Of Deep Waters and Thin Air
Pulmonary Edema in Swimmers Versus Mountaineers

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With reported incidences typically $\approx 1\%$, swimming-induced pulmonary edema (SIPE) is increasingly recognized as a not uncommon syndrome that is triggered by strenuous swimming and characterized by dyspnea, cough, and hemoptysis. Interestingly, SIPE shares common features with another form of pulmonary edema that is caused by strenuous exercise in an evolutionary nonphysiological habitat, namely high-altitude pulmonary edema (HAPE): Both SIPE and HAPE typically affect young healthy individuals, are triggered by strenuous exercise in a cold environment, resolve spontaneously after return to physiological conditions, yet will recur on reexposure in prone individuals. At the pathological level, edema fluid in both SIPE and HAPE patients contains considerable amounts of red blood cells and high-molecular-weight proteins in the absence of markedly elevated inflammatory markers. The pathophysiology of both diseases has long puzzled the field and hampered the development of effective counterstrategies, because their features tend to evade the traditional classification of pulmonary edema.

The classic Starling equation defines net fluid flow $J_v$ across the capillary barrier as

$$J_v = L_p \cdot \Delta \left[ (P_c - P_f) - \sigma_\phi (\Pi_c - \Pi_f) \right]$$

where $L_p$ is hydraulic conductivity (a measure of water permeability), $A$ is the barrier surface area, $\sigma_\phi$ is the oncotic reflection coefficient (a measure of the barrier’s resistance to protein movement), and $P_c$, $P_f$, $\Pi_c$, and $\Pi_f$ are the hydrostatic (P) and oncotic (\( \Pi \)) pressures in the capillary (c) or interstitial (f) compartment, respectively. Accordingly, we differentiate between 2 classes of pulmonary edema, namely hydrostatic edema caused by increased driving pressure (increased $\Delta P$ or reduced $\Pi_f$), and permeability-type edema caused by high $L_p$ or low $\sigma_\phi$ and traditionally considered a result of infectious or sterile inflammation. The dilemma emerges because the lack of inflammatory markers in SIPE or early HAPE argues against a classic permeability-type edema, whereas the regular presence of red blood cells and high-molecular-weight proteins disagrees with the traditional concept of hydrostatic pulmonary edema.

In this issue of Circulation, a seminal study by Moon and colleagues now sheds new light on the pathomechanisms driving SIPE. In 10 subjects with a previous history of SIPE, pulmonary and systemic hemodynamics, expired gas volume and fractions, and blood gases were monitored at supine dry rest (baseline), after submersion in 18 to 20°C cold water, and during moderate cycle ergometer exercise while submerged. In comparison with a historical control of 20 healthy subjects, SIPE-susceptible subjects had higher mean pulmonary artery pressures (mPAP) and pulmonary artery wedge pressures (PAWP) during submersed exercise despite lower cardiac output (CO). These findings are reminiscent of studies in HAPE-susceptible subjects that show an exaggerated mPAP response to HAPE-relevant triggers such as hypoxia and exercise. None of the subjects showed signs of recurrent SIPE. Although a direct cause-effect relationship between the observed hemodynamic differences and the development of SIPE thus remains to be proven, the present data are consistent with a hydrostatic mechanism of disease because of increased pulmonary (micro)vascular pressures.

Following pretreatment with 50 mg of the phosphodiesterase 5 inhibitor sildenafil, the protocol was repeated. Although sildenafil only causes modest vasodilatation in the systemic circulation (with the exception of the corpora cavernosa), it has strong vasodilatory effects in the pulmonary circulation. At dry, supine rest, sildenafil increased CO, and, because mPAP and mean arterial pressure remained constant or even decreased slightly, reduced pulmonary (PVR) and systemic vascular resistance. During submersed exercise, sildenafil decreased mPAP and PVR in comparison with presildenafil measurements, and mPAP and PAWP values were no longer significantly different from the historic control group. Again, these findings mirror studies in healthy mountaineers in which sildenafil reduced systolic pulmonary artery pressure at rest and during exercise at both low and high altitude.

Given the communalities in pathology and response to sildenafil in SIPE and HAPE, it is tempting to speculate on similar parallels regarding 2 manifest questions: (1) If HAPE and SIPE are forms of hydrostatic lung edema, then why is the edema fluid rich in high-molecular-weight protein and red blood cells? (2) What mechanisms underlie the observed changes in pulmonary (micro)vascular pressures? Notably, the Starling equation considers the emergence of hydrostatic edema as the result of increased fluid flux across an intact endothelial barrier with an unaltered permeability that at large

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Circulation. 2016;133:951-953. DOI: 10.1161/CIRCULATIONAHA.116.021553

Circulation is available at http://circ.ahajournals.org

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prevents the extravasation of macromolecules and blood cells. Depending on the magnitude of the pressure increase, however, neither will endothelial permeability remain unchanged, nor will vascular barrier integrity remain intact. In elegant electron microscopic studies, the groups of West and Weibel showed that elevated hydrostatic pressure can cause microscopic breaks in the endothelial and epithelial membranes of the blood-gas barrier, a phenomenon now known as capillary stress failure. Exercise-induced capillary stress failure is common in galloping horses that routinely develop left atrial pressures ≥70 mm Hg and accounts for pulmonary hemorrhage in highly trained thoroughbreds. Although equivalent ultrastructural evidence is lacking in human lungs, capillary stress failure has analogously been proposed in both SIPE and HAPE. Yet, structural breaks of the alveolocapillary barrier typically require considerable capillary transmural pressures ≥40 mm Hg in rabbits and ≥100 mm Hg in the horse lung. Relevant increases in vascular permeability occur, however, already at much lower pressures, because the endothelial membrane is in fact anything but an inert barrier and responds actively to mechanical stimuli such as pressure and stretch. Recent work has identified the signaling pathways in the pulmonary endothelium that mediate these responses. A key element in this mechanotransduction cascade is the polymodal Ca<sup>2+</sup> channel transient receptor potential vanilloid 4, which opens in response to increased lung capillary pressures, allowing for endothelial Ca<sup>2+</sup> influx that in turn increases vascular permeability by activating the endothelial contractile machinery. Consistent with a pressure-induced increase in lung vascular permeability, and in opposition to the classic Starling concept, bronchoalveolar lavage fluid in patients with an unequivocal diagnosis of hydrostatic lung edema shows markedly elevated protein levels, although not as high as in patients with permeability-type lung edema. Hence, the presence of high-molecular-weight proteins and even red blood cells in the edema fluid of SIPE and HAPE patients is not in contradiction with an underlying hydrostatic mechanism of disease.

As to the mechanisms underlying the different hemodynamic responses in SIPE- and HAPE-susceptible subjects versus respective controls, the situation is less clear. Impaired left ventricular systolic or diastolic function have been proposed to trigger or predispose for SIPE; yet, all SIPE-susceptible patients in the present study had normal echocardiography at rest, and 9 of 10 had been evaluated for coronary artery disease with no pathological results. Submersion in cold water and concurrent increased sympathetic tone redistribute blood volume from systemic capacitance vessels to intrathoracic organs, predominantly the lung. This effect may per se increase transcapillary fluid flux J<sub>f</sub>, because capillary recruitment will increase surface area A in the Starling equation. The resulting increase in intrathoracic blood volume will cause an acute and sustained increase in pulmonary capillary pressures. Consistently, submersion into cold water (dunk) caused a rapid increase in PAWP from 13.0±3.2 to 18.1±3.9 mm Hg in SIPE-susceptible subjects in the present study. Notably, postdunk PAWP values were markedly lower (13.5 mm Hg; P=0.07) in the historic control of healthy subjects with no prior history of SIPE. Regrettably, baseline measurements at dry rest are not comparable between SIPE-susceptible and control subjects because of different positions (supine versus sitting); hence, it remains unclear whether SIPE-susceptible subjects had a higher baseline PAWP to start with, or an increased PAWP response to the dunk. Both higher blood volume and increased venous tone (either at baseline, or in response to cold water immersion) have been proposed to account for the increased PAWP response in SIPE-susceptible subjects. Notably, however, exercise-induced pulmonary edema has also been reported in elite cyclists, marathon runners, and cross-country skiers, all of whom exercise in vertical or sitting positions where intrathoracic blood volume shifts are expected to be minor. Given the consistent association between exercise and edema in these conditions, it is tempting to speculate on a critical role for CO in the onset of lung capillary leak; in the present study, however, CO was lower in SIPE-susceptible than in control subjects during submersed exercise and increased after treatment with sildenafil.

At this point, the comparison with HAPE may once more be informative. At high altitude, there is an obvious connection between hypoxia and increased pulmonary artery pressure through hypoxic pulmonary vasoconstriction; yet, how contraction of arteriolar resistance vessels will increase vascular pressure in downstream capillaries is less clear. To date, 3 not mutually exclusive explanations have been put forward: (1) HAPE may initially arise from a subset of capillaries that branch off directly from the larger arteries and, thus, are unprotected when pulmonary artery pressures increase; (2) capillary pressures may rise because of concomitant pulmonary venoconstriction; and (3) heterogeneous vasoconstriction may result in uneven distribution of perfusion and local areas of high flow and pressure. These concepts not only illustrate that drawing conclusions on local microhemodynamics from macrohemodynamic measurements can be problematic, but they also stress the potential role of pulmonary vasoconstriction in lung edema formation. A closer look at the data by Moon and colleagues may suggest a similar element of vasoconstriction in SIPE: Despite lower CO values, the transpulmonary pressure gradient (ie, the difference between mPAP and PAWP) tended to be higher in SIPE-susceptible subjects than in controls during both the dunk and subsequent submersed exercise. Conversely, sildenafil reduced the transpulmonary pressure gradient in SIPE-susceptible subjects at rest, subsequent to the dunk, and during submersed exercise despite a concomitant increase in CO. Consequently, PVR was higher in SIPE-susceptible subjects than in controls during submersed exercise, but decreased significantly with sildenafil. Higher PVR values in SIPE-susceptible subjects cannot be explained by increased total blood volumes or blood volume shifts, because capillary dilation or recruitment would reduce rather than increase PVR. Rather, these data strongly suggest a vasoconstrictive component that is alleviated by sildenafil in line with its well-characterized vasodilatory effects in the pulmonary circulation. Vasoconstriction, by actuating through mechanisms analogous to those outlined above for HAPE, may amplify global and, in particular, local increases in lung capillary pressures, thereby contributing relevantly to SIPE. Different from HAPE, however, the initial trigger for pulmonary vasoconstriction in SIPE is not hypoxia, but may...
inhibit adrenergic stimulation, and reactive vasoconstriction in response to increased capillary pressures (a phenomenon known as Kitajew reflex), as well.

Notably, not only endothelial leak at increased hydrostatic pressures, but also pulmonary vasoconstriction in response to hypoxia and hypoxia-independent stimuli are mediated at large by the Ca\(^{2+}\) channel transient receptor potential vanilloid 4.\(^{19}\) With transient receptor potential vanilloid 4 antagonists presently undergoing clinical testing for the treatment of cardiogenic lung edema,\(^{20}\) transient receptor potential vanilloid 4 blockade may ultimately present a putative strategy to prevent edema formation in SIPE- or HAPE-susceptible subjects.

**Disclosures**

None.

**References**


**Key Words:** Editorials • altitude sickness • capillary permeability • pulmonary circulation • pulmonary edema • swimming
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Circulation. 2016;133:951-953; originally published online February 16, 2016;
doi: 10.1161/CIRCULATIONAHA.116.021553
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/133/10/951

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