

Draining the Pleural Space

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Lymphatic vessels drain lymph from interstitial spaces and serosal cavities to eventually empty into the blood venous stream. This task is more difficult when the liquid to be drained has a very subatmospheric pressure, as it occurs in the pleural cavity. This peculiar space must maintain a very low fluid volume at negative hydraulic pressure to guarantee a proper mechanical coupling between the chest wall and lungs. Moreover, lubrication of the constant sliding pleurae to avoid any damage to those very thin structures, constant liquid renovation preventing excessive drying, or accumulation must be fulfilled at the same time.

lymphatic vessel

pleural cavity

diaphragm

chest wall

lung

1. Lymph Draining and Propulsion

The lymphatic system drains liquid, macromolecules and cells from the surrounding interstitial space and serosal cavities, to guarantee the proper tissue fluid balance^[1]. Lymph formation occurs into *lymphatic capillaries*, which are blind-ended vessels originating in peripheral tissue, devoid of lymphatic muscle cells (LMCs). Those vessels are lined by a single layer of overlapping endothelial cells (LECs) forming primary unidirectional valves, allowing lymph entry and preventing the backflow into surrounding tissue^{[2][3][4][5]}. The forces required for lymph formation and propulsion are modelled according to the modified Starling's Law Equation (1)^[6]. The hydraulic pressure gradient is the main determinant of lymph flow (J_{lymph}) across the capillaries' wall and through the lymphatic network.

$$J_{lymph} = -L_p \cdot S \cdot (\Delta P_{TM})^{(1)}$$

where L_p is the endothelial permeability to water coefficient, S the surface area of fluid exchange and ΔP_{TM} the transmural hydraulic pressure gradient between the lymphatic capillary lumen (P_L) and the interstitium (P_{in}). J_{lymph} is directly dependent upon the plasma filtered from blood capillaries into the interstitium and the mechanical compliance of the receiving space: the more fluid enters the interstitium the greater fluid volume is drained by lymphatics, whose intraluminal pressure (P_L) is typically subatmospheric.

Due to anchoring filaments^[7], lymphatic capillaries are tightly attached to the extracellular matrix^{[6][8]} and tissue displacement causes *extrinsic forces* to cyclically expand and compress lymphatic vessels, affecting ΔP_{TM} , thus lymph formation. Lymph is then propelled through larger *collecting lymphatics*, surrounded by LMCs displaying unique features^[9]. Intraluminal competent valves separate adjacent lymphangions (the functional pump units of the lymphatic system) and prevent massive lymph backflow^{[4][8][10]}. Lymph progression is then due to a net

intraluminal hydraulic pressure gradient acting across the trans-valve region (ΔP_{TV}). *In vivo* micropuncture studies measured a ΔP_{TV} of ~ -1 – 1.5 cmH₂O^[11] which forces the valve to open. More recently, P_L measurements in mesenteric lymphatics having different pressure regimens showed multiple gating patterns, depending on the baseline P_L and on the vessel wall's distension^[12]. Indeed, valve closure may occur with an adverse ΔP_{TV} as low as 0.1 cmH₂O for baseline P_L below 2 cmH₂O, but a ΔP_{TV} higher than 2 cmH₂O is required to force valve closure with a baseline P_L of 10 cmH₂O or above. Moreover, pressure ranges for valve opening and closure are not symmetrical, causing valves to be biased in an open position having multiple physiological implications and can also lead to a limited lymph backflow^{[13][14]}. Nevertheless, lymph is propelled against an overall hydraulic pressure gradient to the blood venous system^{[11][15]}. Lymphatic spontaneous phasic contractions (*intrinsic forces*)^[16] arising in collecting vessels walls combined to extrinsic mechanisms, drive lymph propulsion centripetally, critically affecting intraluminal pressure gradients. Spontaneous contractions of the lymphatic muscle^{[9][17][18][19][20]} typically spread from a subset of LMCs in the vessel wall and propagates along the lymphatic network through gap junctions between LMCs and/or LECs^[15].

2. The Pleural Space

The pleural space in the thoracic cavity is a very peculiar serosal compartment whose integrity is vital for a physiological breathing. The mechanical properties of lungs and chest wall are set so that each of them tends to reach its mechanical resting volume: lungs tend to the very low minimal air volume (lower than zero vital capacity) whereas the chest wall tends to a value $\sim 80\%$ of the vital capacity^[21]. In so doing, they both tend to increase the pleural cavity volume, inducing P_{liq} (pleural hydraulic pressure, analogous to P_{in} for the pleural cavity) to reach subatmospheric pressure values during normal, spontaneous breathing. In humans, at end-expiration at the height of the right atrium P_{liq} is ~ -5 cmH₂O, becoming more negative during inspiration. Pleural P_{liq} only becomes positive during forced expiration. The negative P_{liq} ensures the proper mechanical coupling between the chest wall and the lungs, but it implies that the removal of liquid filtered from capillaries and surrounding tissues is more difficult to achieve.

3. Lymphatic Vessels of the Diaphragm

Lymphatic vessels of the diaphragm allow fluid homeostasis of the pleural (and peritoneal) cavities, due to their subatmospheric P_L . On the pleural side, lymphatic vessels are organized in linear vessels, with a parallel or transverse arrangement with respect to the skeletal muscle fibers orientation, or in complex merging structures (lymphatic loops)^{[22][23]}. Unlike pleural lymphatics, on the peritoneal side, lymphatics are radially arranged from the abdominal wall to the central tendon^[24]. They primarily remove peritoneal fluid, but also pathogens and/or immune cells related to inflammatory state affecting the viscera, such as the gastrointestinal tract or the urogenitary system. Lymph drained from serosal cavities enters the diaphragmatic network through mesothelial stomata^[25], reaching flat submesothelial lymphatic *lacunae* (**Figure 1**, asterisks), considered as larger lymphatic capillaries. Lacunae are unevenly distributed and located beneath the mesothelium and above the skeletal muscle layer^[26]. They empty

into transverse lymphatic vessels draining into collecting lymphatics deeper in the interstitium^[27]. Lymph is then routed towards the mediastinal lymph nodes, merging to the blood stream via the thoracic duct.

Intrinsic and/or extrinsic forces deeply affect diaphragmatic lymphatics' draining and propulsive capability. Regarding extrinsic forces, the cyclical contraction of the diaphragm during the respiratory cycle plays a pivotal role in determining lymphatic function. Cyclical mechanical stresses transmitted to lymphatics primarily affect ΔP_{TM} and the intraluminal pressure gradient ($\Delta P_L = P_{L,1} - P_{L,2}$) between two lymphatic segments. The external stress transmission efficiency depends upon both the mechanical properties of the lymphatics' wall and the surrounding tissue, being more effective in stiffer rather than more distensible regions^[28]. Moreover, depending on vessels' orientation with respect to the skeletal muscle fibers, extrinsic forces can either shrink or enlarge the vessel lumen, affecting lymphangions' volume and hydraulic P_L and P_{in} profiles.

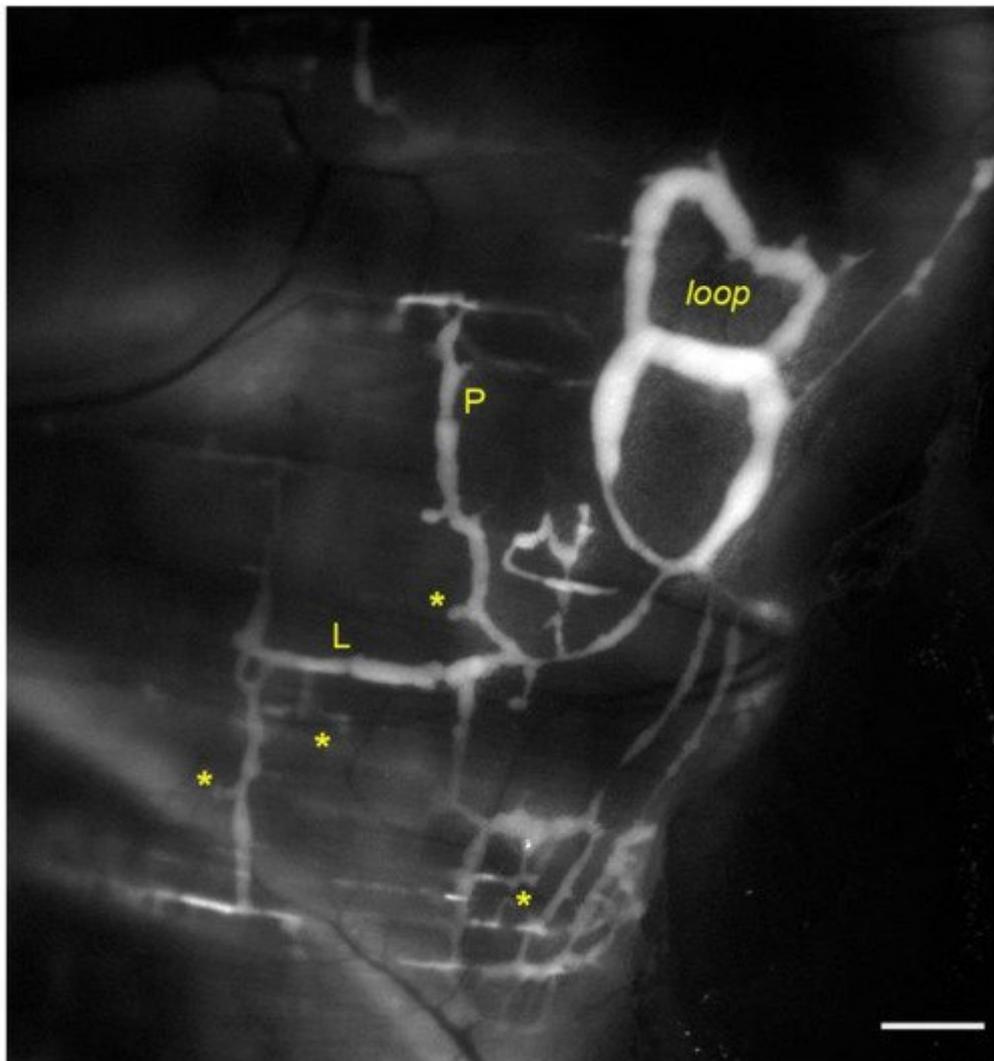


Figure 1. *In vivo* fluorescent stained lymphatic network on the pleural side of rat diaphragm. Lymph enters lymphatic *lacunae* (asterisks) and is propelled through vessels longitudinally (L) and/or perpendicularly (P) arranged with respect to the skeletal muscle fibers orientation. Lymphatic collectors located at the muscle

periphery, next to the costal margin, are typically organized in complex loop structures (**loop**) and display intrinsic contractility (scalebar 1 mm).

Diaphragmatic skeletal muscle contractions reduce vessels' diameter by ~39% in superficial, perpendicularly oriented lymphatics (**Figure 1, P**), decreasing P_L by ~12 cmH₂O and enhancing the pressure gradient driving force (ΔP_{TM}) favoring lymph formation. Conversely in deeper collectors the diaphragm contraction increases P_L by ~11 cmH₂O, favoring lymph propulsion. In longitudinally oriented lymphatics (**Figure 1, L**) diaphragmatic muscle contraction shortens the vessel by ~30% and the diameter enlarges by ~23%. P_L decreases in both superficial submesothelial and deeper vessels by ~22.5 cmH₂O and ~10.5 cmH₂O respectively, thereby supporting further lymph propulsion^[29]. The different regional effect may be explained considering that deeper lymphatics are less compliant being entirely surrounded by stiffer skeletal or tendinous fibers^[28]. Moreover, another source of extrinsic forces is the rhythmic tissue displacement due to heart activity, as cardiogenic movements induced by arterial pressure pulses propagate through neighbor regions, affecting the diaphragmatic lymphatic bed and the adjacent interstitium. Cardiogenic activity can simultaneously sustain lymph formation and propulsion along the lymphatic network of the diaphragm. Indeed, data obtained in rats shows that in ~60% of cases ΔP_{TM} sustains lymph formation during either systolic or diastolic phases, whereas in ~40% of cases ΔP_{TM} becomes transiently positive, possibly driving fluid backflow into the interstitial space but also sustaining oscillatory lymph propulsion along lymphatic collectors^[30].

Diaphragmatic collecting lymphatics located at the far peripheral muscular region adjacent to the costal margin are typically organized in complex loops (**Figure 1, loop**). These vessels are endowed with a properly organized dense mesh of lymphatic muscle (**Figure 2, panel A**) spontaneously contracting^{[23][31]} aiding lymph propulsion. In this body district, intrinsic spontaneous contractions rely on a "Funny"-like current (I_f) due to HCN (Hyperpolarization-activated Cyclic Nucleotide-Gated) channels^{[32][33]}, as it occurs in the heart pacemaker. This intrinsic contractility can be reduced by Cesium^{[33][34]} or even abolished by two well-known HCN channel blockers, Ivabradine^[35] and/or ZD7288^[34]. In analogy to the cardiac cycle, the intrinsic contractile mechanism can be divided into an active systolic contraction followed by a diastolic relaxation, and it can be quantified in terms of contraction frequency (CF) and contraction amplitude (Δd , the difference between the end-diastolic and the end-systolic diameters)^[36].

In rat diaphragm extrinsic forces are the most efficient and guarantee a proper one-way propulsion by forcing intraluminal valves into an open/closed cycle^[29], preventing backflow. In fact, the extrinsically induced lymph progression along the vessel network is ~30 times longer, and lymph flow is 10-fold higher, than the ones induced by a single intrinsic contraction. Nevertheless, lymph flow remains laminar also for extrinsic pumping mechanism^[14].

Then, why is the intrinsic mechanism also needed in diaphragmatic lymphatics? It seems to be restricted to the muscular peripheral vessels^[23], located in an area where the respiratory-related extrinsic forces are less effective, probably due to the anisotropic stress distribution in the diaphragmatic dome^[37]. Indeed, it is worth noting that lymphatics vessels in the medial muscular region also possess LMCs, although they do not spontaneously contract, being the lymphatic muscle not properly arranged to aid lymph propulsion^[23]. Moreover, the abundance of

LMCs in the vessel wall, beyond a certain level, may not be determinant for the contraction amplitude (Δd), as it reaches a finite saturation limit for increasing LMCs density, not corresponding to complete occlusion of the lymphatic lumen^[38] (Figure 2, panel B).

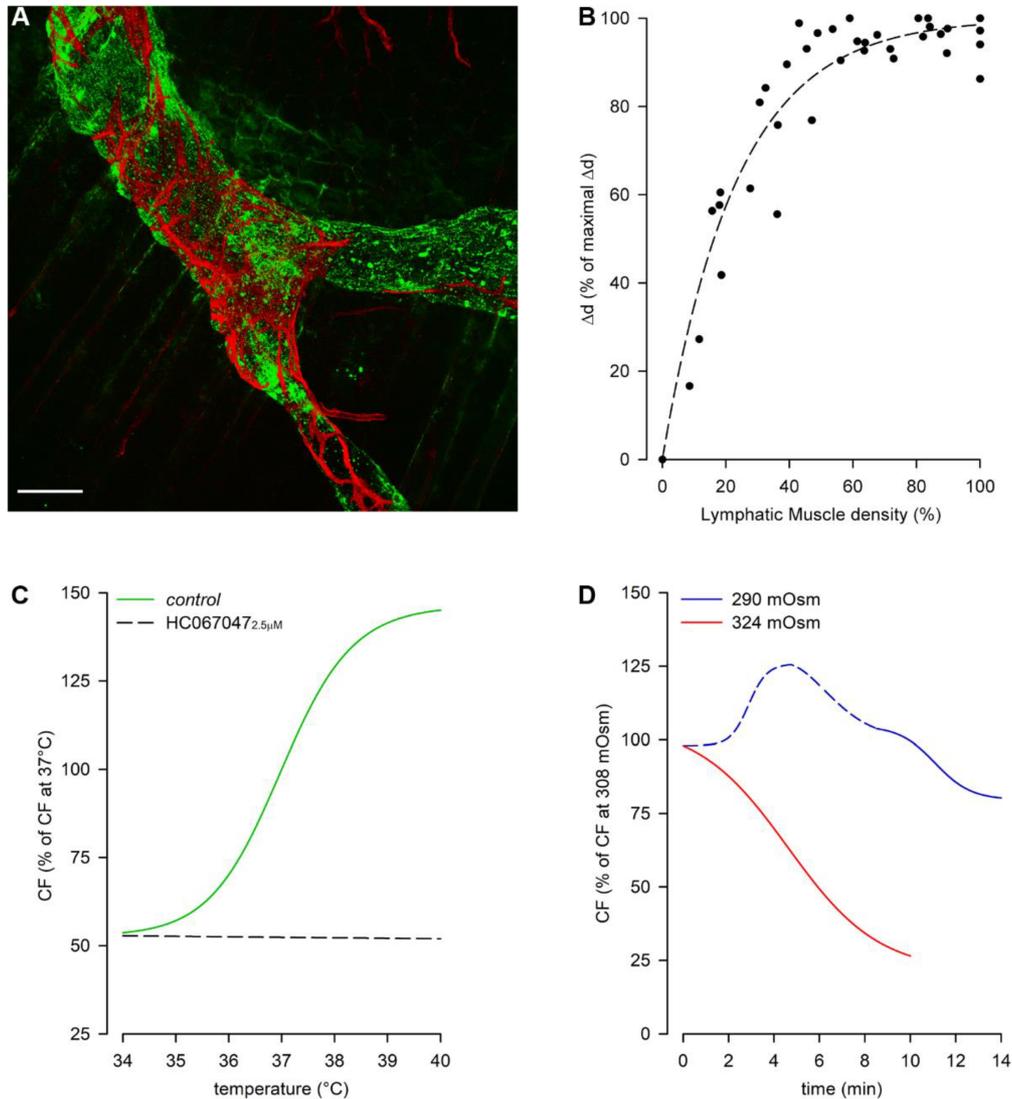


Figure 2. Rat pleural diaphragmatic lymphatics (A) Confocal image of a lymphatic vessel *in vivo* stained with FITC-dextrans (green signal) and whole mount stained for LMCs (red signal), highlighting the organization of the lymphatic muscle mesh surrounding the vessel (scalebar 100 μm). (B) Plot of intrinsic Δd correlating to the lymphatic muscle density in the vessels' wall. (C) Plot of the dependence of intrinsic CF from temperature in the range 34–40 °C (green trace), which is completely abolished by the selective TRPV4 channels antagonist HC067047 (black dashed line). (D) Plot of osmolarity-induced modulation of intrinsic CF: the hyperosmolar environment (red trace) induces a sigmoidal decrease in CF, whereas hyposmolarity induces an acute early CF increase (blue dashed line) followed by a later decrease (blue solid line).

Spontaneous LMCs contractions seem to allow lymph recirculation into peripheral lymphatic loops, thus preventing fluid accumulation which may result in the development of oedema. They can be modulated by tissue temperature,

as lymphatics rapidly adjust CF to temperature changes in the physiological range 35–39 °C (**Figure 2**, panel C, green trace), as it can occur during circadian oscillations of temperature, in case of fever or during physical exercise. In rat diaphragmatic lymphatics raising temperatures exert an increase in CF (positive chronotropic effect), while simultaneously reduce Δd (negative inotropic effect). However, as the chronotropic effect prevails, raising the temperature rapidly increases lymph flow^{[39][40]}. Diaphragmatic lymphatics lay in the thermal core at 37 °C, and sense changes in temperature via the TRPV4 (Transient Receptor Potential channel Vanilloid 4) thermal sensor^[41], blocked by its specific antagonist HC067047^[42], giving rise to a temperature-insensitive behavior (**Figure 2**, panel C, black dashed line). Conversely, specifically activating TRPV4 receptors through GSK1016790A^[43] results in a behavior mirroring the response to increasing temperature. Changes in the surrounding osmolarity give rise to a more complex pattern^[44]. When rat diaphragmatic lymphatics are exposed to a hyperosmotic environment up to 324 mOsm (**Figure 2**, panel D) CF decreases in an osmotic-dependent manner, which seems to represent a tissue fluid-saving mechanism. On the other hand, the exposure to a hyposmotic interstitial fluid at 290 mOsm exerts a biphasic behavior, displaying an early transient CF increase (**Figure 2**, panel D, blue dashed line), which probably responds to the necessity of removing a greater fluid volume filtered. However, later CF decreases attaining an osmolarity-independent steady plateau (**Figure 2**, panel D, blue solid line). As in both hyper- and hypo-osmotic environments no inotropic effects can be found, changes in lymph flow are qualitatively similar to the ones in CF^[44].

The coexistence of both intrinsic and extrinsic mechanisms driving lymph dynamics makes the diaphragm a very intriguing model to study the mechanisms of lymphatic functionality. Indeed, in most tissues lymph formation and propulsion mainly relies on extrinsic forces as it occurs in highly moving tissues such as other skeletal muscles, lungs and the heart^{[8][45][46][47]}. Conversely, in lymphatics immersed in soft tissues, almost completely devoid of tissue displacement, the lymphatic draining capability totally depends upon intrinsic contractility.

4. Pleural Intercostal Lymphatics

The pleural cavity is covered by parietal and visceral mesothelial pleura, which respectively overlay the internal intercostal respiratory muscles and the lungs. Parietal pleural lymphatics of the intercostal spaces open directly in the pleural cavity, thus forming a direct funnel to the draining lymphatic system^[48]. Those vessels might share some of the features of the diaphragmatic vessels, especially those related with the extrinsic forces sustaining lymph formation and propulsion. Larger lymphatic vessels lay parallel and in proximity with the ribs and/or sternum offering a suitable site for hydraulic pressures measurement^[49]. During spontaneous breathing the simultaneous recording of P_L and P_{in} in rats' intercostal vessels shows a variability of both, related to the phase of the respiratory cycle^[50]. P_L and P_{in} reach their lowest values at the end of the inspiratory phase (about -28.5 and -16.5 cmH₂O respectively), with P_L remaining subatmospheric and below P_{in} most of the times. This, in turn, results in a ΔP_{TM} favoring lymph formation in most vessels during the whole respiratory cycle, with an apparent prevailing role of tissue displacement over the respiratory rate to drive lymph draining. However, in a small fraction of the intercostal vessels ΔP_{TM} favors lymph propulsion for the entire respiratory cycle, whereas for some vessels their behavior changes from formation to propulsion in the transition between inspiration and expiration. Therefore, the

spontaneous respiratory activity maximizes lymph formation while preserving lymph progression along the lymphatic network, being both mechanisms essential for pleural liquid volume homeostasis

The situation completely changes during controlled mechanical ventilation, even by setting respiratory parameters equal to spontaneous breathing. P_{in} and P_L values increase with increasing lung volume, reaching their maximal value at end-inspiration (about 38 cmH₂O for both) and, most notably, P_L becomes positive. The difference between P_L and tissue P_{in} diminishes throughout the whole respiratory cycle, almost nullifying ΔP_{TM} , with a severe impact on both lymph formation and propulsion. The analysis in the frequency domain of the various components of P_{in} , P_L and ΔP_{TM} reveals that in spontaneous breathing all of them are dominated by the respiratory rate. Conversely, during mechanical ventilation the relative power of the respiratory-driven frequency component of ΔP_{TM} is greatly reduced and becomes almost as low as the one of the cardiogenic oscillations in pressure^[50].

Overall, in the transition from spontaneous breathing to mechanical ventilation, both draining and propulsive functions of costal lymphatics are severely depressed, leaving only the lesser functional cardiogenic activity to sustain a very limited lymph fluid removal from the pleural space. Thus, lymph formation is severely attenuated during mechanical ventilation, being P_{liq} subatmospheric, increasing the hydration state both of pleural space and lung tissues. This phenomenon alone might therefore partially explain mild- to moderate oedematous conditions and difficulties in breathing often evident in patients which undergo prolonged periods of mechanical ventilation at positive alveolar air pressures.

5. Lymphatic Vessels of Lungs

The lymphatic system draining the lungs can be divided into lymphatics serving the upper airways, the tracheobronchial tree, and the lung parenchyma. Pulmonary lymphatics are organized into pleural vessels, located in close contact with the lung parenchyma, and interlobular or intralobular lymphatics of the loose connective tissue. The latter include bronchovascular, perivascular, peribronchiolar and interalveolar lymphatic vessels^{[51][52][53][54]}. Lymphatic clearance routes change with lung height, as in the upper regions lymph formation prevails in bronchovascular lymphatics, whereas in the lower ones it is predominant in subpleural/septal zones^[55]. Overall, lymph clearance is greater in lymphatics located in lower than in upper regions of the lung^[56]. In humans, the lymphatic system begins to develop between the 6th and 7th week of pregnancy, whereas in mice it appears around embryonic day 10 (E10.0). During embryogenesis the expression of VEGFC (Vascular endothelial growth factor C)^[57] and VEGFR3 (Vascular endothelial growth factor receptor 3)^[58] is involved in pulmonary lymphatics formation, critical for lung development. Indeed, mice lacking lymphatic vessels die at birth due to respiratory failure, despite a normally developed lung parenchyma and a proper amount of surfactant. However, the wet/dry ratio indicates the development of pulmonary oedema, significantly reducing the compliance of lung parenchyma and thickening the interstitium. As a result, mice are unable to inflate lungs at birth^[59]. Moreover, mice lacking the $\alpha 9$ integrin appear normal at birth, but they develop late-onset respiratory distress and die between 6–12 days after birth due to pleural fluid effusion and liquid accumulation^[60].

The difficulty to stain the lymphatic vessels but not the surrounding interstitial and/or alveolar spaces is still a technical limit that jeopardizes every attempt to *in situ* measure P_L in the intact pleural cavity. Nevertheless, measures of pulmonary P_{in} have been performed with the intact pleural space, showing a very negative environment, with pressures ranging from about -13.5 cmH₂O at end-expiration to $-20/-27$ cmH₂O at end inspiration, during spontaneous breathing^{[61][62]}. These extreme negative hydraulic pressures are a prerequisite to maintain a very thin and dry alveolar interstitial space, optimizing the gas exchange. Moreover, the pulmonary interstitial space possesses a so-called “safety factor”^[63], due to a very stiff extracellular matrix, forcing P_{in} to rapidly increase above zero when liquid accumulates in the interalveolar spaces. In addition, a greater interstitial fluid volume induces anchoring filaments to stretch, thus exerting a radial tension on the lymphatic capillaries’ wall which opens primary valves increasing lymph formation^[6]. Pulmonary lymphatic vessels contribute to the proper lung extracellular matrix organization by maintaining hyaluronan (HA) homeostasis removing the excess of HA fragments through the LYVE1 receptor (Lymphatic Vessel Endothelial Hyaluronan Receptor 1)^[64]. Water binds to HA increasing P_{in} favoring fluid clearance by lymphatic vessels^[65]. Lung oedema may develop due to an increase in fluid filtration across blood capillaries exceeding the lymphatic transport capacity. The wet/dry ratio increases up to values that cannot be compensated by lymphatic reabsorption, which seem to be correlated to large matrix fragmentation which damages the lung parenchyma and air-blood barrier. Indeed, the glycosaminoglycans degradation to low molecular weight fragments, especially HA and chondroitin-sulphate, impact the lung interstitial scaffold dramatically decreasing the effectiveness of the “safety factor”^{[65][66]}. Similar effects are also related to the stress/strain of different ventilatory strategies. In rat, positive end-expiratory pressure (PEEP) combined with mechanical ventilation at high tidal volume (V_T) display damaging effects on the lung parenchyma, due to tissue overdistension. Furthermore, injurious effects of mechanical ventilation are exacerbated by oedemagenic conditions. On the contrary, combining low V_T mechanical ventilation to PEEP results to be protective toward lung parenchyma fragmentation^[66]. Moreover, PEEP would increase P_{in} , thus favoring lymph formation and oedema reduction.

The few P_L measurements from lung lymphatic vessels cannot allow but to speculate on their physiological properties and role in fluid drainage from lung interstitial space. From what has been observed both in the diaphragmatic and parietal lymphatics, it could be argued that during inspiration the stretch experienced by lung parenchyma could be transmitted to lymphatic vessels, being the extrinsic mechanism pivotal for pulmonary lymphatic function as lung collecting vessels lack LMCs^[67]. This, in turn, might cause a more negative P_L , which is the prerequisite to drain lymph from a very subatmospheric lung P_{in} . Recently developed transgenic animal models could potentially be useful tools to close the gap in this field of lymphatic physiology^{[68][69][70]}.

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