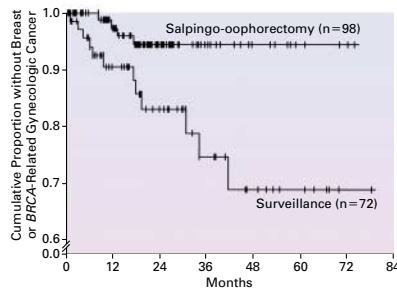




This Week in the Journal

May 23, 2002



Risk-Reducing Salpingo-oophorectomy in Women with *BRCA* Mutations

In this study of 170 women with a *BRCA1* or *BRCA2* mutation that greatly increases the risk of ovarian and breast cancer, 98 elected to undergo salpingo-oophorectomy and 72 chose to undergo surveillance. During a follow-up of about two years, the risks of both breast and ovarian cancer were considerably lower among the women who underwent the surgical procedure than among those who chose surveillance.

*The findings of this prospective study complement those of a retrospective study in risk-reducing oophorectomy in women with a pathogenic mutation in the *BRCA1* or *BRCA2* gene (see page 1616). Physicians now have persuasive support for a recommendation to remove the target tissue from women who carry such mutations.*

see page 1609 (editorial, page 1660)

“Bilateral prophylactic oophorectomy reduced the risk of BRCA-related gynecologic cancer by 96 percent.”

Prophylactic Oophorectomy in Women with *BRCA* Mutations

Among 551 women with a disease-associated mutation in the *BRCA1* or *BRCA2* gene who were followed for at least eight years, the at least incidence of ovarian cancer was significantly lower in the group that underwent prophylactic bilateral oophorectomy than in the comparison group of women who did not undergo the surgery. In a subgroup of these women, prophylactic oophorectomy also reduced the risk of breast cancer.

*This retrospective analysis of a large group of women at high risk for ovarian cancer provides persuasive evidence in favor of prophylactic oophorectomy for women with a disease-associated mutation in the *BRCA1* or *BRCA2* gene. For the individual woman with such a mutation, counseling about the risks and benefits of the procedure and about the maintenance of fertility is imperative. This study complements the prospective analysis by Kauff et al. (see page 1609).*

see page 1616 (editorial, page 1660)

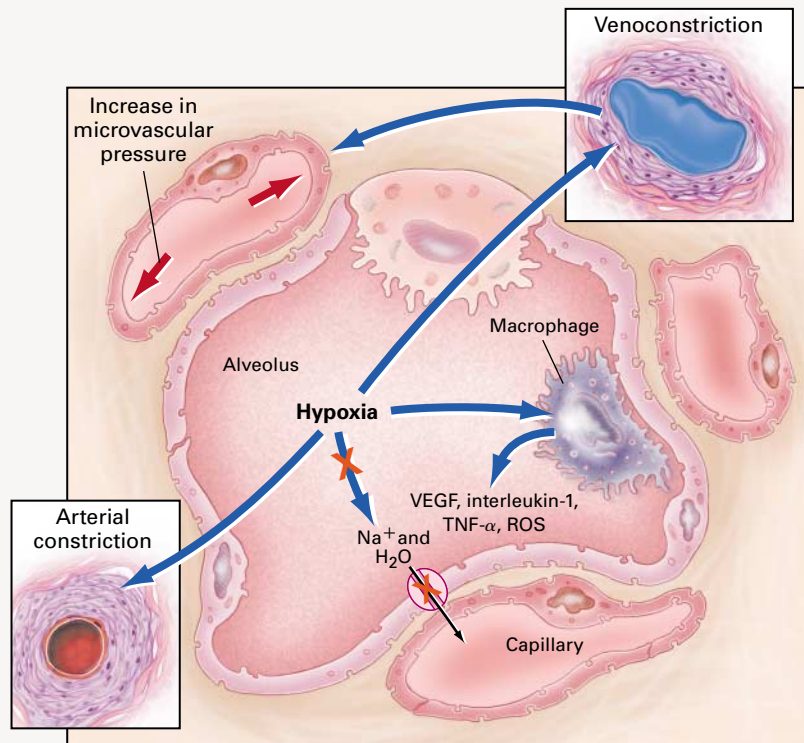
PERSPECTIVE

High-Altitude Pulmonary Edema

The spectrum of acute mountain sickness ranges from mild, nonspecific symptoms to high-altitude pulmonary edema and high-altitude cerebral edema. Most deaths from high-altitude illness occur with high-altitude pulmonary edema, the risk of which is related to the rate of ascent, individual susceptibility, and the level of exertion. Cold ambient temperature constitutes an additional risk factor. High-altitude pulmonary edema occurs worldwide, with the incidence peaking in the winter months because of ski tourism. Mountain climbers and skiers who have had an episode of high-altitude pulmonary edema are susceptible to unpredictable recurrence when they are again exposed to high altitudes.

The condition is treated with supplementary oxygen and descent to a lower altitude as soon as feasible or, when descent is not possible, simulated descent with the use of a portable hyperbaric chamber. When neither descent nor simulated descent is possible, administration of the calcium-entry blocker nifedipine may help. The administration of the carbonic anhydrase inhibitor acetazolamide may be useful, since this compound causes bicarbonate diuresis and respiratory stimulation. Neither furosemide nor dexamethasone, which are used for high-altitude cerebral edema, has been shown to be effective against high-altitude pulmonary edema.

Short of remaining “flatlanders,” those who are prone to high-altitude pulmonary edema should ascend to high altitudes slowly, avoid overexertion, and consider taking extended-release nifedipine every 12 hours. Particularly if they are



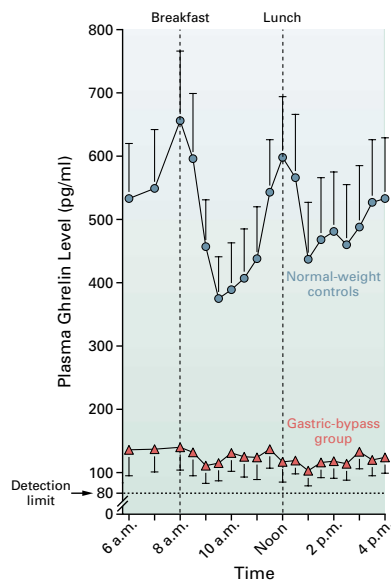
High-altitude pulmonary edema has a complex pathobiology, in which venoconstriction causes an increase in both alveolar-capillary pressure and vascular-fluid shear stress. Uneven regional blood flow may cause flooding of some capillaries. Capillary permeability may increase, as reactive oxygen species (ROS), chemical mediators of inflammation, and such growth factors as vascular endothelial growth factor (VEGF), interleukin-1, and tumor necrosis factor α (TNF- α) are released from pulmonary structural cells and alveolar macrophages, as well as from neutrophils and platelets that become trapped in the pulmonary microvasculature. Ion channels, such as the epithelial sodium channel, and the Na⁺/K⁺-ATPase, which act as “defenders” of dry alveolar space, are challenged by hypoxia (as indicated by the red X).

also prone to high-altitude cerebral edema, such persons might consider taking acetazolamide starting two days before a planned ascent.

It is known that young persons who are prone to high-altitude pulmonary edema may have an exaggerated pulmonary hypertensive response to hypoxia and may exhale less nitric oxide than those without such susceptibility. However, whether these responses are causally related to high-altitude pulmonary edema is unknown. The con-

dition is characterized by clinical signs and symptoms that can range from cough and dyspnea to rapidly progressive pulmonary edema and even death. High-altitude pulmonary edema is generally readily reversible when the patient returns to a lower altitude, which is the main feature that distinguishes it from the acute respiratory distress syndrome.

There are two principal theories about the pathogenesis of high-altitude pulmonary edema — in broad strokes, a mechanical theory



Ghrelin Levels after Diet-Induced Weight Loss or Gastric Bypass

Patients who undergo gastric bypass surgery have dramatic and sustained weight loss. They feel less hungry after eating, although they still perceive foods with high caloric value as enjoyable. Ghrelin is an orexigenic hormone whose levels in normal subjects increase before meals and decrease after meals. In this study of patients who achieved stable weight after gastric bypass surgery, circulating ghrelin levels were low and did not show meal-related periodicity.

Ghrelin may affect both the desire to eat and satiety. If the investigators' hypothesis is proved correct, inhibition of the synthesis or action of ghrelin could serve to inhibit appetite and aid in weight loss.

see page 1623 (editorial, page 1662)

and a theory of inflammation. It has been known for quite a long time that patients with the condition have high pulmonary-artery pressure, and the analysis of bronchoalveolar-lavage fluid from such patients has shown high protein levels and high levels of inflammatory mediators.

An exciting new theory is reported in this issue of the *Journal* (see pages 1631–1636). Sartori et al. measured, at low altitude, the nasal transepithelial potential difference in persons who were susceptible to high-altitude pulmonary edema and found it to be, on average, one third lower than that in persons who were not susceptible to the condition. The implication is that persons who are susceptible to high-altitude pulmonary edema may have an impairment of transepithelial sodium and water clearance in the lungs, which might be genetically determined. Hypoxia may cause further impairment of sodium transport, in part because it leads to a decrease in the expression of genes that encode

subunits of the sodium channel and $\text{Na}^+/\text{K}^+-\text{ATPase}$. What we do not know is whether impaired removal of water and sodium from the alveolar spaces is sufficient to explain the development of high-altitude pulmonary edema in those who are prone to it or whether hypoxia combined with exercise renders the alveolar-capillary boundary leaky.

Animal models of lung injury indicate that the endogenous release of catecholamines up-regulates sodium and fluid transport (clearance), as beta-adrenergic agonists do by way of cyclic AMP. Postulating that inhalation of the β_2 -adrenergic agonist salmeterol would perhaps “repair” the defective alveolar water and sodium clearance, Sartori et al. had some mountaineers who were susceptible to high-altitude pulmonary edema inhale the drug before ascending to high altitude, and this prophylactic treatment decreased the incidence of the condition by about 50 percent in susceptible subjects, as compared with those in a placebo group.

The two groups had a similar degree of pulmonary hypertension (as estimated by Doppler echocardiography). Whether salmeterol pretreatment affected the pulmonary microvascular pressure is unknown. β -Adrenergic-receptor agonists can have antiinflammatory effects, but whether pretreatment with salmeterol decreased chemotaxis of inflammatory cells into the alveolar spaces or “discouraged” interactions among inflammatory cells is also unclear. In addition, it remains to be determined whether salmeterol normalizes the nasal transepithelial potential difference. Whether inhaled salmeterol will work in the prevention or treatment of high-altitude pulmonary edema is still unknown. Answers to these questions will be important in understanding and treating this condition.

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Photograph by Daniel Sigg, M.D.

Salmeterol for the Prevention of High-Altitude Pulmonary Edema

High-altitude pulmonary edema occurs in otherwise healthy persons when they are at high elevations. Since β -adrenergic agonists increase clearance of alveolar fluid and attenuate pulmonary edema in animal models, these investigators studied the effect of inhaled salmeterol (a β -adrenergic agonist) or placebo in 37 subjects who were prone to high-altitude pulmonary edema. In addition, nasal transepithelial potential difference, a marker of fluid clearance in distal airways, was studied in 33 mountaineers who were susceptible to this condition and 33 who were resistant to the condition. Prophylactic inhalation of salmeterol halved the incidence of high-altitude edema in susceptible subjects. Nasal transepithelial potential difference was significantly lower in susceptible subjects.

Defective sodium-driven clearance of alveolar fluid may be important in the genesis of high-altitude pulmonary edema in humans and may provide a target for therapy.

see page 1631 (Perspective, page 1606)

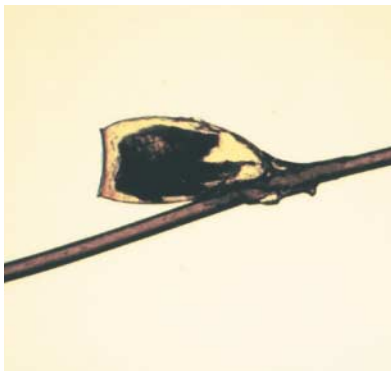
“Thirty-six percent of patients had given an advance directive indicating a desire for physician-assisted death.”

End-of-Life Decisions by Patients with Amyotrophic Lateral Sclerosis

Physicians in the Netherlands described on a questionnaire the deaths of their patients with amyotrophic lateral sclerosis. Of the 203 patients, 35 (17 percent) had chosen euthanasia and died that way. An additional six patients died as a result of suicides that involved assistance from a physician. The choice of euthanasia or physician-assisted suicide was not associated with the patient's income or educational level.

In the Netherlands, physician-assisted death is allowed if strict guidelines are followed. This study documents the fact that one in five patients with this progressive neurologic disease chose death either by euthanasia or by physician-assisted suicide.

see page 1638 (editorial, page 1663)



Nit ($\times 100$).

Clinical Practice: Head Lice

An eight-year-old girl is sent home after the school nurse detects head lice. She will not be permitted to return to school until the absence of infestation is documented. What treatment strategy is most likely to allow her to return to school with a minimal risk of infecting her classmates?

see page 1645