Acute Pulmonary Edema in Healthy Subjects

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INTRODUCTION: Healthy individuals may present with acute pulmonary edema when exposed to extreme environments (high-altitude or deep diving) or while performing strenuous exercises. Recent data support the hypothesis that these forms of acute pulmonary edema might be due to a limited number of stimuli, often overlapping each other, inducing pulmonary capillary stress failure.

DISCUSSION: Pathophysiology of nontoxic pulmonary edema occurring in healthy people is still incompletely understood, but recent data suggest a role of three factors (hypoxia, increase in ambient pressure, and physical exercise) that, alone or in combination, may increase pulmonary capillary pressure up to a level overcoming the mechanical resistance of the blood-gas barrier. Evidence has been recently provided to support the existence of a genetic pattern predisposing healthy subjects to pulmonary edema. This paper reviews the evidence supporting a common background for pulmonary edema triggered by extreme environments or heavy effort; a preventive and therapeutic strategy will also be proposed. From these data, hypotheses on the pathophysiology of other forms of noncardiac related pulmonary edema, as those associated with obstructive sleep-apnea syndrome or during post-surgery intensive care, will be proposed.

KEYWORDS: hypoxia, physical exercise, immersion, high altitude.

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Acute pulmonary edema may be due to an increase of transcapillary hydrostatic pressure, exceeding plasma oncotic pressure (cardiogenic edema), or to an increased permeability of the alveolar-capillary membrane, mostly due to toxic agents (noncardiogenic edema). Occasionally, healthy individuals may present with acute pulmonary edema when exposed to high altitudes (high-altitude pulmonary edema; HAPE), while diving or swimming (swimming-induced pulmonary edema; SIPE) or during intense physical effort (exercise-associated pulmonary edema). The consequences of this unexpected syndrome may sometimes be dramatic; in 2013 a top-level diver died surfacing from a 72-m breath-hold dive after experiencing intense dyspnea; autopsy revealed massive alveolar hemorrhagic edema to be the cause of death.[1] Beyond the risk of a severe acute illness, the study of this syndrome is also relevant from a pathophysiological point of view, since it allows us to explore the exhaustion of adaptation mechanisms to extreme stimuli in healthy (or even in "super-healthy") subjects.

Recent observations suggest that the various forms of pulmonary edema arising in healthy subjects (PEHS) may share some important clinical features (i.e., genetic predisposition and presence of an alveolar fluid rich in high-molecular-weight proteins).[2,10] On these bases, recent papers hypothesized that PEHS may be a syndrome triggered by a limited number of factors, increasing blood pressure in pulmonary circulation up to the level of capillary stress failure.[21,34] This paper will discuss the evidences supporting a fundamental model in which the interplay of only three elements (hypoxia, increased ambient pressure by body immersion, and increased cardiac output induced by physical exercise), acting in genetically predisposed individuals, may be at the basis of all the forms of PEHS.

EPIDEMIOLOGY

Incidence of PEHS is low in the general population, but may be higher in particular subgroups, such as top-level endurance

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athletes, divers, and high-altitude climbers. In these categories, subclinical signs of interstitial pulmonary edema have been frequently reported by different diagnostic techniques. Approximately 50% of well-trained endurance athletes have effort-induced hypoxemia;[44] a diffusion impairment due to interstitial pulmonary edema has been considered one of the potential causes of this phenomenon.[13,36] Ultrasound signs of increased lung extravascular water content have been reported in 74% of athletes at the end of an ultra-triathlon race,[43] in the vast majority of climbers at altitude higher than 3000 m,[45] and in 45% of breath-hold divers at the end of a day of intense diving training.[19]

Overt pulmonary edema has far lower incidence; it has been reported occasionally in long distance runners at sea level, but its incidence increases in aquatic sports, rising to 1.4% in swimming triathletes, and even to 25% in combat troops during a long-distance heavy swimming test (where heavy prerace overhydration may have contributed to the particularly high incidence of this series).[56] Using an anamnestic questionnaire, high-level breath-hold divers reported a 25% incidence of previous episodes of immersion-related pulmonary edema.[9] Finally, high-altitude pulmonary edema has been reported in 0.5–7% of healthy lowlanders climbing to altitudes higher than 4000 m (according to ascent speed).[54]

PATHOPHYSIOLOGY

A limited number of factors (namely hypoxia, body immersion and physical exercise) may prime PEHS by increasing pulmonary blood pressure and/or blood volume in the capillary network and inducing capillary stress failure. Preliminary evidences of genetic predisposition to PEHS have recently been reported.

Hypoxia

During high-altitude climbing, oxygen partial pressure decreases, according to Dalton's law, in parallel to environmental pressure; the resulting reduction of alveolar Po_2 is a powerful stimulus to pulmonary arteriolar constriction[54] whose cellular mechanisms have been recently extensively reviewed.[15] HAPE-prone subjects have been reported to have an excessive pulmonary vascular reactivity to hypoxia,[20] leading to an exaggerated rise in pulmonary arterial pressure that may lead to pulmonary capillary stress failure and pulmonary edema, particularly when associated with an increased cardiac output due to physical effort.[57] Several mechanisms may explain why an exacerbated hypoxic arteriolar contraction could lead to an increased pressure in downstream capillaries and induce interstitial and alveolar edema. On one hand, pulmonary arterial blood pressure rise may be so marked that fluid leakage may also occur at precapillary level.[60] Moreover, an uneven hypoxic pulmonary vasoconstriction, described in HAPE-prone humans,[12] could make some areas of pulmonary capillary bed unprotected toward hypoxia-induced pulmonary arterial hypertension. Remarkably, HAPE susceptibility has been recently reported to be associated to a more uniform distribution of regional ventilation, supporting a vascular, rather than ventilatory, basis for uneven pulmonary vasoconstriction.[40] Finally, a concomitant hypoxia-induced venoconstriction could increase pulmonary capillary pressure.[22] Further nonhemodynamic factors, namely the production of a noninflammatory protein-rich exudate,[54] reducing the oncotic pressure gradient across the capillary wall, may contribute to capillary fluid leakage. An increased capillary permeability, mediated by the effects of hypoxia-induced oxidative stress[4] and by the activation of specific stretching receptors situated in the blood-gas barrier (transient receptor potential vanilloid 4; TRPV4),[21,61] may facilitate protein spill from capillary blood to the interstitium.

In addition to high-altitude hypobaria, hypoxia may also be induced by long lasting apnea. During breath-hold dive at depth, the absolute value of alveolar Po_2 remains high, in spite of metabolic consumption, in parallel to the high environmental pressure. In the last part of the dive, when environmental pressure is rapidly decreasing during ascent, severe hypoxia may develop. A study on maximal voluntary breath-holding in three top-level divers showed a huge decline in alveolar Po_2 (from 140 to 31 mmHg) associated with an impressive reduction of O_2 saturation (in one case decreasing to 38%).[17] Alveolar hypoxia obtained with prolonged apnea can therefore trigger hypoxic pulmonary vasoconstriction and hypertension.

Isolated myocardial fibers exposed to hypoxia showed a depression of both contractility and relaxation indices,[50] but the negative effects of hypoxia on systolic and diastolic function may be compensated, in whole organisms, by both reflex-induced enhancement of sympathetic activity[52,53] and activation of the Frank-Starling mechanism.[42] Therefore, while hypoxia-mediated myocardial dysfunction may contribute to pulmonary edema in subjects with reduced left ventricular functional reserve due to subclinical cardiac disease, its role in pathophysiology of pulmonary edema in healthy subjects appears unlikely.

Finally, the above-mentioned increase in capillary permeability induced by the oxidative stress brought on by the repeated hypoxia-reoxygenation cycles typical of breath-hold diving[4] may promote the interstitial and alveolar leakage of high molecular weight proteins.

Increased Environmental Pressure (Body Immersion)

Exposure to a markedly elevated ambient pressure is rarely achievable in nature, except during immersion and diving. The hydrostatic pressure exerted by water during a simple head-out surface immersion is able to induce a blood shift from the peripheral to intrathoracic venous and capillary bed estimated in around 700 ml.[5] The increase in central blood volume is due to several mechanisms. On one hand, the increased hydrostatic pressure induces an increase in plasma volume (due to a shift of interstitial fluid through the capillary wall)[23] and counterbalances the effects of gravity on blood distribution.[55] Moreover, cold-related constriction of peripheral veins reduces venous capacitance volume.[11] Finally, an increase in the

transdiaphragmatic pressure gradient, due to the higher compressibility of the abdomen compared to the chest, and to the reduction of pulmonary gas volume, increases the driving force favoring central venous return.[47] The resulting blood shift toward pulmonary circulation may congest the capillary bed and predispose to pulmonary capillary stress failure.[57] Besides the strictly mechanical effect, stretching of pulmonary capillaries may activate endothelial TRPV4, increasing capillary permeability to proteins and fostering interstitial edema.[61] Comparison of the effects of immersion on pulmonary circulation with findings observed in subjects exposed to microgravity may offer interesting food for thought. Data obtained during the Space Shuttle program showed that microgravity induced a remarkable cephalic relocation of blood from the lower body to chest and head (estimated in 1–2l)[25] with no evidence of increased extravascular lung water in spite of a relevant increase of blood settled in the pulmonary capillary bed (+28%).[46] These data suggest that the simple increase of intrathoracic blood content is not sufficient to induce pulmonary edema and that the increase of environmental pressure during immersion and diving is also needed.

Actually, a diver descending to depth must cope with huge changes in environmental pressure, linearly increasing at a rate of 1 Atmospheres Absolutes (ATA) every 10 m of depth. As a matter of example, during his "no limits" breath-hold dive at 253 m depth, the pressure on the body of the Austrian freediver Herbert Nitsch rose from 1 ATA to more than 26 ATA and decreased back to 1 ATA in a few minutes. During such rapid depth changes (both descent and ascent), air filled cavities should equalize their pressure with the environment. If equalization fails, an imbalance with ambient pressure may generate in some incompressible region of the respiratory system. During descent, pressure in the airways may become lower than the environmental one, thus inducing mucosal hyperemia, edema and even bleeding (the so called "descent barotrauma"). Several reports describe descent barotrauma involving middle ear, larynx and paranasal sinuses[28] but, in the case of thick inflammatory exudates occluding bronchioles, the same mechanisms could also act more peripherally, provoking hyperemia and edema in lower airways too. Moreover, in the case of deep breath-hold diving, environmental pressure can compress the chest to the residual volume of the lungs; a further increase in depth (i.e., in ambient pressure) could not be equalized by a further reduction in alveolar air volume and could induce a capillary-alveolar pressure gradient able to provoke edema (lung barotrauma of descent or lung-squeeze).[28] Even if incidence of SIPE is higher in divers reaching higher depths, this mechanism seems inadequate to explain the well-documented episodes of acute pulmonary edema reported after repeated breath-hold dives at relatively shallow depths,[9] suggesting the existence of other immersion-related mechanisms and/or the concurrence of multiple stressors.

Recent studies using a submersible echocardiograph[31] suggested that chest compression exerted by environmental pressure increase might affect heart function and contribute to explaining breath-hold diving related pulmonary edema. Divers studied during a 10-m breath-hold dive showed Doppler-echocardiographic signs of impaired diastolic left ventricular filling, mimicking the hemodynamic pattern observed in constrictive/restrictive heart diseases (i.e., a peaking of early diastolic filling flow, with an increase in its velocity and a reduction of its duration).[31,32] The combined effect of chest volume reduction and intrathoracic blood volume displacement induced by immersion at depth could actually exert a restriction to left ventricular diastolic filling[31,32]; the dependence of this restrictive pattern on chest compression is confirmed by its disappearance with chest re-expansion during diving.[33] Left ventricular filling impairment could increase left atrial pressure (LAP) and pulmonary arterial wedge pressure and contribute to pulmonary capillary stress failure.

The depths being equal, scuba and breath-hold divers are exposed to the same pressures, but the reported rates of SIPE are largely different (sporadic cases in scuba vs. a prevalence of 25% in high-level and trained breath-hold divers).[9] The higher incidence of SIPE in breath-hold divers may be due to a combination of hypoxia and left ventricular diastolic impairment resulting from the compression of alveolar spaces by the elevated ambient pressure (that in scuba diving is compensated by compressed-air breathing).

Physical Exercise

High intensity physical exercise may induce a four- to fivefold increase in cardiac output. In spite of pulmonary vascular resistances reduction, due to both arteriolar vasodilation and recruitment of underperfused vessels,[27] such a huge increase in cardiac output entails an increase in mean pulmonary arterial pressure and LAP and, hence, in capillary blood pressure that may overcome the mechanical resistance limits of the blood-gas barrier. West[59] estimated that, during high-intensity exercise, pulmonary capillary blood pressure in humans may rise to 40 mmHg. This value, in animal models, was associated with structural damage of the endothelial or epithelial layer of the blood-gas barrier.[59]

Running thoroughbred horses represents the paradigmatic example of exercise-induced pulmonary edema.[58] After a race, they often have bloody foam at the nostrils, while bronchoscopic evaluation shows a high prevalence of blood in their airways; the remarkable pulmonary capillary blood pressure value of 100 mmHg has been reported in thoroughbred horses galloping on a treadmill.[16]

The phenomenon of ventricular interdependence may contribute to left atrial pressure increase during strenuous effort and, hence, to pulmonary capillary stress failure. The prolonged and huge increase in cardiac output during long-distance running induces an acute right ventricular dilation, hampering interventricular septal motion and left ventricular systolic function.[29] Moreover, endurance training has been reported to have long lasting depressive effects on septal systolic function, due to right ventricular volume overload, as evaluated by analysis of circumferential strain.[6]

Considerable debate still exists about the possible induction of acute pulmonary edema in exercising humans at sea level.

Actually, only anecdotal cases have been reported in top-level athletes at the end of ultralong-distance races, while the concurrence of immersion or moderate altitude seem to be essential to facilitate the onset of hemoptysis and pulmonary edema in exercising humans.[59]

Genetic Predisposition

Some evidence supports the existence of a genetic predisposition to HAPE. The influence of genetic makeup on susceptibility to HAPE has been initially speculated on the basis of epidemiological observations on different populations of highlanders. The surprisingly normal pulmonary arterial pressure in Tibetan natives, the population with the oldest high-altitude ancestry in the world, may reveal the effects of evolutionary pressure, slowly selecting favorable genotypes to cope with chronic hypoxia.[41] Several studies extensively investigated the mechanisms at the basis of predisposition to HAPE. Pulmonary arteriolar hyperreactivity to hypoxia, considered an essential intermediate step to capillary hypertension and stress failure, has been ascribed to a reduced chemoreceptor sensitivity, leading to a lower ventilatory response, a lower alveolar Po_2 and, in turn, a higher pulmonary vasoconstrictive stimulus.[54] Moreover, a genetic-based imbalance between endothelial vasoactive mediators has been reported in patients with previous HAPE episodes. Specifically, HAPE-prone subjects have an overrepresentation of genotypes associated to a reduced NO-mediated pulmonary vasodilation, either directly due to a reduced activity of endothelial NO-synthase, or to a reduced production of apelin, a powerful activator of NO-synthase regulated by Hypoxia Inducible Factor.[2,3,37] An additional contributor to HAPE predisposition may originate from a reduced alveolar fluid clearance capability, hypothesized in studies reporting a reduced Na reabsorption in nasal epithelial cells of HAPE-susceptible subjects.[49] In this context, it may be worth noting that NO has a stimulating effect on alveolar Na reabsorption[39] and that, therefore, a deficit in NO production could have a dual role in HAPE pathogenesis.

A different genetic predisposing pathway has been recently hypothesized in studies comparing HAPE-prone and HAPE-resistant Han Chinese subjects, showing significant differences in genotypic distributions of human glucocorticoid receptor (NR3C1).[14] Receptor isoforms leading to impaired response to glucocorticoid hormones may induce a higher pulmonary capillary permeability, fostering interstitial edema.

Conflicting data exist on a possible common genetic background predisposing to both SIPE and HAPE. As a matter of

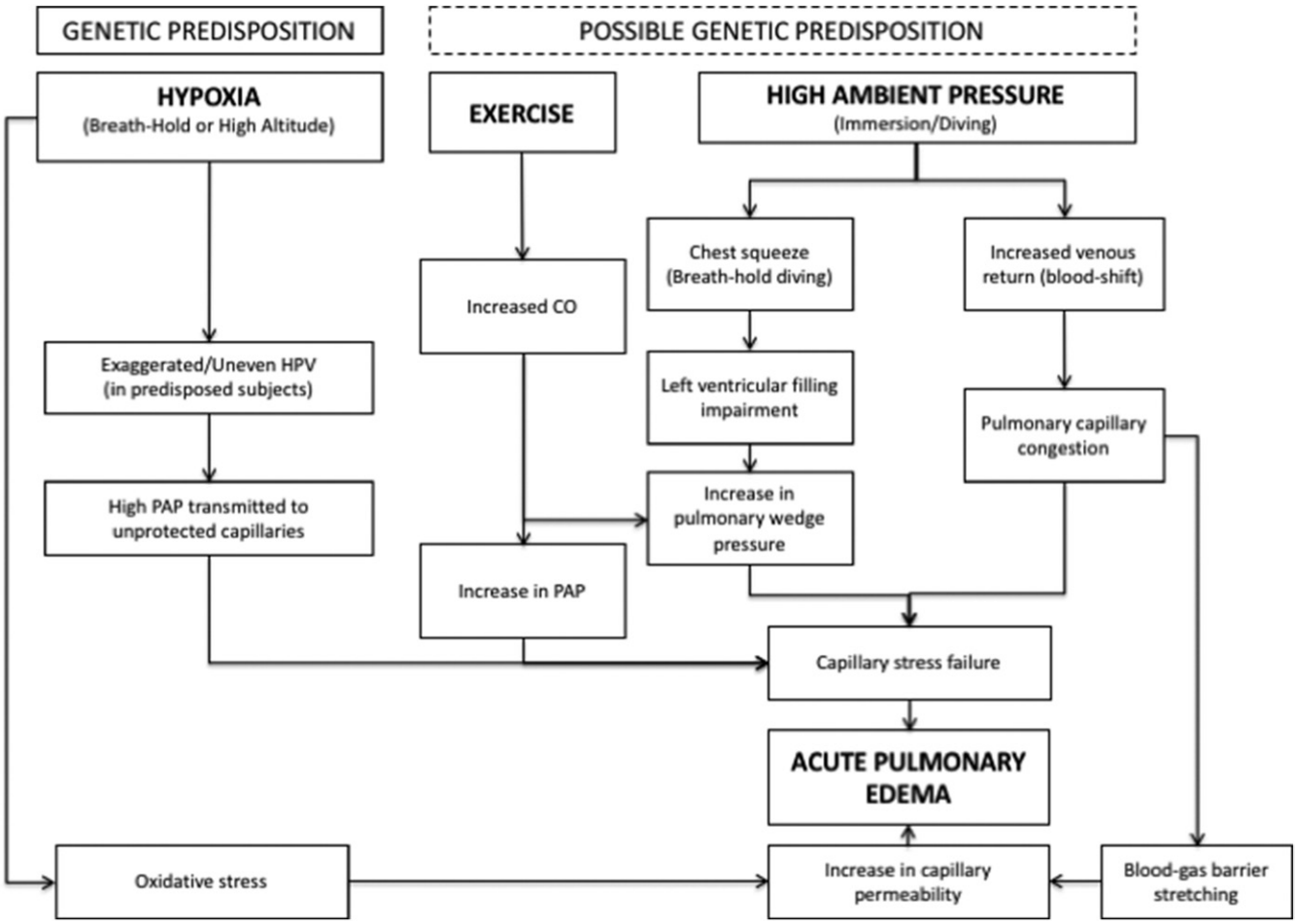

Fig. 1. Schematic representation of factors leading to PEHS. CO = cardiac output; HPV = hypoxic pulmonary vasoconstriction; LV = left ventricle; PAP = pulmonary arterial pressure; PEHS = pulmonary edema of healthy subjects.

fact, a recent study showed that SIPE-prone subjects have a high prevalence of the same genotypes, associated to a reduced activity of endothelial NO-synthase, predisposing to HAPE.[10] On the other hand, subjects with previous episodes of SIPE did not show an abnormal pulmonary arterial reactivity to hypoxia.[30]

Other intriguing results seem to envisage a common background, based on pulmonary arterial hyperreactivity, in subjects prone to PEHS. Grunig et al.[24] showed, in subjects with previous episodes of HAPE, an abnormal pulmonary vascular reactivity to supine bycicle exercise under normoxic conditions. Moreover, a recent study reported a significantly higher pulmonary pressure increase during submerged exercise in SIPE-prone divers; a NO-mediated mechanism of pulmonary arterial hyperreactivity to exercise is suggested by the observation that premedication with sildenafil blunted pulmonary blood pressure rise.[38]

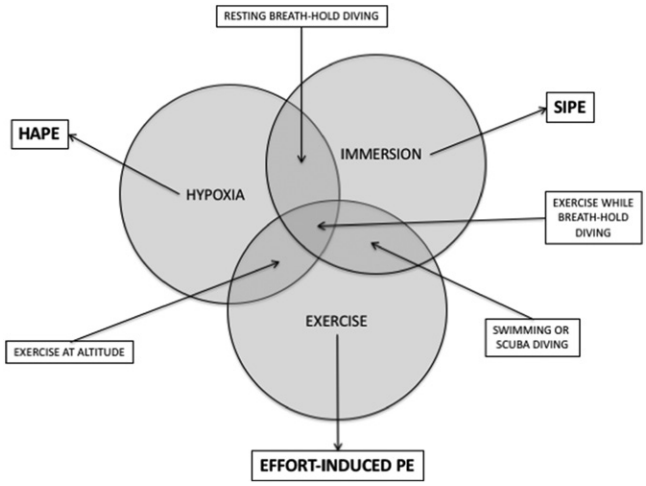

Fig. 2. Schematic representation of the interplay between triggering factors for PEHS. HAPE = high-altitude pulmonary edema; PEHS = pulmonary edema of healthy subjects; SIPE = swimming induced pulmonary edema.

OVERVIEW AND CLINICAL PERSPECTIVE

Fig. 1 schematically represents the pathways connecting three basic stimuli (hypoxia, body immersion, and physical effort) to the onset of acute pulmonary edema in healthy subjects. Each of these stimuli, if appropriate in intensity, may be sufficient to trigger the acute episode, but in most cases the concurrence of several submaximal stimuli is observed. Breath-hold diving deserves a particular mention, since breath-hold divers swimming at depth are exposed to the maximal convergence of triggering stimuli: hypoxia, chest compression, immersion, and physical exercise (**Fig. 2**). Moreover, deep breath-hold diving may also induce lung squeeze, a case of pulmonary edema due to a purely physical mechanism. Taken together, these data may explain the high prevalence of PEHS in breath-hold diving athletes.

The pathophysiological model of PEHS may contribute to understand the pathophysiology of some uncommon forms of acute pulmonary edema arising in subjects without cardiac diseases, such those associated to obstructive sleep apnea syndrome (OSAS)[8,18] or in postsurgery care.[26,48] In the first, the combination of hypoxia and elevated transpulmonary pressure, due to respiratory obstruction, may cooperate in precipitating pulmonary edema. In postoperative care, negative inspiratory pressure and hypoxia due to a suboptimal airway management may add up to fluid overload and, in mechanically ventilated patients, to alveolar overdistension secondary to elevated ventilation pressures, activating stretching receptors of the blood-gas barrier and, hence, increasing capillary permeability.[51]

The hypothesis of a common pathophysiology of apparently far different syndromes as pulmonary edema triggered by high altitude, exercise, immersion (or even OSAS and postoperative cares), may help in developing and implementing a common preventive and therapeutic strategy. Firstly, an accurate avoidance of simultaneous exposure to triggering stimuli should be recommended. Moreover, a preliminary assessment of pulmonary vascular reactivity by measuring systolic pulmonary arterial pressure and/or NO expiratory excretion during hypoxic[7] or exercise stress test[24] could identify individuals at risk for pulmonary edema. Finally, pharmacological prevention or treatment, based upon drugs increasing NO availability[35] or inhibiting TRPV4 receptors,[51] could be hypothesized.

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