

Microcirculation Mini Review: Loven's Reflex Is Reproduced in The Lungs and Contributes in Pathophysiology of High-Altitude Pulmonary Edema: A Hypothesis

Bahaeldean E. Elawad

Department of Physiology, Faculty of Medicine,
University of Umm-ALqura, Holy Makkah. Kingdom of Saudi Arabia

ABSTRACT

High altitude pulmonary edema is a serious potentially fatal state. This article hypothesizes that, Loven's reflex is reproduced in the lungs and contributes to the pathophysiology of high-altitude pulmonary edema. In conclusion, Loven's reflex induces a positive feedback mechanism which exaggerates hypoxic pulmonary vasoconstriction, elevates pulmonary arterial pressure, and promotes the development of high-altitude pulmonary edema.

Keywords: Loven's reflex; Hypoxic pulmonary vasoconstriction; Relatively less pulmonary vasoconstriction; High altitude pulmonary edema.

In a healthy adult of 70-Kg body weight, total body water is about 42 liters; two thirds of which is intracellular fluid (ICF) and one third is extracellular fluid (ECF). The two main compartments of the ECF are the interstitial fluid (ISF), which makes up about three fourths of the ECF, and the plasma, which makes up about one fourth of the ECF. The plasma is the non-cellular portion of the blood that continuously and rapidly exchanges oxygen and nutrients and waste products of metabolism with the interstitial fluid. This is the primary function of the circulatory system. This exchange occurs at the level of microcirculation which is in direct contact with the parenchymal cells. Thus, the viability of cells to support homeostasis is absolutely dependent on proper function of microcirculation (1). Other functions of the microcirculation include transport of nutrients, hormones, drugs, and mediating the functional activity of immune system and haemostasis (2,3).

Microcirculation is the ultimate vascular network of the circulatory system. Microcirculation consists of micro-vessels with diameter of less than 20 μm , which connect the arterial and venous system. These micro-vessels are arterioles, capillaries, venules, and lymphatics (4).

Arterioles (5-100 μm in diameter) have thick smooth muscle lining and an endothelial lining layer. Arterioles give rise directly to capillaries (5-10 μm in diameter) or, in some tissues, to metarterioles (10-20 μm in diameter), which then give rise to capillaries. Metarterioles can bypass the capillaries and connect directly with venules. Arterioles that give rise directly to capillaries (terminal arterioles) are the primary determinant of blood flow through these capillaries; by constriction or dilatation. The capillaries form an interconnecting network of tubes with an average length of 0.5-1 mm.

Metarterioles are thoroughfare channels that link arterioles and capillaries. Precapillary sphincters are small cuffs of smooth muscles at the metarterioles, from which blood flows through the capillary channel. This flow is known as nutrient flow, since it is responsible for the primary exchange function of microcirculation. In some parts of microcirculation, blood flow bypasses the capillary bed, moves through an anatomical arterio-venous shunt which directly connects the arteriole with the venule. This type of blood flow is known as non-nutrient flow, because it doesn't allow for nutrient exchange. Such non-nutrient channels are common in the skin and are important in terms of heat exchange and heat regulation (5).

Exchange between intravascular and ISF was laid down by Ernest Starling in 1896. Starling's hypothesis states that fluid movement due to filtration across the wall of the capillary is dependent on the balance between the hydrostatic pressure gradient and the oncotic pressure gradient across the capillary (6). There are four Starling's forces determine fluid filtration through the capillary membrane, these are: capillary hydrostatic pressure (P_c), interstitial hydrostatic pressure (P_i), plasma colloid osmotic pressure (π_c), and interstitial colloid osmotic pressure (π_i). P_c forces fluid outward through the capillary membrane to the interstitium; it is also known as capillary filtration pressure. In systemic capillaries, P_c falls gradually from beginning to the end of capillary (7).

P_i can be negative or positive. In organs such as the kidneys, brain, and skeletal muscles which are encased in a tough fibrous capsule, the P_i is positive, thereby opposing filtration of the fluid out of capillaries. In the skin which is exposed to atmospheric pressure, the P_i is several mm Hg less than the P_c . Negative P_i pressure increases the outward forces that pull fluid out of the capillary into the interstitium. This explains both edema at hot weather and the physical loss of heat by radiation through ISF.

Interstitial space represents 1/6 of the body. It is supported by collagen and elastic fibers and filled with proteoglycan molecules that combine with each other to form a tissue gel. This tissue gel acts like sponge to entrap the ISF and provide even distribution to all cells, even those distant from the capillaries. Although most of the fluid is entrapped in the tissue gel, small trickles of free fluid develop between the proteoglycan molecules. Normally only small amount of free fluid is present.

π_c which averages about 28 mm Hg. Colloid solution is one in which there are evenly dispersed particles. It tends to cause osmosis of the fluid inward through the capillary membrane. The proteins are the only dissolved substances in the plasma that do not readily pass through the capillary membrane. These substances exert an osmotic pressure referred to as the colloid osmotic pressure. It reflects the osmotic effect of plasma proteins in drawing fluid into the capillary. The term colloid osmotic pressure is used to differentiate the osmotic effect of the particles in a colloidal solution from those of the dissolved crystalloids such as sodium. The normal concentration of plasma proteins averages about 7.3 g/dl. About 19 mm Hg of the colloid osmotic pressure is due to the dissolved protein, but an additional 9 mm Hg is due to the positively charged cations, mainly sodium ions, that bind to the negatively charged plasma proteins. This is called the Donnan equilibrium effect. About 80% of the total colloidal osmotic pressure of the plasma results from the albumin fraction, 20% from the globulin, and only a tiny amount from the fibrinogen. One gram of albumin (MW of 69000) contains almost six times as many molecules as one gram of fibrinogen (MW of 420000) and two times of globulin

(MW of 140000). Osmotic pressure represents the mechanical pressure or force that would be needed to oppose the osmotic movement of water.

Not all of the protein present is effective in retaining water, so the effective capillary oncotic pressure is lower than the measured oncotic pressure. Thus, Staverman's osmotic reflection coefficient is used to correct the magnitude of the measured oncotic pressure gradient (8).

Reflection coefficient is the relative impediment to the passage of a substance through a capillary membrane. The reflection coefficient for water is zero and that of albumin (to which the endothelium is essentially impermeable) is 1. Filterable solutes have reflection coefficient between zero and 1. In addition different tissues have different membrane reflection coefficient. For example, cerebrospinal fluid and the glomerular filtrate have very low protein concentration and the reflection coefficient for protein in these capillaries is close to 1. On the other hand, proteins cross the wall of hepatic sinusoids relatively easily and the protein concentration in interstitial space is very high. The reflection coefficient in sinusoids is low. The reflection coefficient in pulmonary capillaries is intermediate in value, about 0.5

With regard to systemic capillaries, it is the number, not the size, of the particles in solution that controls the osmotic pressure.

π_i tends to cause osmosis of fluid outward through the capillary membrane.

The balance of these forces (determinants of capillary filtration) allows for estimation of effective filtration pressure (EFP) which is the net driving pressure across capillary membrane. EFP is the difference between hydrostatic pressure gradient, which tends to push fluid outward into interstitium, and oncotic pressure gradient, which tends to draw the fluid into capillary (9,10).

$$EFP = \{(P_c - P_i) - \sigma (\pi_c - \pi_i)\}$$

State of equilibrium exists as long as equal amounts of fluid enter and leave the interstitial space. This is not the case with the effect of the above mentioned four forces. Normally, slightly more fluid leaves the capillary than can be reabsorbed. The lymphatic system represents an accessory system that removes excess fluid, osmotically active proteins, and large particles from the interstitial space back to the circulation. These proteins have no other way to be returned to the plasma (11).

The removal of proteins from the interstitial space is an essential function, without which death would occur in about 24 hours (12). The lymphatic system also returns lipids and metabolic waste from interstitium to the circulation. The lymphatic system is composed of lymphatic vessels (thoracic duct is the largest lymphatic vessel), lymph nodes, and lymphoid tissues. The terminal lymph vessels are closed-end network of lymph capillaries. These lymph capillaries resemble the blood capillaries, with two important differences: tight junctions are not present between endothelial cells, and fine filaments anchor the lymph vessels to the surrounding connective tissue. With the aid of intermittent muscle contraction and an extensive system of one-way valves, these lymph vessels return the plasma capillary filtrate to the circulation. They drain into large vessels that finally enter the right and left subclavian

veins, where they connect with the respective jugular veins. If protein were not removed by the lymph vessels, it would accumulate in the interstitium and act as an oncotic force that draws fluid from the blood capillaries and produces edema (12).

The net flux of fluid across capillary membrane depends not only on the EFP but also on capillary filtration coefficient (K_f). This is the filtration constant of the capillary membrane which is the product of surface area and the permeability per unit of surface area of the capillary membrane.

$$\text{Net flux} = K_f \{(P_c - P_i) - \sigma (\pi_c - \pi_i)\}$$

In systemic capillaries, the net driving force is outward at the arteriolar end and inward at the venous end of the capillary. This change in net driving pressure is due to the decrease in the P_c along the length of the capillary. Typically, P_c is 28-40 mm Hg at the arteriolar end of the capillary, about 17 mm Hg at the middle of the capillary, and 10-15 mm Hg at the venous end of the capillary. The values for P_c are not fixed and vary quite widely in different tissues and indeed within the same tissue. The P_i , π_c , and π_i , are kept constant at a value of zero to negative, 28, and 8 mm Hg respectively. Starling's equation cannot be used quantitatively in clinical work because it requires measurement of six unknowns. It can be used in a general way to explain edema.

In glomerular capillaries, the K_f is high, mostly because of high permeability but also because of large surface area. Glomerular capillary hydrostatic pressure is the highest capillary pressure in the body and doesn't decrease much along the course of the capillary, it remains relatively constant. It is about 60 mm Hg at the afferent arteriole and 58 mm Hg at efferent arteriole. The glomerular capillary hydrostatic pressure is affected by the balance between afferent and efferent arteriolar tone. Because of the large hydrostatic driving pressure and impermeability of glomerular capillary membrane to proteins, the glomerular oncotic pressure increases gradually along the length of capillary. It is at a value of 21 and 33 mm Hg at afferent and efferent arteriole respectively. Such increase in glomerular oncotic pressure is important for reabsorption from the proximal tubule into peritubular capillaries. Hydrostatic pressure in Bowman's space is kept constant at a value of 15 mm Hg. Thus, the EFP at the afferent arteriolar end is 24 mm Hg and 10 mm Hg at the efferent arteriolar end of the glomerular capillary.

With regards to pulmonary circulation, alveolar-capillary membrane has a very thin wall, about 0.3 μm in average, which minimizes the barrier to diffusion. The pulmonary capillaries form a dense network in the alveolar wall (intra-alveolar vessels) in form of thin film of blood. This provides a large capillary surface area. The pulmonary vascular resistance is very low; the mean pulmonary arterial pressure is just sufficient to perfuse the apical areas of the lungs in the erect healthy adult. Pulmonary capillary hydrostatic pressure is the lowest capillary pressure in the body. It is about 13 mm Hg at arteriolar end and 6 mm Hg at venous end of capillary. The interstitial hydrostatic pressure, capillary oncotic pressure, and interstitial oncotic pressure are kept constant at values of zero to negative, 25 mm Hg, and 17 mm Hg respectively. The reflection coefficient is 0.5. (12)

Edema is not a disease but rather a manifestation of altered physiologic function. It can occur in healthy and sick persons. Edema is defined as expansion of ISF to a level sufficient to produce palpable swelling. It doesn't become evident until the ISF volume has been increased by 2.5-3.0 Lit; which seems to be the absorptive capacity of the tissue gel (13).

The Swedish physiologists Otto Christian Loven (1835-1904), described in rabbits an inhibitory reflex in skin in response to noxious stimulus (14).

Loven found that the electrical stimulation of the central stump of the dorsal nerve of the hind paw, a branch of the superficial peroneal nerve (*nervus dorsalis pedis*), resulting in ipsilateral saphenous artery vasodilatation; No vasodilatation but sometimes vasoconstriction in the ear lobe; and systemic vasoconstriction causing an increase in blood pressure. Loven concluded that vasomotor fibers innervating the saphenous artery or ear lobe vessels must be different from the vasomotor fibers responsible for the increase in systemic blood pressure. In addition, vasodilatation of skin vessels is generated reflexly by stimulation of afferents which innervate the same skin territory that is innervated by the cutaneous vasoconstrictor fibers or a close-by territory. Loven did not comment on his results as being generated by decreased activity in vasoconstrictor neurons or activation of vasodilator neurons; the details of the concept of nerve-mediated vasoconstriction and vasodilatation developed much later by Bayliss (15).

Bayliss reproduced the Loven's reflex in skeletal muscles indirectly. He demonstrated that electrical stimulation of the distally cut lumbar dorsal root (L6) elicited vasodilatation in the hind limb, whereas electrical stimulation of the median nerve elicited vasoconstriction in the hind limb.

Bayliss and other authors (16) believe that the reflex vasodilatation resulting from stimulation of likely nociceptive afferents innervating the same tissue whereas the efferent sympathetic fibers is likely to be a general phenomenon everywhere in the body (17).

Therefore, Loven's results were generalized to organs other than the skin, although Loven never investigated the reflex inhibition in other organs.

The pathways of nociceptive inhibitory reflexes are most likely spinal with supraspinal influences (18,19). However, the exact course of pathways and whether inhibitory interneurons are involved or not remains to be elucidated. The Loven's reflex has been forgotten since the 1950s (20).

The potential clinical implications of the Loven's reflex are considerable. Inhibitory spinal reflex systems are observed during inflammatory process (21), complex regional pain syndrome (22), and deep somatic tissue injury both during paraspinal manual interventions to relieve pain as well as promotion of cure of functional disease (23).

Normally, most lung units receive an amount of ventilation equal to or close to the amount of blood flow; such units are balanced with a ventilation-perfusion ratio (V_A/Q) of 1 or close to 1. When an alveolar-capillary unit has more air than blood flow, the ratio of that unit is greater than 1; if more blood flow than air is present, the ratio is less than one. Most of the ventilation and perfusion goes to lung units with V_A/Q around 1 (9).

Hypoxic vasoconstriction is a clinically important phenomenon that is unique to the pulmonary circulation; other vascular beds dilate in response to hypoxia. Whenever there is a decrease in the partial pressure of oxygen in alveoli (P_{AO_2}), a local vasoconstriction of pulmonary blood vessels is produced. This hypoxic pulmonary vasoconstriction (HPV) results in lowering of blood flow through that lung unit and redistribution of blood flow to better ventilated alveoli (24). The physiologic significance of HPV at low altitude is obvious in the presence of localized hypoxia in the lung, such as pneumonia or lung collapse. However, when the whole lung is exposed to hypoxia, as at high altitude, HPV may be disadvantageous. The exact mechanism of HPV is not known, however reactive oxygen species may play a central role via intracellular calcium release (25).

HPV results in substantial increase in pulmonary vascular resistance and pulmonary arterial pressure (26)

High altitude pulmonary edema (HAPE) is a serious, potentially fatal state (27).

HAPE induces ventilation perfusion imbalance manifested by coughing of frothy sputum, chest tightness or pain, and dyspnea on exertion (28). HAPE can be complicated by an increase in the afterload of the right ventricle with consequent hypertrophy and right-sided heart failure, dyspnea at rest, crackles, cyanosis, and mortality rate of up to 50%, if left untreated (29).

This article hypothesizes that, Loven's reflex is reproduced in the lungs and contributes in the pathophysiology of HAPE. Hypoxia is a noxious stimulus that can elicit Loven's reflex (30). Because of the global effect of hypoxia on pulmonary circulation at high altitude, Loven's reflex results into "relatively less pulmonary vasoconstriction" in some alveolar-capillary units, rather than vasodilatation. This results in shifting of blood flow to these "relatively vasodilated" alveolar-capillary units.

This redistribution of blood flow overwhelms the oxygenation capacity of the alveoli serving these "relatively dilated vessels". That is to say relatively more blood in pulmonary capillary than can be fully oxygenated by the alveolar air.

This results in regional overperfusion of pulmonary capillaries with low V/Q ratio of these alveolar-capillary units (31). Consequently, there will be increase in venous admixture, mixing of unoxygenated and oxygenated blood. This leads to more hypoxemia, reduction of partial pressure of oxygen in arterial blood (P_{aO_2}), and more HPV. Hypoxia will continue eliciting Loven's reflex and eventually a vicious cycle of positive feedback loop. Loven's reflex can explain, at least partially, the nonhomogenous HPV (32) in patients with HAPE. The degree of increment of pulmonary arterial pressure alone cannot justify development of HAPE (33).

This article proposes that, the "rising" magnitude of HPV and "rising" level of pulmonary arterial pressure rather than the absolute value of pulmonary hypertension is responsible for HAPE. This is induced by the positive feedback loop of Loven's reflex in the lungs. Whether HAPE is due to increased pulmonary capillary hydrostatic pressure and/or increased alveolar-capillary membrane permeability is still controversial (34). Nevertheless, then increased pulmonary blood flow to alveolar-capillary units of less constricted "relatively

dilated" arterioles caused by Loven's reflex will induce some sort of mechanical pressure on pulmonary capillaries (stress failure). This can lead to pressure-induced changes in permeability and, if it is severe enough, allows movement of proteins into pulmonary interstitial space. This draws fluid out of the plasma into pulmonary interstitium (35,36). This may explain the radiographic findings of interstitial infiltrates that seen before the development of overt manifestations of HAPE. There are physiologically three major factors which prevent further accumulation of fluid in the pulmonary interstitium. The first factor is the low compliance of pulmonary interstitium which implies that marked increase in interstitial hydrostatic pressure opposes further excessive capillary filtration (37). The second one is the much increase in lymph flow which carries large amount of water back to the circulation. The third is the wash-down of interstitial fluid proteins as lymph flow increases (38).

The positive feedback mechanism of Loven's reflex will exaggerate this pathophysiologic scenario with more leakage of plasma proteins and water into pulmonary interstitium and consequently full-blown clinical picture of HAPE ensues.

In conclusion, Loven's reflex induces a positive feedback mechanism which exaggerates HPV, elevates pulmonary arterial pressure, and promotes the development of HAPE.

References

1. Seifter JL. Body fluid compartments, cell membrane ion transport, electrolyte concentrations, and acid-base balance. *Semin Nephrol* 2019;39(4):368-379
2. Bateman RM, Sharpe MD, Ellis CG. Bench-to-bedside review: microvascular dysfunction in sepsis-hemodynamics, oxygen transport, and nitric oxide. *Crit Care*. 2003;7(5):359-73. Only 5% of circulating blood present in capillaries.
3. Tansey EA, Montgomery LEA, Quinn JG, et al. Understanding basic vein physiology and venous blood pressure through simple physical assessments. *Adv Physiol Educ* 2019;43(3):423-429
4. Ince C, Mayeux PR, Nguyen T, et al. The endothelium in sepsis. *Shock*. 2016;45(3):259-70
5. Sturtzel C. Endothelial cells. *Adv Exp Med Biol* 2017; 1003:71-91
6. Phillippi JA. On vasa vasorum: a history of advances in understanding the vessels of vessels. *Sci Adv* 2022;(8)16: eabI6364
7. Starling EH. On the absorption of fluids from the connective tissue space. *J Physiology* 1896; 19:312-326
8. Beard DA, Feifl EO. Understanding Guyton's venous return curves *Am J Physiol Heart Circ Physiol* 2011;301(3):H629-33
9. Staveman AL. The theory of measurement of osmotic pressure. *Rec Trav Chim* 1951; 70:344-352
10. Hall JE. The microcirculation and lymphatic system: capillary fluid exchange, interstitial fluid, and lymph flow. In: Hall JE, editor. *Guyton and Hall Textbook of Medical physiology*. 13th ed. Philadelphia, PA: Elsevier (2016).
11. Jacob M, Chappel D. Reappraising Starling: the physiology of the microcirculation. *Curr Opin Crit Care* 2013;19(4):282-289

12. Breslin JW, Yang Y, Scallan JP, et al. Lymphatic vessel network structure and physiology. *Compr Physiol* 2018; 9:207-99
13. Scallan JP, Zawiega SD, Castorena-Gonzalez JA, et al. Lymphatic pumping: mechanics, mechanisms, and malfunction. *J Physiol* 2016;594(20):5749-5768
14. Rose BD. *Clinical Physiology of acid-base and electrolyte disorders*. (4th ed., pp.447, 173-175, 781). New York McGraw-Hill
15. Loven C (1866) Über die Erweiterung von Arterien in Folge einer Nervenirregung {On the vasodilation of arteries as a consequence of nerve stimulation} *Ber verh Königl-Sächs Ges Wiss: Math-Phys Classe* 18:85-110
16. Bayliss VM (1908) On reciprocal innervation in vaso-motor reflexes and the action of strychnine and of chloroform thereon. *Proc Roy Soc B* 80:339-375
17. Blumberg H, Wallian BG 1987 Direct evidence of neurally mediated vasodilatation in hairy skin of the human foot *J Physiol* 382:105-121
18. Kirrilova-Woytke, Baron R, Jänig W 2014 Reflex inhibition of cutaneous and muscle vasoconstrictor neurons during stimulation of cutaneous and muscle nociceptors *J Neurophysiol* 111:1833-45
19. Horeysek G, Jänig W 1974 Reflex activity of postganglionic fibers within skin and muscle nerves elicited by somatic stimuli in chronic spinal cats *Exp Brain Res* 21:155-68
20. Jänig W, Spilok N 1978 Functional organization of the sympathetic innervation supplying the hairless skin of the hind paws in chronic spinal cats. *Pflügers Arch* 377:25-31
21. Wilfrid J. The loven's reflex: the renaissance of a long-forgotten reflex involving autonomic and nociceptive pathways. *Clinical autonomic research* 2021; 31:149-152
22. Jänig W 2020 Sympathetic nervous system and pain. In: Pogatzki-Zahn E, Schaible H-G (eds). *The senses: a comprehensive reference*, vol 5. Elsevier, P349-378
23. Jänig W, Baron R 2003 complex regional pain syndrome: mystery explained? *Lancet Neurol* 2:687-697
24. King HH, Jänig W, Patterson MM (eds) 2011 *The science and clinical application of manual therapy*. Churchill Livingstone Elsevier, Edinburgh
25. Sylvester J, Shimoda L, Aaronson P, et al. Hypoxic pulmonary vasoconstriction. *Physiol Rev* 2012; 92:367
26. Strielkov I, Pak O, Sommer N, et al. Recent advances in oxygen sensing and signal transduction in hypoxic pulmonary vasoconstriction. *J Appl Physiol* 2017;123:1647-56
27. Wikins M, Ghofrain H, Weissmann N, et al. Pathophysiology and treatment of high-altitude pulmonary vascular disease. *Circulation* 2015; 131:582-90
28. Luks A, Swenson E, Bartsch P. Acute high-altitude sickness. *Eur Respir Rev off J Eur Respir Soc* 2017; 26:160096
29. Gonzalez A, Molano D, Nieto V, et al. Interventions for preventing high altitude illness: part 2. Less commonly-used drugs. *Cochrane Database Syst Rev* 2018;12(3):CD012983
30. Nieto V, Molano D, Medina R, et al. Interventions for prevention of high-altitude illness: Part 1. Commonly-used classes of drugs. *Cochrane Database Syst Rev* 2017;27 (6):CD009761

31. Doufas A, Tian L, Davies M, et al. Nocturnal intermittent hypoxia is independently associated with pain in subjects suffering from sleep disorder breathing. *Anesthesiology* 2013; 119:1149-1162
32. Halastala M, Lamm W, Karp A, et al. Spatial distribution of hypoxic pulmonary vasoconstriction in the supine pig. *J Appl Physiol* 2004; 96:1589-1599
33. Dehnert C, Risse F, Ley et al. Magnetic resonance imaging of uneven pulmonary perfusion in hypoxia in humans. *Am J Respir. Crit. Care Med* 2006; 174:1132-1138
34. Dehnert C, Mereles, Greiner S, et al. Exaggerated hypoxic pulmonary vasoconstriction without susceptibility to high-altitude pulmonary edema. *High Alt Med Biol* 2015; 16:11-17
35. Jacob D, Andrew L. High altitude pulmonary edema. Treasure Island (FL): Startapearls Publishing 2023 January
36. Sujith V, Rosa M. Unilateral pulmonary edema after visiting high altitude. *Annals of the American Thoracic Society* 2017;14(4):589-593
37. Chun Zhou, C. Michael Francis, Ning yong Xu, et al. The role of endothelial leak in pulmonary hypertension (2017 Grover Conference Series) 2018;8(4):
38. Stephen J, Robert L. Pulmonary interstitial resistance. *Annals of Biomedical Engineering* 1973; 15:173-182
39. Colice G. Pulmonary edema. *Clin Geriatr Med* 1986;2(2):411-32