiorini M, Mairbäurl H, Vock P, Swenson E. Pulmonary extravascular fluid accumulation in climbers (Letter). Lancet 2002;360:571.
4 Singh I, Kapila CC, Khanna PK, Nanda RB, Rao BDP. High-altitude pulmonary oedema. Lancet 1965;I(Jan. 30):229–34.
5 Hackett PH, Rennie D, Levine HD. The incidence, importance, and prophylaxis of acute mountain sickness. Lancet 1976;II(Nov. 27):1149–54.
6 Kobayashi T, Koyama S, Kubo K, Fukushima M, Kusama S. Clinical features of patients with high-altitude pulmonary edema in Japan. Chest 1987;92:814–21.
7 Sophocles AM Jr. High-altitude pulmonary edema in Vail, Colorado, 1975–1982. West J Med 1986;144:569–73.
8 Hultgren HN, Honigman B, Theis K, Nicholas D. High-altitude pulmonary edema at a ski resort. West J Med 1996;164(3): 222–7.
9 Hochstrasser J, Nanzer A, Oelz O. Das Höhenödem in den Schweizer Alpen. Beobachtungen über Inzidenz, Klinik und Verlauf bei 50 Patienten der Jahre 1980–1984. Schweiz Med Wochenschr 1986;116:866–73.
10 Hultgren HN, Marticorena EA. High altitude pulmonary edema. Epidemiologic observations in Peru. Chest 1978;74: 372–6.
11 Scoggin CH, Hyers TM, Reeves JT, Grover RF. High-altitude pulmonary edema in the children and young adults of Leadville, Colorado. N Engl J Med 1977;297:1269–72.
12 Gabry AL, Ledoux X, Mozziconacci M, Martin C. High-altitude pulmonary edema at moderate altitude (<2,400 m; 7,870 feet). Chest 2003;123:49–53.
13 Bärtsch P, Roach R. Acute mountain sickness and high-altitude cerebral edema (Chapter). In: Hornbein TF, Schoene R, eds. High altitude – an exploration of human adaptation. New York: Marcel Dekker Inc.; 2001. pp. 731–76. (LENFANT, C., exec. ed. Lung biology in health and disease; v. 161).
14 Cremona G, Asnaghi R, Baderna P, Brunetto A, Brutsaert T, Cavallaro C, et al. Pulmonary extravascular fluid accumulation in recreational climbers: a prospective study. Lancet 2002;359: 303–9.
15 Mason NP, Petersen M, Mélot C, Imanov B, Matveykine O, Gautier MT, et al. Serial changes in nasal potential difference and lung electrical impedance tomography at high altitude. J Appl Physiol 2003;94:2043–50.
16 Bärtsch P, Waber U, Haeberli A, Maggiorini M, Kriemler S, Oelz O, Straub WP. Enhanced fibrin formation in high-altitude pulmonary edema. J Appl Physiol 1987;63:752–7.
17 Vock P, Fretz C, Franciolli M, Bärtsch P. High-altitude pulmonary edema: Findings at high-altitude chest radiography and physical examination. Radiology 1989;170:661–6.
18 Vock P, Brutsche MH, Nanzer A, Bartsch P. Variable Radiomorphologic Data of High Altitude Pulmonary Edema – Features from 60 Patients. Chest 1991;100(5):1306–11.
19 Vock P, Fischer H, Bärtsch P. Radiomorphology of high altitude pulmonary edema: New views. In: Sutton JR, Houston CS, Coates G, ed. Hypoxia and molecular medicine. Burlington: Queen City Printers Inc; 1993. pp. 259–64.
20 Arias-Stella J, Kruger H. Pathology of high altitude pulmonary edema. Arch Pathol 1963;76:147–57.
21 Nayak NC, Roy S, Narayanan TK. Pathologic features of altitude sickness. Am J Pathol 1964;45:381–91.
22 Hultgren HN, Lopez CE, Lundberg E, Miller H. Physiologic studies of pulmonary edema at high altitude. Circulation 1964; 29:393–408.
23 Penaloza D, Sime F. Circulatory dynamics during high altitude pulmonary edema. Am J Cardiol 1969;23:369–78.
24 Antezana G, Leguia G, Morales Guzman A, et al. Hemodynamic study of high altitude pulmonary edema (12,200 ft)Brendel, W.; Zink, R. A., ed. High altitude physiology and medicine. New York: Springer; 1982. pp. 232–41.
25 Oelz O, Noti C, Ritter M, Jenni R, Bärtsch P. Nifedipine for high altitude pulmonary oedema. Lancet 1991;337:556.
26 Bärtsch P, Maggiorini M, Ritter M, Noti C, Vock P, Oelz O. Prevention of high-altitude pulmonary edema by nifedipine. N Engl J Med 1991;325:1284–9.
27 Scherrer U, Vollenweider L, Delabays A, Savcic M, Eichenberger U, Kleger G-R, et al. Inhaled nitric oxide for high-altitude pulmonary edema. N Engl J Med 1996;334:624–9.
28 Hackett PH, Roach RC, Hartig GS, Greene ER, Levine BD. The effect of vasodilatators on pulmonary hemodynamics in high altitude pulmonary edema: A comparison. Int J Sports Med 1992;13:S68–S71.
29 Oelz O, Ritter M, Jenni R, Maggiorini M, Waber U, Vock P, Bärtsch P. Nifedipine for High Altitude Pulmonary Oedema. Lancet 1989;2(8674):1241–4.
30 Kawashima A, Kubo K, Kobayashi T, Sekiguchi M. Hemodynamic responses to acute hypoxia, hypobaria, and exercise in subjects susceptible to high-altitude pulmonary edema. J Appl Physiol 1989;67(5):1982–9.
31 Eldridge MW, Podolsky A, Richardson RS, Johnson DH, Knight DR, Johnson EC, et al. Pulmonary hemodynamic response to exercise in subjects with prior high-altitude pumonary edema. J Appl Physiol 1996;81(2):911–21.
32 Grünig E, Mereles D, Hildebrandt W, Swenson ER, Kübler W, Kuecherer H, Bärtsch P. Stress doppler echocardiography for identification of susceptibility to high altitude pulmonary edema. J Am Coll Cardiol 2000;35:980–7.
33 Maggiorini M, Mélot C, Pierre S, Pfeiffer F, Greve I, Sartori C, et al. High-altitude pulmonary edema is initially caused by an increase in capillary pressure. Circulation 2001;103:2078–83.
34 Homik LA, Bshouty RB, Light RB, Younes M. Effect of alveolar hypoxia on pulmonary fluid filtration in in situ dog lungs. J Appl Physiol 1988;65:46–52.
35 Hackett PH, Roach RC, Schoene RB, Harrison GL, Mills WJ. Abnormal control of ventilation in high-altitude pulmonary edema. J Appl Physiol 1988;64:1268–72.
36 Matsuzawa Y, Fujimoto K, Kobayashi T, Namushi NR, Harada K, Kohno H, Fukushima M, Kusama S. Blunted hypoxic ventilatory drive in subjects susceptible to high-altitude pulmonary edema. J Appl Physiol 1989;66(3):1152–7.

37 Hohenhaus E, Paul A, McCullough RE, Kücherer H, Bärtsch P. Ventilatory and pulmonary vascular response to hypoxia and susceptibility to high altitude pulmonary oedema. Eur Respir J 1995;8:1825–33.
38 Selland MA, Stelzner TJ, Stevens T, Mazzeo RS, McCullough RE, Reeves JT. Pulmonary function and hypoxic ventilatory response in subjects susceptible to high-altitude pulmonary edema. Chest 1993;103:111–6.
39 Viswanathan R, Jain SK, Subramanian S, Subramanian TAV, Dua GL, Giri J. Pulmonary edema of high altitude II. Clinical, aerohemodynamic, and biochemical studies in a group with history of pulmonary edema of high altitude. Am Rev Respir Dis 1969;100:334–41.
40 Podolsky A, Eldridge MW, Richardson RS, Knight DR, Johnson EC, Hopkins SR, et al. Exercise-induced VA/Q inequality in subjects with prior high-altitude pulmonary edema. JAppl Physiol 1996;81(2):922–32.
41 Naito T, Miyahara Y, Ikeda S. Ventilatory and pulmonary vascular responses to acute hypoxia are nonuniform in healthy man. Respiration 1995;62:185–9.
42 Duplain H, Vollenweider L, Delabays A, Nicod P, Bärtsch P, Scherrer U. Augmented sympathetic activation during short-term hypoxia and high-altitude exposure in subjects susceptible to high-altitude pulmonary edema. Circulation 1999;99: 1713–8.
43 Bärtsch P, Shaw S, Franciolli M, Gnädinger MP, Weidmann P. Atrial natriuretic peptide in acute mountain sickness. J Appl Physiol 1988;65:1929–37.
44 Koyama S, Kobayashi T, Kubo K, Fukushima M, Yoshimura K, Shibamoto TKS. The increased sympathoadrenal activity in patients with high altitude pulmonary edema is centrally mediated. Jpn J Med 1988;27(1):10–6.
45 Lear GH. Neurogenic pulmonary oedema. Acta Paediatr Scand 1990;79:1131–3.
46 Sartori C, Vollenweider L, Löffler B-M, Delabays A, Nicod P, Bärtsch P, Scherrer U. Exaggerated endothelin release in high-altitude pulmonary edema. Circulation 1999;99:2665–8.
47 Droma Y, Hayano T, Takabayashi Y, Koizumi T, Kubo K, Kobayashi T, Sekiguchi M. Endothelin-1 and interleukin-8 in high altitude pulmonary oedema. Eur Respir J 1996;9:1947–9.
48 Busch T, Bärtsch P, Pappert D, Grünig E, Elser H, Falke KJ, Swenson ER. Hypoxia decreases exhaled nitric oxide in mountaineers susceptible to high altitude pulmonary edema. Am J Respir Crit Care Med 2001;163:368–73.
49 Duplain H, Sartori C, Lepori M, Egli M, Allemann Y, Nicod P, Scherrer U. Exhaled nitric oxide in high-altitude pulmonary edema: role in the regulation of pulmonary vascular tone and evidence for a role against inflammation. Am J Resp Crit Care Med 2000;162:221–4.
50 Swenson ER, Maggiorini M, Mongovin S, Gibbs JSR, Greve I, Mairbäurl H, Bärtsch P. Pathogenesis of high-altitude pulmonary edema: Inflammation is not an etiologic factor. JAMA 2002;287:2228–35.
51 Droma Y, Hanaoka M, Ota M, Katsuyama Y, Koizumi T, Fujimoto K, Kobayashi T, Kubo K. Positive association of the endothelial nitric oxide synthase gene polymorphisms with high-altitude pulmonary edema. Circulation 2002;106:826–30.
52 Weiss J, Haefeli WE, Gasse C, Hoffmann MM, Weymann J, Gibbs S, Mansmann U, Bärtsch P. Lack of evidence for association of high altitude pulmonary edema and polymorphisms of the NO pathway. High Alt Med Biol 2003;in press.
53 Bärtsch P, Swenson ER, Maggiorini M. Update: High altitude pulmonary edema. In: Roach RC et al., eds. Hypoxia: From Genes to the Bedside. New York: Kluwer Academic/Plenum Publishers; 2001. pp. 89–106.
54 Hultgren HN. High altitude pulmonary edema. In: Staub N, ed. Lung Water and Solute Exchange, 7, Lenfant Series. New York: Marcel Dekker Inc.; 1978:237–69.
55 Hackett PH, Creagh CE, Grover RF, Honigman B, Houston CS, Reeves JT, Sophocles AM, van Hardenbroek M. High altitude pulmonary edema in persons without the right pulmonary artery. N Engl J Med 1980;302:1070–3.
56 Berg JT, Breen EC, Fu Z, Mathieu-Costello O, West JB. Alveolar hypoxia increases gene expression of extracellular matrix proteins and platelet-derived growth factor-B in lung parenchyma. Am J Resp Crit Care Med 1998;158:1920–8.
57 Hakim TS, Kelly S. Occlusion pressures vs. micropipette pressures in the pulmonary circulation. J Appl Physiol 1989;67: 1277–85.
58 Rock P, Patterson GA, Permutt S, Sylvester JT. Nature and distribution of vascular resistance in hypoxic pig lungs. J Appl Physiol 1985;59:1891–901.
59 Whayne Jr. TF, Severinghaus JW. Experimental hypoxic pulmonary edema in the rat. J Appl Physiol 1968;25:729–32.
60 Raj JU, Chen P. Micropuncture measurement of microvascular pressures in isolated lamb lungs during hypoxia. Circ Res 1986;59:398–404.
61 Zhao Y, Packer CS, Rhoades RA. Pulmonary vein contracts in response to hypoxia. Am J Physiol 1993;265:L87–L92.
62 Younes M, Bshouty Z, Ali J. Longitudinal distribution of pulmonary vascular resistance with very high pulmonary flow. J Appl Physiol 1987;62:344–58.
63 Schoene RB, Swenson ER, Pizzo CJ, Hackett PH, Roach RC, Mills WJ, Henderson WR, Martin TR. The lung at high altitude: bronchoalveolar lavage in acute mountain sickness and pulmonary edema. J Appl Physiol 1988;64:2605–13.
64 Kubo K, Hanaoka M, Yamaguchi S, Hayano T, Hayasaka M, Koizumi T, et al. Cytokines in bronchoalveolar lavage fluid in patients with high altitude pulmonary oedema at moderate altitude in Japan. Thorax 1996;51:739–42.
65 Kaminsky DA, Jones K, Schoene RB, Voelkel NF. Urinary leuktriene E (4) levels in high-altitude pulmonary edema: A possible role for inflammation. Chest 1996;110(4):939–45.
66 Bärtsch P, Haeberli A, Franciolli M, Kruithof EKO, Straub PW. Coagulation and fibrinolysis in acute mountain sickness and beginning pulmonary edema. J Appl Physiol 1989;66:2136–44.
67 West JB, Mathieu-Costello O, Jones JH, Birks EK, Logemann RB, Pascoe JR, Tyler WS. Stress failure of pulmonary capillaries in racehorses with exercise-induced pulmonary hemorrhage. J Appl Physiol 1993;75:1097–109.
68 Carpenter TD, Reeves JT, Durmowicz AG. Viral respiratory infection increases susceptibility of young rats to hypoxia-induced pulmonary edema. J Appl Physiol 1998;84:1048–54.
69 Durmowicz AG, Nooordeweir E, Nicholas R, Reeves JT. Inflammatory processes may predispose children to develop high altitude pulmonary edema. J Pediatr 1997;130:838–40.
70 Ferrari E, Chevallier T, Chapelier A, Baudouy M. Travel as a risk factor for venous thromboembolic disease: a case-control study. Chest 1999;115:440–4.
71 Wodopia R, Ko HS, Billian J, Wiesner R, Bärtsch P, Mairbäurl H. Hypoxia decreases proteins involved in epthelial electrolyte transport in A549 cells and rat lung. Am J Physiol Lung Cell Mol Physiol 2000;279:L1110–L1119.
72 Vivona ML, Matthay MA, Chabaud MB, Friedlander G, Clerici C. Hypoxia reduces alveolar epithelial sodium and fluid transport in rats: reversal by beta-adrenergic agonist treatment. Amer J Respir Cell Molec Biol 2001;25:554–61.
73 Egli M, Cook S, Hugli O, Hummler E, Nicod P, Scherrer U. Delayed resolution of pulmonary edema in mice with defective sodium transport-dependent alveolar fluid clearance (Abstract). FASEB J 2001;15:860.
74 Sartori C, Allemann Y, Duplain H, Lepori M, Egli M, Lipp E, et al. Salmeterol for the prevention of high-altitude pulmonary edema. N Engl J Med 2002;346:1631–6.
75 Bärtsch P, Mairbäurl H. Salmeterol for the prevention of high-altitude pulmonary edema. N Engl J Med 2002;347:1283.
76 Sartori C, Lipp E, Duplain H, Egli M, Hutter D, Allemann Y, Nicod P, Scherrer U. Prevention of high altitude pulmonary edema by beta-adrenergic stimulation of the alveolar transepithelial sodium transport (Abstract). Am J Respir Crit Care Med 2000;161:A415.
77 Mairbäurl H, Weymann J, Möhrlein A, Swenson ER, Maggiorini M, Gibbs JS, et al. Nasal potential difference at high altitude (4559 m): evidence for secretion. Am J Respir Crit Care Med 2003; 167:862–7.
78 Swenson ER. Carbonic anhydrase inhibitors and ventilation: a complex interplay of stimulation and suppression. Eur Resp J 1998;12:1242–7.
79 Bärtsch P. High altitude pulmonary edema. Med Sci Sports Exerc 1999;31(1):S23–S27.
80 Hohenhaus E, Niroomand F, Goerre S, Vock P, Oelz O, Bärtsch P. Nifedipine does not prevent acute mountain sickness. Am J Respir Crit Care Med 1994;150:857–60.
81 Deem S, Hedges R, Ker M, Swenson ER. Acetazolamide reduces the rate and magnitude of hypoxic pulmonary vasoconstriction in isolated perfused rabbit lung. Respir Physiol 2000; 123:109–19.
82 Taber RL. Protocols for the use of portable hyperbaric chamber for the treatment of high altitude disorders. J Wildern Med 1990;1:181–92.
83 Zhao L, Mason NA, Morrell NW, Kojonazarov B, Sadykov A, Maripov A, et al. Sildenafil inhibits hypoxia-induced pulmonary hypertension. Circulation 2001;104:424–8.

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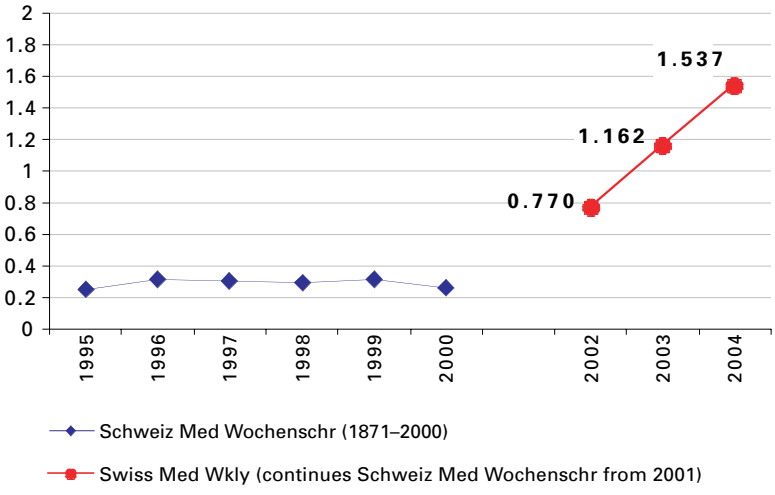

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