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Cardiopulmonary Consequences of Post Thoracic Surgery Pulmonary Hypertension: Cause or Consequence of Lung Edema?

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Abstract

The major complication of post-thoracic surgery is a severe disturbance of lung extravascular water that is the main cause of morbidity and mortality and therefore still represents an unmet medical challenge. Accordingly, the need to devise novel therapies ought to go through a more thorough understanding of the pathophysiological mechanisms. This review presents an updated description of the time evolution of this process providing the pathophysiological reason for its explosive development. Despite various names ("idiopathic edema", acute lung injury -ALI, atelectasis, ARDS), a common patho-physiological pathway can be traced for respiratory dysfunction in post-operative thoracic surgery. We will present the evidence for the loss of control on the volume of extravascular lung water from the new perspective of the derangement and disorganization of interstitial proteoglycans, a family of link molecules controlling microvascular permeability and mechanical stability of the extravascular matrix. We analyze in detail specific conditions of lung water disturbance pertaining to cardiac surgery, lung transplant and lung resection surgery. In particular, we will discuss the functional link between lung edema formation and increase in pulmonary vascular resistances, and wish to develop the concept that pulmonary hypertension and right ventricle overload ought to be regarded as the consequence of a decrease in vascular bed reflecting microvessels compression in the edematous tissue both in the acute phase as well as in the fibro-proliferative repair process.

Keywords: Lung edema; Matrix proteoglycans; Cardiac surgery; Lung transplant; Lung resection; Right ventricle overload; Pulmonary hypertension

Introduction

Cardiac and lung pathology are strictly related as they impact reciprocally on the respective organ function. Severe complications of post-thoracic surgery are acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) referred on clinical basis as primary respiratory dysfunction. These pathologies, being commonly interpreted as the inflammation induced injury on the vascular endothelium and alveolar epithelium, still represent an unmet medical challenge. Thus, the need to devise novel therapies ought to go through a more thorough understanding of the pathophysiological mechanisms. In this article we will specifically consider the cardiopulmonary consequences of post-thoracic surgery from the new perspective of the disorganization/fragmentation of the lung extracellular matrix as an important cofactor causing the severe alteration of lung fluid balance.

The Control of Fluid Balance in the Lung

It might be useful to briefly summarize how the air-blood barrier (0.2-0.3 microns in thickness, (Figure 1A) retains a minimum amount of extravascular water that optimizes gas diffusion [1]. This condition is assured (Figure 1B) by the combined action of a powerful lymphatic drainage and a very low permeability of the capillary endothelium [2]. As a resultant of these two features, the pressure of the water phase in the extravascular compartment is kept sub-atmospheric (~ -10 cmH_2O) and microvascular filtration is as low as $1 \cdot 10^{-4}$ ml/cm^2 in 24h.

The volume of the lung extravascular water is strictly controlled so that the lung appears quite resistant to the development of edema, despite being exposed by nature to conditions causing an increase in microvascular filtration such as capillary recruitment when cardiac output increases.

At least three mechanisms cooperate to strongly limit an increase in extravascular water volume [2]. First, the glycosaminoglycan chains of proteoglycans, an important non-fibrillar component of the extracellular matrix, are highly hydrophilic and can bind excess water to form gel-like structures; this result in an increase in the steric hindrance of proteoglycans leading to a decrease in the porosity, particularly at the level of the basement membrane, thus maintaining microvascular permeability low. Second, the extracellular matrix is very rigid (low compliance) thanks to the assembly of large matrix proteoglycans [3]: this determines that, as shown in (Figure 2), a minor increase in extravascular water in response to increased microvascular filtration (a condition defined on physiopathological basis as interstitial edema), causes a marked increase in interstitial pressure (e.g., from ~ -10 to ~ 5 cmH_2O, so called "tissue safety factor") [2] that, in turn, buffers further filtration. Third, arteriolar vasoconstriction is triggered in lung regions where edema is developing so as to limit capillary filtration [4,5].

Pathophysiology of Lung Edema

The development of severe edema is known as a tumultuous event taking place in minutes [3]. Experimental models in animals allowed to attribute the sudden increase in extravascular lung water [3] to the loss of the "tissue safety factor" (Figure 3A) due to the loss of integrity of the proteoglycan components of the macromolecular structure of the lung extravascular space (Figure 3B). Fragmentation/degradation of these link proteins lead to an increase in matrix compliance and

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microvascular permeability. The loss of integrity of proteoglycans results from the combined action of several factors: the sustained increase in parenchymal stresses, the weakening of the non-covalent bonds of the matrix proteoglycans due to increased water binding, the activation of tissue metalloproteinases [3], the action of reactive oxygen species (ROS).In all forms of lung edema, a severe condition develops when the loss of integrity of the interstitial matrix proceeds beyond a critical threshold. Interestingly, a difference was observed among edema models in the time sequence of fragmentation for various proteoglycans families. Large matrix proteoglycans are first degraded in the cardiogenic model, while in the lesional model, proteoglycans of the basement membrane are first degraded. In hypoxia, both proteoglycans families are involved [3].

The increase in microvascular permeability is due to the formation of paracellular gaps (pore size 50-100 nm) that allow easy leak of albumin. Finding of red blood cells in the alveolar fluid reflects major lesions of the air blood barrier. Gapsare the consequence of the change in shape of endothelial and epithelial cells resulting from the balance of contractile centripetal forces opposed to tethering forces due to adhesive cell-cell and cell-matrix interaction. Both set of competing forces influence cytoskeleton remodeling and contraction, disruption of cell junctions and formation of paracellular gaps. Pro-inflammatory

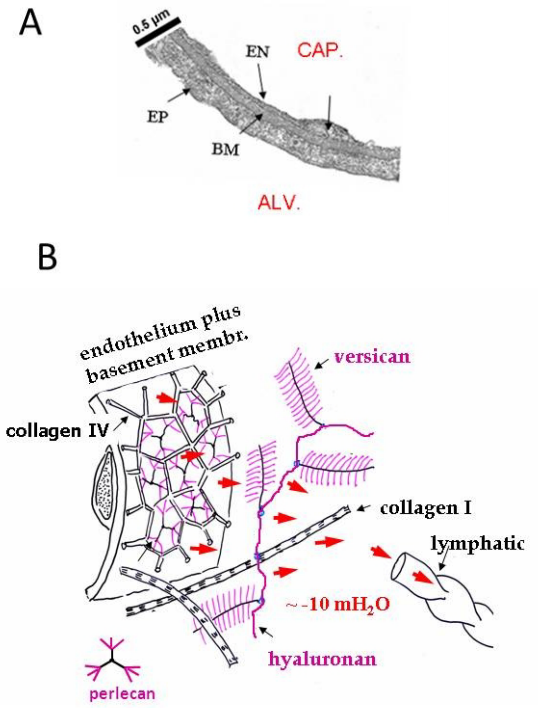

Figure 1: Mechanical and fluid dynamic equilibrium at the level of the air-blood barrier (ABB).

A: Transmission electron microscopy image of the ABB to show the extreme thinness of the endothelial and epithelial cells and intervening interstitial basement membrane (EN, EP and BM, respectively).

B: the lymphatic pump sets a sub-atmospheric pulmonary interstitial pressure that, in turn, entrains a minimalmicrovascular filtration owing to the low permeability of the capillary endothelium. In black laminar (collagen IV) and fibrillar (collagen I) components of the macromolecular interstitial matrix; in pink the family of proteoglicans link proteins controlling endothelial permeability (perlecan) and mechanical stability of the extracellular matrix (hyaluronan and versican).

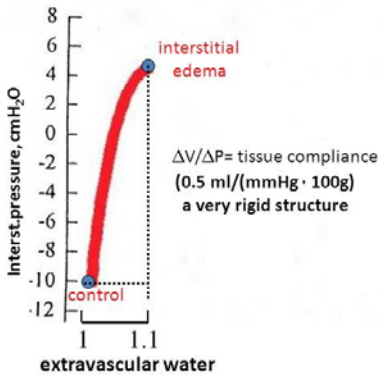

Figure 2: The mechanical factor responsible for the control of lung extravascular water volume. Owing to the low compliance of the macromolecular interstitial matrix, an increase in microvascular filtration results in a marked increase in interstitial pressure for a minor (not exceeding 10%) increase in extravascular water volume: this mechanical condition (defined as interstitial edema) opposes further filtration.

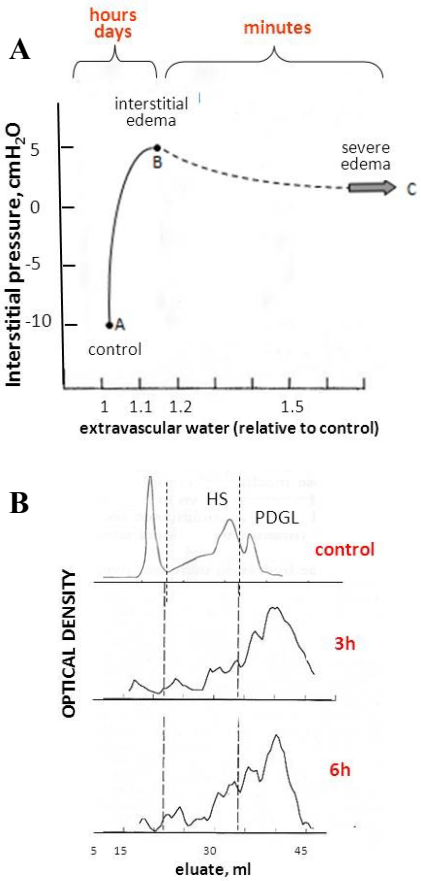

Figure 3: The mechanisms of acute development of severe edema. A: the lung strongly resists to severe edema as long as interstitial pressure opposes microvascular filtration (interstitial edema). Severe edema develops in minutes when interstitial pressure drops to zero. B: the decrease in interstitial pressure reflects the disassembly of the proteoglycan component of the extracellular matrix as shown by separating the families of proteoglycans by gel filtration chromatography. The peaks corresponding to the highest Molecular Weight (MW)(chondoritinsulphate, CS, MW> 0.5 KDa) and intermediate MWof the basement membrane (heparansulphate, HS, 0.5KDa>MW>0.1KDa) are progressively disappearing with time. The corresponding increase of the peak of small MW proteoglycans reflects the accumulation of fragments from higher MW proteoglycans.

cytokines TNF-α, IL-6, thrombin, histamine, TNF-alpha, IL-8, and IL-1 are all increased [6,7]. In a model of pulmonary endothelial cells subject to cyclic stretch, thrombin also activates the GTPase Rho protein that affects actin cytoskeletal assembly [7,8]. Downstream of Rho activation there is the increase in myosin light chain phosphorylation, stress fiber formation and cytoskeletal contraction, depending on the intracellular calcium concentration [9].The mechanism by which mechanical signals are transduced to the intracellular environment is still unclear but may involve the glycocalyx, a meshwork of glycoproteins and glycolipids polymers on cell surface. In particular, the syndecanheparan sulfate proteoglycan may function as mechanical sensor as it fulfills the requirements of a mechano-electrical transducer [10]. The shear stress provides the energy for the proteoglycan conformational changes resulting in mechano-transduction that leads to activation of the stretch-activated cation channels TRPV4 (11,12)whose inward current depolarizes the cell membrane, thus simultaneously enhancing the Ca^{2+} permeability. Ca^{2+} ions flowing into the cell induces intracellular Ca^{2+}-store release and the overall rise in the intracellular calcium concentration activates key signaling pathways that mediate cytoskeletal reorganization (through myosin-light-chain-dependent contraction) and the disassembly of the junctions that ultimately results in an increase in barrier permeability.

The Reparative Process

Interstitial edema represents a sharp edge between tissue repair and severe disease. Lung cellular activation for matrix remodelling was shown to be characterized by differential expression of signalling-transduction platforms on plasma membrane of lung cells [13-18] and the hypothesis was put forward for corresponding differential activations of these platforms (lipid rafts or caveolae) to trigger re-deposition of specific matrix components. Lung edema characteristically shows a patchy distribution, revealing regional differences in the efficiency of control of extravascular water volume. These differences have been recently documented in a hypoxic edema model [5] and the hypothesis suggested was that alterations in the geometry of the microvascular-alveolar design might favor a perturbation in local interstitial fluid dynamics. Lack of clearance of the fragments, neutrophil and macrophage activation [19], production of ROS, leading to diffuse alveolar damage and inhibition of the active alveolar fluid reabsorption [20] hinder the reparative process. The initiation and progression of lung fibrosis is determined at least in part by how lung cells interact with the surrounding extracellular matrix microenvironment. Epithelial cells and fibroblasts (or myofibroblasts) contribute to the deposition of a provisional matrix at sites of injury and the balance in the activity of metallo-proteinases (MMP-2 and 9) and corresponding TIMP is critical in this phase [21].In particular, the increased MMP-9 activity was found to contribute tore-deposition of a rigid matrix, a critical point to allow reabsorption of edema fluid [22,23]. Excessive deposition of interstitial matrix leads to fibrosis, a fibro-proliferative disorder representing a major cause of morbidity and mortality. Rapid recovery of the epithelial barrier and proteolysis of provisional matrix are likely to limit fibro-proliferation. Immune response has been considered a focal point to discuss a fibro-proliferative disease, yet this interpretation does not hold when immune-suppressive therapy has no benefit. There are data indicating that fibrotic fibroblasts manifest pathological control of pathways governing proliferation and matrix deposition. It remains still to be clarified how exogenous signals from matrix, cytokines, chemokines, and growth factors induce such an altered response [24]. The histological pattern of idiopathic pulmonary fibrosis is a patchy distribution of fibro-proliferative process sparing some respiratory units but affecting others nearby, reflecting a similar distribution of edema due to increased microvascular permeability: it appears then tempting to put forward the hypothesis that a chronic condition of high permeability barrier may underlie the fibro-proliferative process [5].

Specific Conditions Pertaining to Thoracic Surgery as Potential Causes of Perturbation in Extravascular Lung Water

Lung edema is a severe complication of post-thoracic surgery, and represents the major cause of morbidity. Despite various names ("idiopathic edema", ALI, atelectasis, ARDS), a similar patho-physiological pathway can be traced based on acute increase in microvascular filtration and fragmentation of the proteoglycan component of the interstitial matrix, thus, simply, edema formation [3].

Cardiac Surgery

Pulmonary complications are referred after coronary artery bypass graft with cardiopulmonary bypass, even in the absence of previous pulmonary diseases [25] and furthermore, cardiopulmonary bypass doubles the risk of postoperative hypoxemia [26]. These complications range from subclinical level to acute lung injury with respiratory distress syndrome and lung atelectasis is considered a major cause of the disease [27,28]. In fact, lung collapse occurs early during surgical intervention and lasts for several days. It is also reported that the degree of post-operative hypoxemia correlates with increased duration of mechanical ventilation [29].

Leukocyte depletion does not lead to decreased mortality or better clinical outcomes [30], supporting the contention that re-deposition of a mature interstitial matrix is a key factor for repair.

Suggestions to reduce the adverse effect of cardiopulmonary bypass [30] include:

a) abolition of this practice or reducing its duration

b) decrease the extracorporeal-circuit surface area (use of miniaturized-circuits)

c) have heparin-coated circuit-surfaces

d) maintain pulmonary perfusion to prevent ischemia-reperfusion

e) use anti-inflammatory "lung-protective" drugs

f) adopt blood ultrafiltration to scavenge pro-inflammatory factors

g) reduce cardiotomy suction

h) protection against myocardial ischemia- reperfusion.

Lung Transplant

Lung transplantation is life-saving for patients with end-stage lung diseases. The transplanted lung is deprived of lymphatic whose regeneration might require about 3 weeks [31]. Primary graft dysfunction is a complication of lung transplantation that affects an estimated 10 to 25% of lung transplants developing in the first 72 h with a marked systemic inflammatory response leading to an acute lung injury [32]. Primary graft dysfunction is the leading cause of early post-transplantation morbidity and mortality. Thirty-day mortality rates are up to eightfold higher in patients with severe primary graft dysfunction. In addition, patients who survive to 12 months after severe primary graft dysfunction have significantly impaired working capacity and an increased risk of bronchiolitis obliterans syndrome [33-36].

Ischemia-reperfusion is a considered the main pathogenic factor

of primary graft dysfunction resulting in progressive deterioration of lung structure and function extending up to 3 months after reperfusion. Patients surviving the acute phase may either recover or enter a 'chronic'fibro-proliferative state. In an experimental model, the short and long-term lung modification induced by ischemia-reperfusion resembles those found in both primary graft dysfunction and ARDS observed after lung transplantation [37]. The disturbance is due to an increase in microvascular permeability, production of metallo-proteinase (MMP) causing a major derangement of the interstitial matrix, surfactant conversion, decreased lung compliance and increased pulmonary artery pressure. Lung edema appears critically related to the loss of integrity of the extracellular matrix assuring a "tissue safety factor" against microvascular filtration. All these responses as well as lung histology showing a considerable decrease in air/tissue volume ratio, cell hyperplasia and disturbed angio-prolipheration, are similar to focallung alterations described as mal-adaptation in experimental model of chronic hypoxia [5].

Lung conservation and reperfusion techniques must prevent ischemia-reperfusion injury [38].

The preservation of lung architecture during conservation has been considered an important cofactor against ischemia-reperfusion injury, accordingly, re-establishment of optimal lung geometry has been recommended by maintaining lungs inflated during preservation on the account that changes in alveolar architecture caused by atelectasis expose the lungs to inhomogeneous parenchymal and shear stress distribution that may favor an increase in microvascular permeability on reperfusion [39]. Another important indication comes from the observation that transplantation of lungs fromdonors without heartbeat or brain-dead donors preserved with normothermic ex vivo perfusion for 4 hours allow to improve the clinical outcome [40].

The degree of severity of primarygraft dysfunction represents a significant independent risk factor for the development of bronchiolitis obliterans syndrome characterized by a marked systemic inflammatory response [41,42].

Brochiolitis obliterans is considered an exuberant and disordered repair process with an increased activity of MMP-9 [43].

The incidence of primary graft dysfunction relative to the underlying diagnoses has been reported as follows: emphysema 61%, idiopathic pulmonary fibrosis 73%, cystic fibrosis 57%, primary pulmonary hypertension 55%; furthermore, the use of cardiopulmonary bypass during pulmonary re-implantation has been associated with increased incidence and severity of primary graft dysfunction [44].

Lung Resection Surgery

Lung edema represents the major cause of morbidity after lung resection surgery (different definitions of the clinical conditions are referred asidiopathic edema, ALI, ARDS).

Evacuation of air/liquid from the cavity is the most immediate problem after lung resection surgery to allow re-expansion of the remaining lung [45]. Lung over-distension represents the main cause of lung edema as stretching of lung parenchyma due to over inflation results in a marked sub-atmospheric interstitial pressure that, in turn, favors matrix/endothelial lesions and increase in microvascular filtration [3]. As to the strategy of post-operative lung re-expansion, it is important to remark that the compliance ($\Delta V/\Delta P$) of the remaining part of the lung is decreased in proportion to the amount of resected lung. For example, if 50% of the lung has been removed, the compliance of the remaining lung is halved: therefore, re-expansion of the remaining lung to fully match the original chest volume would require setting a pleural pressure much more sub-atmospheric than the pre-operative on eat the expense also of an incredible deformation of the remaining lung. In practice, an air bubble ought to remain in the pleural cavity on chest closure. Overdistension is prevented by setting a post-operative pleural pressure (lung recoil pressure) equal to the preoperative one. As shown in Figure 4, pleural pressure would obviously differ on comparing emphysema to fibrosis: it is noteworthy that emphysematous lungs are more exposed to post-operative air leak and edema [45,46].

Other co-factors leading to edema formation are:

- prolonged mechanical ventilation with excessive tidal volume
- over perfusion of the remaining lung resulting in capillary recruitment, greater flow velocity and endothelial shear [47];
- postoperative local hypoxia[48,49];
- fragmentation of extracellular matrix [3];
- lack of clearance of the matrix fragments, neutrophil and macrophageactivation [50];
- production of ROS,diffuse alveolar damage, and inhibition of the activealveolar fluid reabsorption [51];

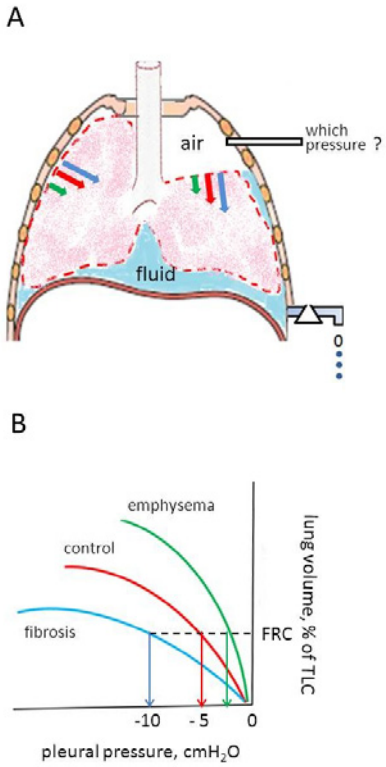

Figure 4: The strategy to re-expand the lung after lung resection surgery. A:forcing the remaining lung against the chest wall after lung resection surgery, obviously implies deformation and over-distension. To avoid this, an air bubble has to remain in the thorax and the pressure in the bubble should be equal to the pre-operative pleural pressure. B:pleural pressure can only be assessed by determining the volume-pressure curve of the lung before operation. The figure highlights the differences in pleural pressure according to the condition of the lung (lung recoil pressure, indicated by the different colors).

- large amounts of intraoperative fluid administration [52,53], particularly when coupled to increased microvascular permeability, as clearly shown by experimental models of lung edema [3].

It is important to bear in mind that the suction pressure of the draining tube should only serve to help in reaching a new mechanical and fluid dynamic equilibrium at pleural level. The gas occupying the volume left free by the resected portion will be reabsorbed following a diffusion/solubility kinetics in the blood (faster for CO_2) and will be replaced by a combined contribution of partial overdistension of the remaining lung, pleural fluid and displacement of the mediastinum and diaphragm. As much as in physiological conditions, the absorption pressure of the pleural lymphatic will determine the final 'postoperative residual pleural space', that will result from a modified chest wall-lung mechanical coupling.

Pulmonary Hypertension, Pulmonary Wedge Pressure and Right Ventricle Overload

Pulmonary hypertension represents an overload for the right ventricle that remains a major problem in the long-term follow-up, leading to impairment of patient working capacity, arrhythmia, and premature death. The degree of tolerance of the cardiovascular system to right ventricular overload is still controversial. Pulmonary hypertension is common to all conditions of severe lung edema and it is well known that the increase in pulmonary artery pressure is proportional to the degree and extension of lung edema. The question is then why edema leads to an increase in pulmonary vascular resistances. This point was recently clarified by a study relating the patency of microvessels to the peri-microvascular interstitial pressure in edematous lung regions [5]. The data clearly showed that in edematous lung regions the density of capillaries was markedly reduced (Figure 5A), and this was attributed to a decrease in capillary patency due to the remarkable increase in peri-microvascular interstitial tissue pressure (Pi) above capillary pressure (Pc) (Figure 5B). The decrease in patency of collapsible tubes exposed to increased surrounding pressure, referred to as "Starling resistor", has been described for pulmonary vessels [54] but overlooked over the years due to lack of knowledge of perivascular interstitial pressure values. Furthermore, a Starling resistor effect has been invoked as a potential cause of decrease in microvascular bed in lung edema [55]. The knowledge of peri-microvascular interstitial pressure in frankly edematous tissue, now available [5], provides strength to the hypothesis that a decrease in vascular bed is an important cofactor causing pulmonary hypertension in lung edema. Based on this, a comment is due on the significance of the measurement of pulmonary wedge pressure in lung edema. This technique allows to measure vascular pressure downstream of a wedged pulmonary catheter: since blood flow is stopped, one assumes the wedge pressure to equilibrate with the downstream capillary pressure. Yet, as capillaries are collapsible tubes, the pressure values measured by this technique might actually reflect peri-microvascular interstitial, rather than capillary vascular pressure. It sounds than reasonable that the entity of pulmonary hypertension reflects the severity and extension of lung edema.

A further interesting finding of the study by Rivolta et al. [5] was that precapillary vasoconstriction was demonstrated in regions where the edema process has developed, thus diverting blood flow towards lung regions that retained good diffusion properties. Post lung resection surgery is an obvious further cause of decrease in vascular bed.

Pulmonary artery-left atrium shunt has been proposed and preferred to an inter-atrial shunt to moderate or even partially reverse the adverse effects of acute right ventricle pressure overload [56]. Finally, atrial fibrillation is common after lung transplantation despite the absence of graft rejection and cardiac dysfunction [57].

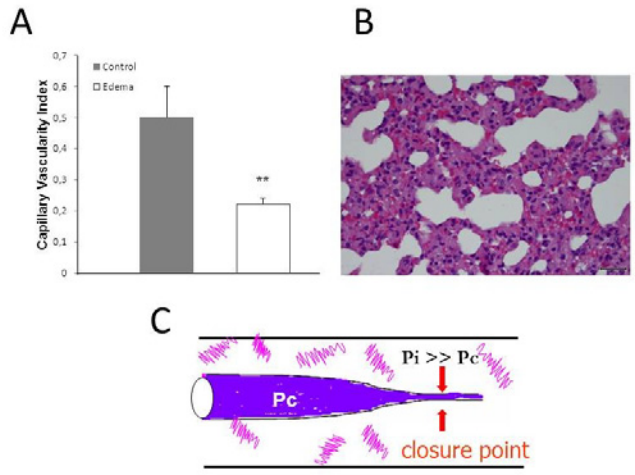

Figure 5: The decrease in vascular bed in severe lung edema. A: decrease in capillary perfusion index in edematous lung regions. B: histology of lung edema. C: modeling the decrease in the capillary patency when peri-microvascular interstitial pressure is remarkably increasedin severe edema (Starling resistor effect).

Pericardial and Lung Compression Due to Lung Edema

This syndrome [58] deals with the remarkable volume increase of the lung when severe edema develops. This obviously correlates with the transformation of an aerated into a solid tissue structure and, at interstitial tissue level, it also relates with a shift from a sub-atmospheric to a highly positive interstitial pressure [5]. Delayed chest closure has been proposed after bilateral lung transplantation when significant bleeding/coagulopathy has occurred [59].

For single lung transplant, lung compression of the transplanted lung has been invoked [60]. This syndrome is erroneously advocated as compression as it likely reflects the fact that the recoil of the transplanted lung is higher than that of the native emphysematous lung. Since the lungs are placed mechanically in parallel, this results in: a) decrease in volume of the transplanted lung, b) over-distension of the native lung and c) displacement of mediastinum towards the transplanted lung. Lung volume reduction surgery for the native lung was suggested: its over-distension to adapt to chest volume would obviously increase its elastic recoil. Equalizing the elastic recoil of the two lungs would re-expand the transplanted lung.

Summary

Primary respiratory dysfunctions due to alterations in lung fluid balance after thoracic surgery still represent a challenging medical problem. This paper traces a common pathophysiological basis for various forms of disturbance in lung fluid balance (idiopathic lung edema, acute lung injury, acute respiratory distress syndrome, atelectasis) from the new perspective of the mechanical derangement of the architecture of the extracellular matrix. Emphasis is put on the fragmentation of matrix proteoglycans causing a loss of elastic response of the matrix and increase in tissue pressure that represents the main mechanism opposing fluid filtration. Another consequence

of proteoglycans derangement is the increase in microvascular permeability. Leukocyte depletion, use of anti-inflammatory drugs and the scavenge of pro-inflammatory factors do not lead to better clinical output, thus proving the importance of a mechanical component as a pathophysiological factor leading to a severe alteration in lung fluid balance. Conditions causing matrix fragmentation are actually shared by the inflammatory response and include hypoxia exposure (triggering activation of metalloproteinases) and ischemia reperfusion injury. In addition, matrix fragmentation is favored by lung over-distension (potentially occurring after lung resection surgery) or inhomogeneous lung expansion (as after cardio-pulmonary by-pass or lung transplant). In frankly edematous lung regions interstitial pressure may increase to the point of squeezing microvessels thus causing a decrease in vascular bed. The entity of this phenomenon reflects the extension of the edema process and may represents an important cofactor inducing pulmonary hypertension and right heart overload. Remodeling of the matrix structure is considered a key factor in the recovery process.

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