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Perioperative Pulmonary Atelectasis – Part I: Biology and Mechanisms

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Abstract

Pulmonary atelectasis is common in the perioperative period. Physiologically, it is produced when collapsing forces derived from positive pleural pressure and surface tension overcome expanding forces from alveolar pressure and parenchymal tethering. Atelectasis impairs blood oxygenation and reduces lung compliance. It is increasingly recognized that it can also induce local tissue biological responses, such as inflammation, local immune dysfunction, and damage of the alveolar-capillary barrier, with potential loss of lung fluid clearance, increased lung protein permeability and susceptibility to infection, factors that can initiate or exaggerate lung injury. Mechanical ventilation of a heterogeneously-aerated lung (*e.g.*, in the presence of atelectatic lung tissue) involves biomechanical processes that may precipitate further lung damage: concentration of mechanical forces, propagation of gas-liquid interfaces, and remote overdistension. Knowledge of such pathophysiological mechanisms of atelectasis and their consequences in the healthy and diseased lung should guide optimal clinical management.

Introduction

The term atelectasis derives from the Greek words *atelez* meaning “imperfect”, and *ektasiz,* “expansion”. Pulmonary atelectasis, thus, refers to the incomplete expansion of alveoli and terminal bronchioles. In its paradigmatic form, atelectasis is represented by complete deaeration of lung units. Atelectasis is pervasive in anesthesia practice, and already in 1963 Bendixen *et al.* demonstrated that general anesthesia with mechanical ventilation resulted in deterioration of intraoperative oxygenation and compliance in patients with normal preoperative lung function.[1] Brismar *et al.* subsequently demonstrated that such deterioration was associated with pulmonary densities revealed by computed tomography.[2] Besides physiological impairment, pulmonary atelectasis could contribute to perioperative lung injury.[3] The clinical presentation of significant atelectasis in surgical patients is variable

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from no sequalae to prolonged oxygen requirement to hypoxemia requiring endotracheal intubation and ventilation to even acute respiratory distress syndrome (ARDS). This article focuses on the perioperative period and aims to review the etiology of pulmonary atelectasis and provide a pathophysiological discussion including biological as well as biomechanical processes.

Physiological principles of bronchiolar and alveolar expansion

Bronchioles and alveoli walls are composed of cells and extracellular matrix, and covered by a liquid film on their luminal side containing surfactant. Each of these elements are exposed to expanding and collapsing forces.

Stresses acting on bronchioles and alveolar walls

Normal stress is the force per unit of area (A) perpendicular to the surface where the force is exerted. Three main components of the normal stresses acting on bronchioles and alveolar walls determine their expansion (Fig. 1)[4]: fluid pressure, tethering stress and surface tension. A conceptual note on the physical meaning of these mechanical components is that, while related, they are not equivalent as pressure is a scalar (a physical quantity having only magnitude) while stress is a vector (a physical quantity with direction and magnitude).

1. *Fluid pressure*: represents the pressure applied by fluids (gas or liquid) to the surface of the alveolar or bronchiolar wall. The net result of the fluid pressures derives from the difference of inside (P_i) and outside (P_o) pressures, expressed by the formulation of transmural pressure:

$$Transmural\ pressure\ =\ Inside\ pressure\ (Pi) -\ Outside\ pressure\ (Po)$$

2. *Tethering stress:* represents radial stresses due to attachments of bronchioles and alveolar walls to adjacent structures through the tissue matrix. The radial tethering stress is mechanically transmitted to alveoli, bronchioles and pleural surface through a network of collagen and elastin fibers composing the extracellular matrix in the pulmonary septa. These fibers are the force-bearing elements. The parenchymal cells themselves (epithelial and endothelial cells) have a lower mechanical contribution. Preserved lung interstitial architecture, thus, ensures the transmission of the tethering stress inside the lung parenchyma.[5] The net effect of those stresses applied inside (F_i/A) and outside (F_o/A) the bronchioles or alveolar walls can be expressed as (Fig. 1):

$$Net\ tethering\ stress = \left(\frac{\sum \mathrm{Fo}}{\mathrm{A}}\right) - \left(\frac{\sum \mathrm{Fi}}{\mathrm{A}}\right)$$

3. *Surface Tension:* represents the inward-acting radial stress arising from the circumferential components of forces applied by the thin layer of fluid lining the bronchioloalveolar walls resulting from the effect of the surface tension (T). For a spherical structure with radius R (alveoli), the Young-Laplace pressure equation expresses the relationship between the pressure difference across the fluid interface (P_w) and the surface tension as:

$$Pw = \frac{2T}{R}$$

For a cylindrical structure of radius R (bronchioles), the relationship is:

$$Pw = \frac{T}{R}$$

Accordingly, the pressure difference across the fluid interface becomes substantial for small *R*. The surface tension is likely more important in the cylindric bronchioles than in alveoli, which are not strictly spherical.[6] Pulmonary surfactant, a lipoprotein complex secreted by type II alveolar epithelial cells, is a critical biomechanical stabilizer to bronchioles and alveoli expansion.[7] Its presence at the air-liquid interface strongly reduces surface tension, decreasing the magnitude of this collapsing contribution.

The balance of these forces and pressures allow for quantitative relationships in specific conditions (Fig. 1):

- In equilibrium, the balance of the expanding and collapsing radial stresses acting on bronchioles or alveolar walls should be zero[4]:

$$(Pi - Po) + \left(\frac{\sum Fo}{A} - \frac{\sum Fi}{A}\right) - Pw = 0$$

- No external tissue attachments are present at the pleural surface. Consequently, F_o=0 and transmural pressure is determined by P_i (=alveolar pressure, P_{alv}) and P_o (=pleural pressure, P_{pl}). Radial stresses corresponding to the sum of inward-acting tissue and surface forces are balanced by the transmural pressure (P_{alv}-P_{pl}) acting on the pleural surface area (A_{pl}). As the radius of the pleural surface curvature is large, the effect of surface tension is negligible (Pw ≈0). Accordingly, the balance of forces at the pleural surface is:

$$(Palv - Ppl) = \frac{\sum Fi}{Apl}$$

- Within the lung, if all airways are patent, pressures on the two sides of alveolar walls (*i.e.,* P_i and P_o) equal the same alveolar pressure (P_{alv}). Therefore, transmural pressure between adjacent alveoli is null, and the outward-acting tethering force (F_o) counteracts inward-acting tissue and surface forces:

$$\frac{\sum Fo}{A} = \frac{\sum Fi}{A} + Pw$$

The elastic recoil of the lung

Lung elastic recoil represents the propensity of lung tissue to shrink and is the main physiological mechanism of passive exhalation. It results from the combined effects of: (1) extracellular matrix elastic fibers *(contributing to F_i);* and (2) bronchioloalveolar surface

tension.[4,7] Accordingly, degradation of the elastic fibers in the extracellular matrix, as during emphysema, reduces elastic recoil, thus, reducing the expiratory capacity and acting against alveolar collapse.[8] Conversely, diseases leading to quantitative or qualitative surfactant impairment increase surface tension and facilitate alveolar collapse.[7]

The interdependent lung expansion

Pulmonary interdependence represents the interplay of mechanical forces amongst lung tissue components – alveolar units, airways, vasculature, and extracellular matrix. For instance, interdependence during lung expansion transmits tethering stress to traction airway walls outwards.[5,9–11] Interdependence relies on normal lung architecture, including the extracellular matrix fibers.[12] In a homogeneous lung, outward tethering stresses ($\Sigma F_o/A_{pl}$) are transmitted from the visceral pleura surface to the innermost lung regions. These stresses are determined by the elastic recoil pressure of the lung $P_{el}(L)$,[13] equal to the transmural pressure at the pleural surface:

$$Pel\left(L\right) = \left(Palv - Ppl\right) = \frac{\sum Fo}{Apl}$$

A positive $P_{el}(L)$, transmitted to the inner lung through interdependence, is the primary determinant of lung expansion. During awake spontaneous breathing, P_{pl} is negative throughout the pleural space leading to a positive $P_{el}(L)$ as P_{alv}=0 (=atmospheric pressure). In contrast, $P_{el}(L) \leq 0$ is associated with unphysiological conditions resulting in lung collapse such as open-chest or general anesthesia with mechanical ventilation.

The transpulmonary pressure (P_L) has been advanced as a surrogate of the elastic recoil pressure of the lung when the alveolar pressure (P_{alv}) can be approximated by the pressure at the airway opening (P_{ao}). This occurs when respiratory flows are zero (usually at end-expiration and end-inspiration) and no gas trapping exists:[13]

$$P_L = Pao - Ppl$$

Hence, a positive transpulmonary pressure throughout the respiratory cycle is required to maintain alveolar expansion.

Mechanisms of atelectasis in the perioperative period

General anesthesia, mechanical ventilation and surgical interventions produce several biophysical factors promoting lung tissue collapse (Fig. 2). Three major interrelated collapsing factors influence the balance of forces discussed above and contribute to perioperative atelectasis: increased pleural pressure, low alveolar pressure and surfactant impairment. As a result of these factors, continuous or intermittent airway and alveolar closure occur, presumably more commonly the first than the latter.[14,15]

Increased pleural pressure

Pleural pressure is the pressure within the pleural cavity. It varies regionally across the pleural space depending on anatomical and physiological interactions between the lung

parenchyma, chest wall and gravity.[16] General anesthesia affects such interactions increasing regional pleural pressure (*e.g.*, dorso-caudal in supine patients), resulting in negative transpulmonary pressure and compressive atelectasis (Fig. 2).

Functional changes of the diaphragm and additional chest wall components

The chest wall can be understood as composed by two functional portions: an elastic portion represented by the rib cage and abdominal wall and a constant weight component exerting a hydrostatic pressure represented by the abdomen. Changes in these portions will affect pleural pressure and lung expansion in the perioperative period, in line with the previously discussed equilibration of forces throughout the lung. The diaphragm is the primary muscle of lung ventilation and, consequently, significantly contributes to lung expansion and atelectasis development during anesthesia. E.g., in anesthetized intubated patients without cardiopulmonary disease, phrenic nerve stimulation to produce diaphragm contraction reduces atelectatic area by approximately 33% as compared to mechanical ventilation with equal tidal volumes.[17]

In supine spontaneously breathing humans, diaphragmatic displacement and lung expansion are larger in dependent than nondependent lung regions.[18,19] This is due to the diaphragm dome shape with a smaller dependent radius of curvature, higher dependent stretch producing more favorable dorsal length-tension relationships, and possibly larger number of muscle fibers[20] and higher compliance of the crural than costal diaphragm[18]. Diaphragm tension reduces the transmission of abdominal pressure to the lungs.[21] Reduction or loss of such diaphragmatic tone during anesthesia, thus, affects the net balance of stresses acting on the lungs not only reducing the preferential dependent displacement of the diaphragm but also facilitating the transmission of abdominal pressure to the lungs. This results in a cephalad shift of the dependent diaphragm with dependent lung compression and atelectasis,[22,23] and no change or caudad shift of nondependent regions.[19,23] Relaxation of accessory respiratory muscles such as intercostals, scalenes and sternocleidomastoids further contribute to reduction in cross-section chest area and lung aeration (Fig. 3). In spontaneously breathing normal subjects receiving volatile anesthesia the activity of parasternal muscles is abolished and phasic expiratory activity in abdominal and lateral ribcage muscles enhanced,[24] contributing to caudad dependent atelectasis.[23] Muscle paralysis compounds to the dependent cephalad shift of the diaphragm and atelectasis during general anesthesia[23], as the balance between alveolar pressure and the gravity dependent hydrostatic pressure of abdominal contents becomes the main determinant of diaphragm motion.[19] Ultimately, atelectasis that is preferentially dependent and caudad is detected in 90% of a broad population of patients without cardiopulmonary disease undergoing general anesthesia,[25] with up to 20–25% of initially normal lung either atelectatic or poorly aerated in transverse computed tomography during anesthesia.[26]

Increased abdominal pressure as present with pneumoperitoneum, obesity, abdominal compartment syndrome, peritonitis, or abdominal shift of intrathoracic blood[27,28] produces further imbalance of net stresses on the lung, as it exposes the dorso-caudal lung to higher pleural pressure and susceptibility to atelectasis,[2,29] with cephalad shift of both diaphragm and intra-abdominal organs.[19,23,27] Of note, cephalad-outward movement of the lower ribs

potentially produced by those factors can increase the cross section of the lower chest and partially compensate for the loss of lung volume.[21]

While gravity has been frequently cited as a key determinant of lung expansion, cephalocaudal gradients of lung expansion present in large animals[30] and humans[22,31] indicate the relevance of factors other than gravity. These include the matching of the lung to the thoracic cavity and the partially independent displacement of lobes, which are relevant determinants of regional lung expansion in supine and prone positions beyond gravitational factors.[30,32] Perioperative chest wall reshaping is influenced by body position, with proning allowing for recruitment of dorso-caudal lung.[33]

Postoperative respiratory muscle dysfunction, particularly diaphragm dysfunction, has been documented after abdominal,[34] thoracic,[35] and cardiac surgery.[36] It facilitates the development of atelectasis as demonstrated by the significantly larger fraction of patients with atelectasis 24h after thoracic surgery in the presence of postoperative ultrasound-diagnosed diaphragmatic dysfunction (35%) than in its absence (13%).[35] Diaphragm dysfunction can persist from a day to a week,[37,38] and even a year.[39] It can occur due to direct injury to the diaphragm[36] or phrenic nerve,[40] or to indirect factors such as phrenic nerve dysfunction[37,41] and impaired thoracoabdominal mechanics.[42] These could compound with previous diaphragmatic compromise, *e.g.*, as present in neuromuscular disorders, sepsis,[43] abdominal hernias[44] and potentially obesity.[45] Of note, diaphragmatic function could conversely affect regional lung inflammation by producing local high transpulmonary pressures as shown by the observation that spontaneously breathing lung injured pigs exposed to low positive end-expiratory pressure (PEEP) present more dependent lung inflammation than those receiving high PEEP.[46]

While anesthetics (*e.g.*, isoflurane, sevoflurane and propofol) can compromise diaphragmatic function[47–49] they do not affect contractility.[50] The diaphragmatic electromyographic activity can also be impaired by unwarranted administration of cholinesterase inhibitors, *e.g.*, neostigmine followed by sugammadex in humans[51] or neostigmine administered after full recovery from neuromuscular block in rats[52].

Intrapulmonary gravity gradient

The weight of the non-dependent lung compresses the dependent lung and pleural space determining pleural pressure increases along the vertical axis[11] with transpulmonary pressure reduction in dependent lung regions.[53,54] Pulmonary edema increases the weight of the lung tissues increasing the risk of dependent atelectasis due to the superimposed hydrostatic pressure.[54,55] Body position influences the effect of intrapulmonary compression by modulating the volume of dependent lung. For instance, the triangular shape of the lungs with the large dorsal base results in a greater volume of dependent lung in the supine than in the prone position.[55,56]

Compression by intrathoracic elements

In supine patients, the mediastinal weight, particularly the heart, has been associated with pleural space compression and preferential retrocardiac lung collapse.[57] Pleural effusions may also compress the lung. However, the effusion volume does not entirely translate into

compression[58] due to the compliance of the chest wall. For instance, in ARDS patients, chest wall expansion in the presence of a pleural effusion accommodates ~70% of the effusion volume.[58,59]

Low alveolar pressure

The concept of critical opening pressure has been introduced as the minimal alveolar pressure (P_{alv} in the previously described formulation) required to counteract the regional effect of collapsing forces.[60] Accordingly, lung units are expanded when alveolar pressure is higher than the critical opening pressure. A parallel concept is that of critical closing pressure, *i.e.*, the alveolar pressure below which open lung units collapse. Mean closing pressure has been estimated as 6 cmH_2O in a small number of anesthetized mechanically ventilated patients,[61] an interesting value to compare to the usual initial clinical setting of 5 cmH_2O. As determined experimentally in animal and computational models,[62,63] the critical closing pressure is lower than the critical opening pressure due to lung hysteresis, *i.e.*, the difference between the inspiratory and expiratory components of the pulmonary pressure-volume curve, produced by opening of previously nonaerated peripheral airspaces.[64] Due to the vertical dependence of pleural pressures, critical opening pressures are higher in dependent regions as lung regions exposed to positive pleural pressure require alveolar pressures higher than these pleural pressures to achieve positive transpulmonary pressure and expansion.

The rationale for the use of PEEP derives from such a concept, ultimately aiming to keep alveolar pressures above critical closing pressures at end-exhalation to prevent lung collapse. Local variation in critical opening and closing pressures conditions the regions expanded and kept inflated throughout the breathing cycle at a given PEEP. Even normal lungs, when mechanically ventilated without PEEP for many hours, will progressively lose aeration preferentially in dorsal regions.[65] Of note, lung hysteresis imply that the PEEP required to keep lung regions open is lower than that required to open them (Fig. 4).[66] This provides support to the practice of recruiting the lungs at pressures higher than those used during steady state mechanical ventilation.

Resistance of upstream airways

The transmission of upper airway pressures to distal lung regions, *i.e.*, the proximity between P_{alv} and P_{ao}, depends on the patency of regional airways (Fig. 2). Increased airway resistance, secondary to airway constriction, obstruction, or compression[13] determines a pressure drop in the distal lung with local alveolar pressures potentially lower than tracheal pressures ($P_{alv}<P_{ao}$). *Obstructive atelectasis* is the term used to describe lung collapse resulting from airway obstruction, usually caused by mucous plugs and retention of secretions superimposed or not to airway constriction. Anesthetics dose-dependently compromise ciliary motility of respiratory epithelial cells (isoflurane, ketamine, thiopental) potentially facilitating obstruction, and this compromise seems weaker with sevoflurane,[67] fentanyl or propofol.[68] Mucociliary clearance appears to be more compromised by cuffed endotracheal tubes than laryngeal mask airways.[69]

Balance of alveolar gas exchange

Lung units presenting larger alveolar gas outflow than inflow will ultimately collapse. This is the basic concept of *absorption atelectasis*.[70] Such an imbalance is mostly determined by low local alveolar ventilation-to-perfusion ($\dot{V}_A/\dot{Q}$) ratios and high FIO_2. Low $\dot{V}_A/\dot{Q}$ determines low inflow of fresh air into alveoli in relation to the local perfusion associated with O_2 absorption. The lowest $\dot{V}_A/Q$ ratios are found in the most gravity dependent regions,[71] where intraoperative atelectasis is typically present.[72,73] High FIO_2 facilitates outflow as alveolar gas absorption by capillary blood is higher with O_2 than with gases presenting lower blood:gas solubility as nitrogen.[74–77] Lower mixed venous oxygen content further increases the rate of oxygen absorption (Fig. 2).

Surfactant impairment

Several factors during general anesthesia could impair surfactant function and contribute to the development of atelectasis: inflammatory response, mechanical ventilation, high oxygen concentration, anesthetics, and pulmonary edema. While these factors produce minimal compromise in short uncomplicated cases, they could become relevant as the surgical insult and patient compromise increase.

Inflammatory lung injury resulting from endotoxemia and bacteremia lead to reduced production of surfactant phospholipids,[78] increased surfactant turnover,[79] decreased tubular myelin[80] and altered surfactant protein A gene expression.[81] Inflammation with surfactant dysfunction is also present during severe respiratory failure and pneumonia.[82] This dysfunction can be mediated by inflammatory cytokines,[83] proteases secreted from immune cells,[84] and increased proteins in alveoli.[85] In line with these findings, *in vivo* lung neutrophilic inflammation developing within few hours of mechanical ventilation in poorly-aerated areas was reported in association with surfactant dysfunction[86], with inflammation worsened by endotoxemia.[87] The translational relevance of such data is suggested by the quantitative and qualitative surfactant impairment observed in surgeries associated with large systemic and pulmonary inflammatory response (*e.g.*, on-pump cardiac surgery) or lung injury.[88,89]

Mechanical ventilation impairs surfactant production by type II alveolar cells [90,91] through alveolar overstretching[92], under-stretching[93] and monotonic stretching[94]. Conversely, deep breaths[95] and biologically variable ventilation[96] increase the release of active surfactant. Short-term exposure to high oxygen concentrations (100%) adversely affects surfactant function by increasing its susceptibility to rupture.[97] Suggestion that inhaled anesthetics could compromise surfactant biosynthesis in time- and dose-dependent patterns comes to date essentially from *in vitro* studies and is rapidly reversible after discontinuation.[98] Pulmonary edema, *e.g.*, from fluid overload, can change surfactant activity and increase surface tension, potentially by the loss of surfactant into the edema fluid.[99] For permeability pulmonary edema, surfactant function can be inactivated by proteins in alveoli secondary to barrier disruption,[82,100] via increasing its conversion to non-surface-active forms.[85]

Pathophysiological effects of pulmonary atelectasis

Global Physiological Effects

Respiratory mechanics and lung volumes: Functional residual capacity is reduced in the supine position, and further by general anesthesia and muscle paralysis. Such decrease is associated with loss of muscle tone, and related reduction of the cross-sectional area of the thorax[23], cephalad displacement of the diaphragm,[19] increased curvature of the vertebral column,[24] and increased intrathoracic blood volume.[22] Of note, change in diaphragm displacement, thorax cross-section or functional residual capacity during general anesthesia were found not to correlate to the magnitude of atelectasis[22,23] suggesting the relevance of other factors for ultimate lung collapse, such as intrathoracic blood volume and decreased volume of the aerated lung.

Atelectasis is associated with lower respiratory system and lung compliances. This is because closure of alveoli and small airways corresponds to the low-volume portion of the pressure-volume curve associated with smaller change in lung volumes in relation to applied pressures, *i.e.*, low compliance (Fig. 4).[101,102] Indeed, in mechanically-ventilated dogs, the respiratory system compliance is linearly related to lung volume.[103] Alveolar and airway closure is affected by supine position and may be further influenced by obesity (Fig. 5).[104] Higher driving pressures ($P_{plateau}$-PEEP = tidal volume/respiratory system compliance) consequently also ensue.[105] End-expiratory lung volumes can be lower than closing capacity during mechanical ventilation likely due to loss of radial traction from parenchymal interdependence.[10,106] The same mechanism may contribute to the increased lung and respiratory system resistance associated with atelectasis in obese patients.[107] Of note, once atelectasis settles, the lung pressure-volume curve also becomes abnormal, further compounding the loss of lung volume.

Gas exchange: The most clinically evident pathophysiological effect of pulmonary atelectasis is hypoxemia.[1,102] Impaired blood oxygenation has been described during routine general anesthesia with both controlled[108] and spontaneous ventilation,[109] and correlated with the degree of atelectasis.[22,110] The mechanisms are low $\dot{V}_A/\dot{Q}$ ratios and intrapulmonary right-to-left shunt.[109,111] In experimental and clinical studies, alveolar recruitment promptly reverses gas exchange dysfunction.[1,101,112] Chronic obstructive pulmonary disease patients are less susceptible to oxygen absorption atelectasis[113] and may develop less atelectasis during mechanical ventilation after cardiopulmonary bypass,[114] presumably due to a combination of loss of elastic recoil and high airway resistance.

Hypoxic pulmonary vasoconstriction: Hypoxic pulmonary vasoconstriction is a reflex constriction particularly of distal pulmonary arteries but also venules in response to hypoxia.[115,116] Oxygen sensing occurs at the alveolo-capillary level,[117] with endothelial cell depolarization and retrograde propagation of the signal via gap junctions to upstream arterioles, where it is transmitted to pulmonary arterial smooth muscle cells to produce vasoconstriction.[117] In health, the onset of the reflex to hypoxic gas mixtures occurs within seconds, and progresses into a plateau period (phase 1) of at least 20 min, and then a further rise (phase 2) starting after ~43 min and reaching a peak at ~2 h.[118] This pattern is consistent with the response times to atelectasis observed in a dog model.[119]

Hypoxic pulmonary vasoconstriction mitigates right-to-left shunt diverting blood away from poorly oxygenated lung areas, thus, supporting adequate arterial oxygenation during general anesthesia.[120,121] The more effective the hypoxic pulmonary vasoconstriction, the lower the effect of atelectasis on right-to-left shunt and consequent hypoxemia. In normal humans, 47% of blood flow is diverted from a hypoxemic lobe within 5 min.[121] Factors that impair hypoxic pulmonary vasoconstriction accentuate hypoxemia produced by atelectasis: pneumonia,[122] ARDS,[123] endotoxemia,[124] sepsis,[125] calcium channel blockers,[126] atelectatic size,[127] or volatile agents (isoflurane, sevoflurane, desflurane) above 1 minimum alveolar concentration.[128–130] Mechanical factors associated with atelectasis could also impair hypoxic vasoconstriction, *e.g.*, unstable alveoli in the collapsed large animal lung could stent open pulmonary corner vessels through outward radial traction, reducing the hypoxic constriction.[131] Intravenous anesthetics present a discrete to nonexistent effect on hypoxic vasoconstriction, as no blunting has been found with propofol,[132] ketamine,[133] or fentanyl,[134] while others found even oxygenation improvement with propofol.[133,135] During general anesthesia, the significant correlation between shunt and atelectatic area calculated from computed tomography in patients without significant lung disease indicates that hypoxic pulmonary vasoconstriction is not complete and contributes to hypoxemia even in normal lungs.[110] In disease conditions, a strong correlation between shunt and atelectatic volume suggests more compromised hypoxic pulmonary vasoconstriction such as observed after mitral valve surgery when compared to coronary artery bypass graft surgery.[136]

In normal humans, increases in mean pulmonary artery pressure of ~10 mmHg are observed due to hypoxic vasoconstriction with arterial oxygen saturation (Sao_2) changes from >95% to 85–90% and of ~16mmHg with Sao_2=75–80%, corresponding to a duplication and more of the pulmonary vascular resistance.[137] In severe cases, right ventricular dysfunction can ensue as a consequence of the afterload elevation during atelectasis.[138,139] Accordingly, alveolar recruitment reduces pulmonary vascular resistance and increases pulmonary blood flow in patients after cardiopulmonary bypass[140] and in dogs with healthy or injured lungs,[141,142] subsequently improving right ventricular function.

Regional molecular and cellular response—Molecular (*e.g.*, cytokine, chemokine and pathways) and cellular (*e.g.*, alveolar endothelial, epithelial and inflammatory) changes during atelectasis imply significant local biological responses and allow for insights into the mechanisms of lung injury. Atelectasis-associated lung injury could relate to direct or indirect, independent or synergistic local biological effects such as inflammation, structural damage, hypoxic injury, surfactant dysfunction, and susceptibility to infection (Fig. 6).

Inflammatory response: Links between atelectasis and inflammation have been indicated by clinical and experimental studies. Indeed, normal lungs exposed to 16 hours of atelectasis and mechanical ventilation with low tidal volumes presented metabolic changes suggestive of incipient inflammation in large animals with aeration heterogeneity comparable to that of humans.[65] The hallmarks of atelectasis-related inflammatory response include the presence of cytokines and immune cells, and their functional alteration (Table 1).

Cytokine response: Atelectasis is often associated with local production of inflammatory cytokines. Multiple clinical studies of one-lung ventilation[143–145] have reported increased levels of pro-inflammatory cytokines in the atelectatic lung, such as interleukin (IL)-1, IL-6, IL-8 and tumor necrosis factor (TNF)-a, all involved in inflammatory injury. These cytokine levels were directly related to the duration of atelectasis[144,145] and potentially increase the susceptibility to postoperative pulmonary complications in patients undergoing lung resection surgery.[143] Moreover, atelectasis could result in significant concentrations of chemotactic cytokines, including chemokine (C-X-C motif) ligand (CXCL)-1,[146] a potent neutrophil chemoattractant; platelet-activating factor,[147] a mediator of platelet aggregation and degranulation, and leukocyte chemotaxis; and keratinocyte-derived chemokine,[148] another immune cell chemoattractant particularly for neutrophils. As a result, cytokines increased in atelectatic areas may cause direct injury, and additionally act as homing molecules recruiting cells (*e.g.*, neutrophils) into these regions that could further magnify damage, *e.g.*, by releasing injurious cytokines.

Inflammatory cell response: Atelectasis contributes to inflammatory cell infiltration, at least in part through the inflammatory cytokines described above. For example, neutrophils, key immune cells in the inflammatory response and tissue damage, are increased in bronchoalveolar lavage fluid of atelectatic regions in mechanically ventilated patients or spontaneously breathing dogs when compared to fluid obtained before atelectasis.[147,149,150] Those inflammatory infiltrates related to atelectasis duration[150] and were further magnified by systemic endotoxemia.[151] Additionally, atelectasis by itself can alter cellular immune function, *e.g.*, enhance alveolar macrophage cytokine secretion in rats,[152] impair macrophage phagocytosis against bacteria *in vitro* in piglets,[153] and reduce local bronchoalveolar lymphocyte function in dogs.[149]

Current evidence reinforces the concept that atelectasis produces inflammatory response with pathophysiological mechanisms different from those occurring in aerated lung regions. Indeed, different transcriptomic patterns in immunity have been documented recently in the atelectatic versus ventilated sheep lung, with less NF-κB-related genes in sterile lungs and higher interferon stimulated genes in the presence of systemic endotoxemia.[154] Such regional differences have also been found in a one-lung ventilation rat model showing increased myeloperoxidase, a neutrophil marker, in atelectasis and CCL2, a macrophage chemoattractant, in aerated lung regions.[146] Accordingly, findings reporting the similarity of inflammatory injury between atelectatic and ventilated lung either in humans[143,145,155] or in animals[146,156] may actually derive from different underlying cytokine and genomics responses in aerated and atelectatic areas. Understanding such regional responses to atelectasis could help to identify potential treatments beyond the usual ventilatory interventions. For example, nanoparticle delivery of microRNAs (*i.e.*, miR-146a) mitigated mouse lung injury during mechanical ventilation.[157]

Structural dysfunction—Pulmonary structure disruption is a hallmark of lung injury. Immobility (lack of cyclic stretch) associated with atelectasis could contribute to structural damage potentially by disorganization of actin networks,[158] loss of adherens junction,[159] and impairment of barrier properties.[160,161] A recent sheep study also provided genomic

support to these findings by revealing in initially healthy atelectatic lungs dysfunction of the lung tissue transcriptome related to structural components: endothelium, epithelium, and actin cytoskeleton.[154]

Other factors potentially present during atelectasis such as inflammation and ischemia can also lead to structural dysfunction, *i.e.*, impairment of sodium and chloride channels (*i.e.*, ENaCα),[162] an ATP dependent process involved in alveolar fluid clearance; and injury of the endothelial glycocalyx layer,[163] a critical component for lung barrier homeostasis. Re-expansion of atelectatic lung, a common process after one-lung ventilation, could be another contributing factor to structural damage due to oxidative stress and inflammation.[164,165] Increased capillary transmural pressure from reversal of hypoxic pulmonary vasoconstriction following re-expansion and decreased pulmonary vascular resistance could mechanically injure the basement membrane of the alveolar–capillary lining.[166]

Yes-associated protein 1 (YAP) signaling is a key pathway in the control of cell proliferation, apoptosis and fate,[167] and related to regulation of actin cytoskeleton dynamics[168] and alveolar epithelium repair and regeneration.[169] YAP signaling has been reported to be less activated in static pulmonary epithelial cells[170] and in atelectatic lung than in normally-ventilated lung.[154] Together these experimental studies suggest the potential role of YAP signaling and its possible use as a treatment target in structural dysfunction during atelectasis.

In line with those findings, microvascular endothelial disruption has been documented in atelectatic rat lung.[138] Such structural compromise could lead to lung edema,[156] microvascular protein leakage,[147,171] and even bacterial translocation to the blood stream,[172] suggesting an additional mechanism contributing to increased lung permeability and decompartmentalization of the lung inflammatory response, increasing the risk for multiorgan dysfunction.[173] Potential therapies for structural dysfunction, *e.g.*, β2 agonists directed at accelerating fluid clearance attempted in an acute lung injury trial (ALTA), are examples of treatment targets derived from basic knowledge,[174] which illustrate the relevance of advancing the area.

Ultraprotective ventilation (limiting stress and strain with limited tidal volume and pressure) during extracorporeal membrane oxygenation (ECMO) for respiratory failure[175–177] is a recently discussed strategy in which the biological effects of static and dynamic stretch may be relevant. The expected advantages of “lung rest” could benefit from barrier (*e.g.,* epithelial and endothelial cells) protective effects of low cyclic stretch,[178,179] and yet conflict with the damaging effects of lung immobility as well as the injurious effects of large static stretch on alveolar epithelial cells and extracellular matrix.[180,181] A recent trial (LIFEGARDS) reported no association of mechanical ventilation settings during the first two days of ECMO with survival of patients with severe lung injury.[182] A possible explanation is that the severity of the inflammatory response in these patients is so high that the ventilatory intervention would not be able to generate a biological response. Thus, optimal ventilatory settings and length of their application for best lung recovery strategies in ECMO patients, including the best balance between immobility and cyclic load, remains an open question.

Hypoxic injury: Lung collapse results in local hypoxia, a potent inducer of lung inflammation[183] and microvascular injury.[184] Attenuating hypoxia or eliminating atelectasis by lung recruitment reverses lung injury induced by alveolar hypoxia.[171] Experimental data suggest that such hypoxia-related lung injury may be associated with NF-κB-dependent CXCL1 secretion from lung epithelial cells;[146] macrophage recruitment and activation;[183] decreased expression of lung neprilysin (a neutral endopeptidase);[184] and excess reactive oxygen and nitrogen species (superoxide anion radical $O_2^{\bullet-}$ and nitric oxide $NO^{\bullet}$).[185]

The hypoxia activated transcription factor hypoxia-inducible factor (HIF)-1 could be another important regulator in atelectatic tissue associated both with pro- and anti-inflammatory mechanisms.[186] HIF-1α is increased and activated in nonventilated atelectatic rat lungs,[146] with distinct cellular effects. In myeloid cells, HIF-1α promotes acute inflammatory response through the regulation of glycolytic capacity.[187] In endothelial cells, HIF-1α reduces mitochondrial respiratory capacity and activates vascular inflammation by promoting glycolysis.[188,189] In contrast, in lung epithelial cells, HIF-1 contributes to anti-inflammation[146] and barrier protection.[190]

Surfactant dysfunction: While surfactant dysfunction produces atelectasis as discussed above, conversely, atelectasis can lead to surfactant dysfunction. Classic studies reported that surfactant compression beyond 50% of its initial area, as potentially present during atelectasis, could result in film rupture on re-expansion and loss of function,[191,192] in line with increased surface forces associated with low PEEP (*i.e.*, deaerated lung) during i*n vitro* ventilation.[193] High surface forces in the alveoli causes transudation of proteinaceous fluid from capillaries into alveoli further contributing to surfactant dysfunction.[194] Such dysfunction following atelectasis has been reinforced by clinical data from patients without cardiopulmonary disease showing that surfactant phospholipids in bronchoalveolar lavage of atelectatic regions were lower after onset of atelectasis, and remained low even after its resolution.[147]

Atelectasis-related pneumonia: Pneumonia is a major postoperative pulmonary complication. Its incidence has been reported as 1.8% in ASA 3 patients undergoing non-cardiothoracic predominantly abdominal and pelvic surgery,[195] 3.5% following cardiac surgery,[196] and up to 25% after major lung resection.[197]

Atelectasis has been often suggested as associated with pneumonia. The biological compromise of the atelectatic lung immune defenses could facilitate the development of pneumonia, as detailed in the *Inflammatory response* section above. Local depletion and dysfunction of surfactant secondary to significant atelectasis or following pulmonary edema could further compromise the anti-infectious response as surfactant possesses antimicrobial properties[198] and enhances macrophage phagocytosis and bacterial clearance.[199] Additionally, mucus plugging or impaired mucus clearance following long periods of atelectasis can increase the risk of infection by compromising mucociliary clearance against organisms entering the lung and trapping them within collapsed regions.[200,201]

Experimental studies support that atelectasis was associated with larger bacterial growth and pneumonia when bacteria were present or instilled into collapsed lungs.[172,200,201] Similarly, mechanical ventilation settings facilitating atelectasis (PEEP=0 cmH_2O) increased lung bacterial burden in rabbits following tracheal bacterial instillation when compared with spontaneously breathing controls.[202] Also, following the systemic intravenous injection of bacteria, the susceptibility to bacterial infection of atelectatic regions was greater than that of aerated regions.[200] Of note, such effects of atelectasis might not be present when collapsed lung tissue is not exposed to any infectious agent, as atelectasis did not increase the incidence of pneumonia in dogs with non-infected lungs in a historical study.[200]

Clinical evidence has been more conflicting than such experimental studies. A large trial during major abdominal surgery indicated the high incidence of atelectasis and pneumonia in patients with ventilation settings predisposing to atelectasis (PEEP=0 cmH_2O).[3] However, the specific role of atelectasis or even an association could not be determined as large tidal volumes were combined with PEEP=0 cmH_2O, and subsequent trials comparing high vs low PEEP in patients at different risk for alveolar collapse in similar settings did not show an effect of PEEP on postoperative pneumonia.[203,204] A potential explanation for those findings could be that the short-lasting intraoperative reduction of intraoperative atelectasis might not be enough for a longer lasting effect in preventing infections through the first 5–7 days following surgery. Indeed, use of interventions addressing not only intra- but also immediate postoperative lung expansion resulted in less postoperative atelectasis and infectious complications in patients receiving lung expansion suggesting a clinical effect.[205] Such hypothesis generating clinical results together with the basic science and translational findings suggest that interventions to at least minimize atelectasis could be relevant, and require further investigation.

Regional mechanical injury

Lung tissues are continuously subjected to different mechanical forces associated with lung inflation during spontaneous and mechanical ventilation, as discussed above (section “Physiological principles of bronchiolar and alveolar expansion”). During atelectasis, lung mechanical forces contributing significantly to lung injury might be ascribed to different biomechanical processes, including cyclic opening and closing, stress concentration, and over-distension of the non-atelectatic lung (Fig. 7).

Cyclic opening and closing—Cyclic opening and closing of lung units (*i.e.,* bronchioles and alveoli), presumably resulting from the unfavorable balance of forces acting on airways and alveoli, is a frequently cited but still incompletely understood mechanism for lung injury associated with atelectasis. Different processes potentially present during repeated opening and closing have been studied to explain the resulting injury, such as cyclic airway and/or alveolar reopening, the propagation of air-liquid interfaces with production of injurious longitudinal gradients of pressure, as well as shear stress.

Airways and/or alveoli reopening: Histological injury in lungs ventilated with PEEP below the inflection point of the pressure-volume curve (Fig. 4), representative of PEEP insufficient to maintain lung units open,[206] lead to the concept of mechanical trauma due to

cyclic opening and closing. The critical opening pressure of an airway depends directly on airway fluid surface tension (γ) and inversely on airway radius (R) ($P_{crit}=8.3\gamma/R$).[207] Such relationship suggests a distribution of opening pressures along the airway tree with higher critical pressures and presumably injury from tidal recruitment at smaller airways.

Airway closure has been documented *in vivo* by computed tomography imaging in injured experimental lung models.[208,209] Cyclic opening and closing of airways results in bronchiolar injury as reported in animal models ventilated with zero[210] or negative end-expiratory pressure.[211] In addition, repetitive alveolar collapse and expansion, directly visualized in surfactant-deactivated lung using *in vivo* microscope,[212] produces histologic injury with thickened alveolar walls, significant intra-alveolar edema, and numerous neutrophils.[212,213] Experiments document significant regional ventilation heterogeneity in poorly aerated regions in healthy lungs comparable to those of humans compatible with intermittent airway closure and reversible with PEEP.[214] The extent to which cyclic opening and closing occurs in human lungs and contributes to injury remains to be defined.

Surface forces during propagation of gas-liquid interfaces: Surface forces can importantly contribute to epithelial injury during ventilation of atelectatic regions and associated opening-closing of airways and alveoli.[215,216] Secretions, surfactant dysfunction, and alveolar edema affect the fluid lining the airway and can lead to the formation of liquid plugs or liquid bridges in the airway lumen in association with lung collapse. Mechanical or spontaneous ventilation of such airways and underlying alveoli produces the propagation of these gas-liquid interfaces, *i.e.*, movement of the liquid plugs/bridges by the incoming air (Fig. 7). The mechanical forces acting on the epithelium lining of airways and alveoli resulting from this movement have been advanced as a key mechanism of cell injury in mechanical ventilation of atelectatic regions.[215,216] The relevance of this mechanism has been experimentally supported in large tidal volume ventilation of normal rat lungs by observation of more wounded epithelial cells when gas-liquid interfaces were present (partial lung instillation of normal saline) than when lungs were either exclusively overdistended or completely saline-filled (*i.e.*, no gas-liquid interface).[217]

Cellular injury produced by propagation of gas-liquid interfaces include cell detachment and necrosis,[218] cell membrane fracture,[219] impairment of cell-cell adhesion[220] and deterioration of cytoskeletal structure[221]. Such damage increase with reduced airway compliance[222] and diameter.[218] The rupture of liquid plugs can also lead to epithelial cell injury due to fluid mechanical stresses in the vicinity and downstream of plug rupture[216] with associated inflammatory response.[223] Different mechanical forces generated during interface propagation and acting on the epithelial cells lining opening airways include pressure and pressure gradients, shear stress and shear stress gradients (Fig. 7), *the pressure gradient* likely being the primary determinant of mechanical damage.[215,224]

Surfactant treatment reduces the mechanical stress imparted by the propagation of gas-liquid interfaces.[225] This is consistent with its success in neonatal use.[226] In adults, failure of surfactant trials may have resulted from inadequate surfactant delivery to the distal airways and alveoli due to low instilled dose volume.[227]

Shear stress: Shear stress is defined as the force divided by the area parallel to the applied force (Fig. 7). Cyclic opening and closing of the small airways or alveolar ducts could generate shear stress, acting on the collapsed and surrounding lung.[215,218] While frequently mentioned as a common cause of injury during repeated opening and closing, no studies directly assessed shear stress *in vivo*. During the propagation of gas-liquid interfaces *in vitro*, shear stress at the air bubble cap was estimated as far greater than that in the regions upstream or downstream of the bubble tip.[215] However, theoretical investigations as detailed above suggested that shear stress is less important than the longitudinal pressure gradient in producing cell injury.[215,224]

Stress concentration—Atelectasis-related mechanical injury can also be produced by "stress concentration", first proposed by Mead *et al*.[4] It is due to the distribution of mechanical forces in the three-dimensional lung structure around a region whose initially surrounding area is reduced by atelectasis. Stress concentration occurs in normal regions at the interface between open and closed lung, which are thus exposed to exaggerated stress (*e.g.*, tethering stress described in physiology section) during ventilation (Fig. 7).[228,229]

This mechanism could explain the injury observed around the atelectatic lung tissues, as presented in an *ex vivo* isolated, perfused rat lung model.[230] Acting as a stress concentrator, atelectasis can generate structural alveolar injury and inflammation in the surrounding lung tissue.[231] Even microatelectasis can lead to histological epithelial injury due to stress concentration as reported in a bleomycin injured rat lung when ventilated with low PEEP and large tidal volume for 3h.[232] In addition, such stress concentration around atelectasis helps explain the clinical phenomenon of increased local neutrophilic activation at the interface between inflated and non-inflated tissue in patients detected by positron emission tomography.[233]

Remote injury-tidal overdistension—Atelectasis leads to loss of aerated lung volume with redistribution of tidal lung volume during ventilation to the remaining smaller aerated lung (Fig. 7).[151] Thus, regional strain increases in such ventilated areas, with susceptibility to hyperinflation detectable by computed tomography.[234–236] This hyperinflation of aerated regions could promote higher lung inflammation than atelectasis at comparable low tidal volume and lower driving pressure.[237] Consistent with these considerations, experimental findings in a rat lavage model of dependent atelectasis showed the coexistence of dependent atelectasis and remote nondependent lung injury characterized by distal airway injury and increased alveolar epithelial mRNA expression of inflammatory cytokines (*e.g.,* IL-6, IL-1 and MIP2).[238] Also, in initially healthy sheep with lung size and heterogeneity comparable to that of humans receiving protective ventilation in the presence of mild systemic inflammation progressive atelectasis was associated with lung strain increased to areas of high aeration.[151] Of note, these regions showed increased inflammation as assessed by positron emission tomography both in large animals[151] and in patients with inflamed lungs,[239] suggesting their contribution to ultimate clinical lung injury.

Closing remarks

The perioperative period is associated with a profound imbalance of the physical forces that maintain, in the awake conditions, the physiological expansion of the lung. Accordingly, pulmonary atelectasis, most frequently located in the dorso-caudal regions, represents an almost constant feature of general anesthesia. Hypoxemia and lowered respiratory system compliance are classical presentations of atelectasis at the bedside. Prolonged lung collapse and the associated biomechanical processes secondary to the ventilation of a heterogeneously-aerated lung may actively participate in significant lung injury. The biological response associated with atelectasis, before and after re-expansion, could further compound with the injurious process. The impact of intraoperative pulmonary atelectasis on postoperative outcomes such as pneumonia and acute lung injury while presumed is still in need of high level evidence. The presented information is expected to provide a basis for future inquire and physiological-based clinical practice. Although the current focus on preventing postoperative pulmonary complications lies on using ventilator strategies to prevent atelectasis or overexpansion of atelectatic lungs, future approaches may take advantage of common or novel perioperative medications, which would address some of the sequalae of significant atelectasis at the cellular and molecular levels.

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Summary statement:

Up-to-date information on the pathophysiological mechanisms producing atelectasis and its functional, biological and biomechanical consequences are reviewed. The mechanistical understanding aims to provide a solid basis for critical assessment of clinical management.

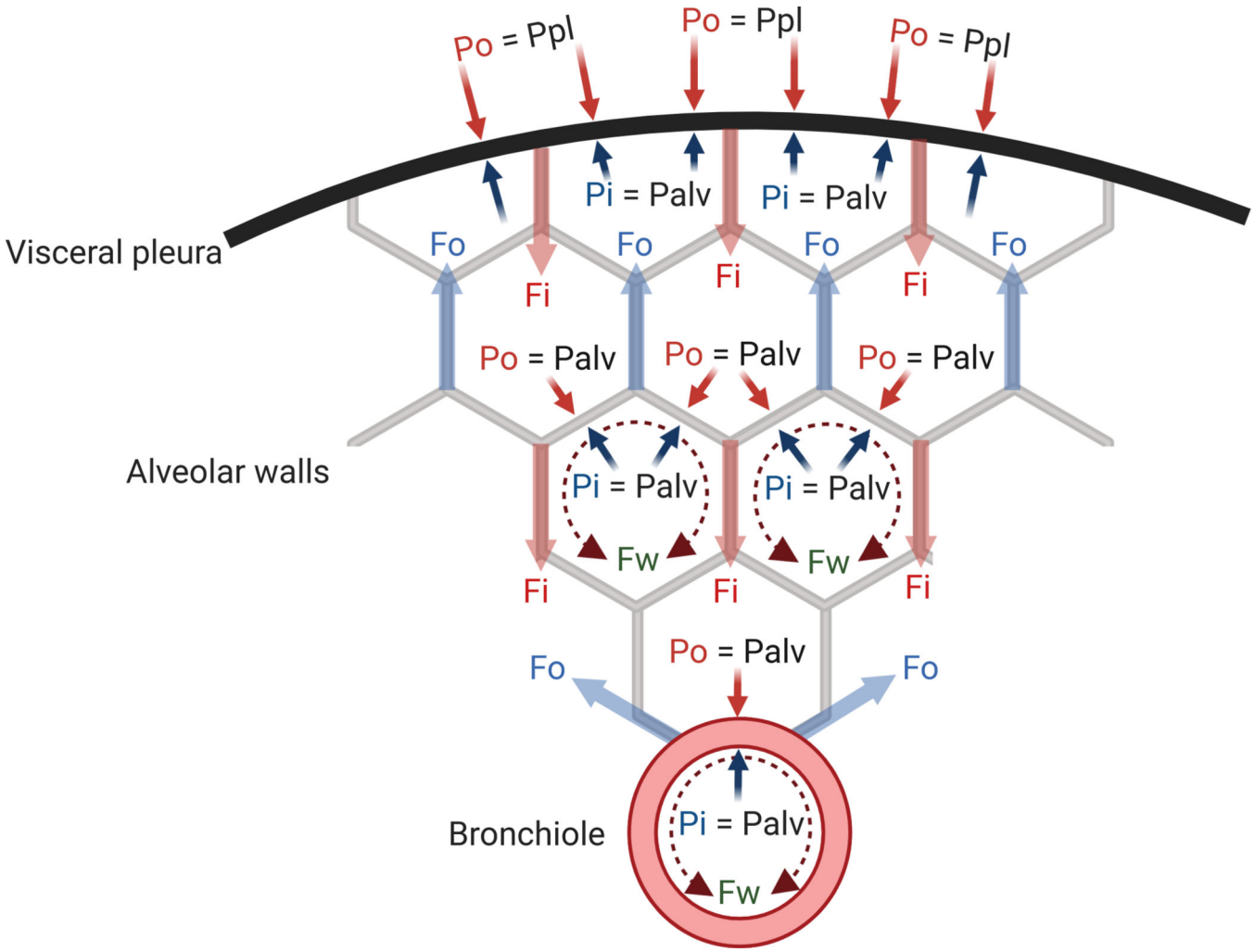

Fig. 1: Pressures and forces acting on alveolar and bronchiolar walls and visceral pleura surface.
F_i = inward tethering; F_o = outward tethering; F_w = circumferential component of force applied by the layer of surface-active fluid; P_{alv} = alveolar pressure; P_i = inside pressure; P_o = outside pressure; P_{pl} = pleural pressure.

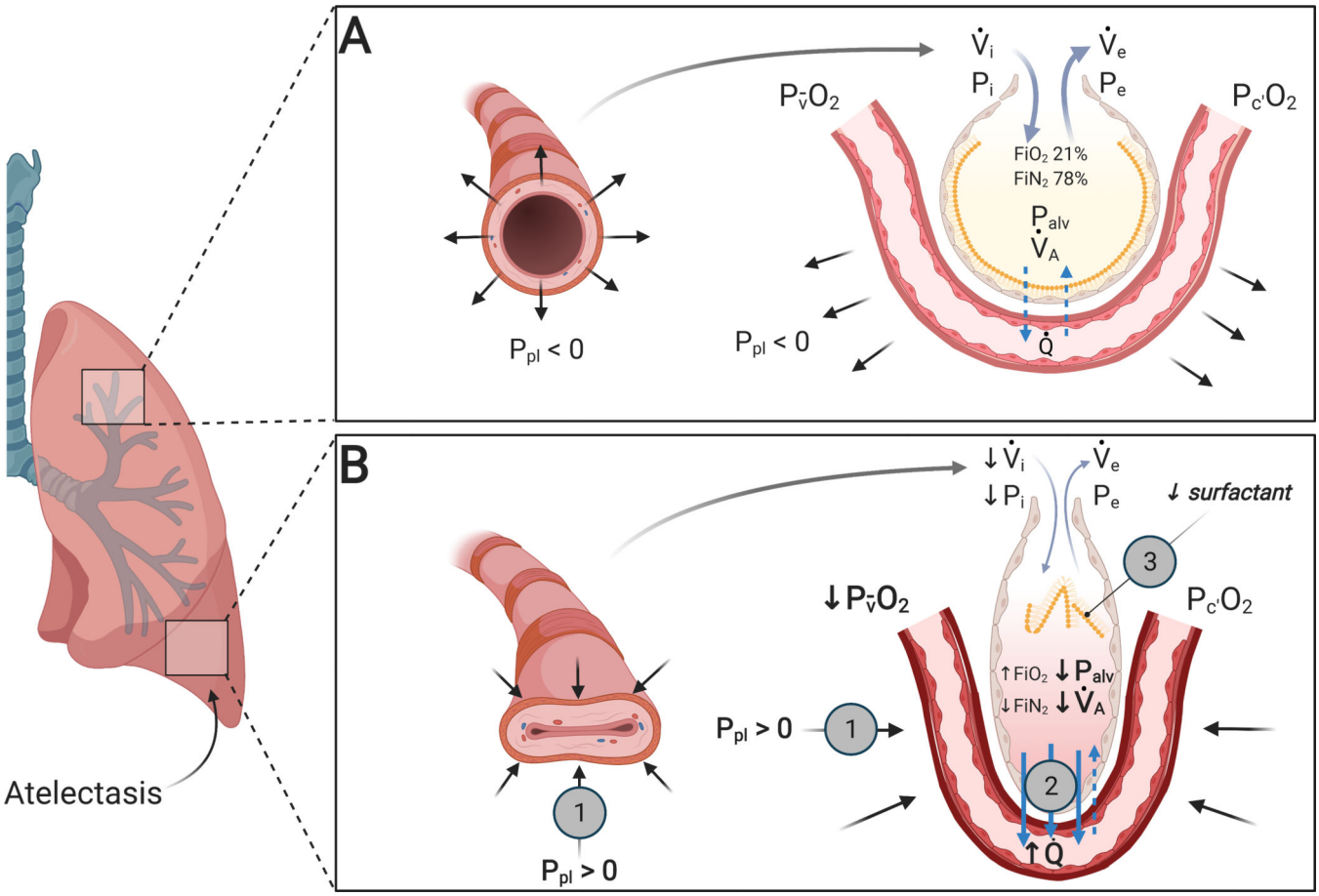

Fig. 2: Mechanisms producing atelectasis in the perioperative period.

(A) Normal lung unit in awake conditions: adequate inspiratory (P_i) and expiratory (P_e) intraluminal pressure and bronchiolar or alveolar tethering stress associated with negative pleural pressure (P_{pl}) allow for the normal opening of the bronchiole and a normal alveolar ventilation ($\dot{V}_A$). Alveolar gas absorption is physiological due to physiological $\dot{V}_A/\dot{Q}$ and atmospheric FIO_2. Normal surfactant reduces alveolar surface tension. (B) Lung unit exposed to perioperative atelectasis: increase in pleural pressure (P_{pl}) due to extrinsic or intrinsic compression (①) is responsible for loss of expansion and reduced alveolar ventilation ($\dot{V}_A$). Increased alveolar gas absorption (②) reduces intraluminal alveolar pressure (P_{alv}). Low $\dot{V}_A/\dot{Q}$, high FIO_2 and low mixed venous oxygen partial pressure ($P\bar{v}O_2$) may participate in such gas exchange imbalance. Quantitative or qualitative surfactant impairment leads to higher surface tension and facilitates alveolar collapse (③). $Pc'O_2$ = end-capillary oxygen partial pressure.

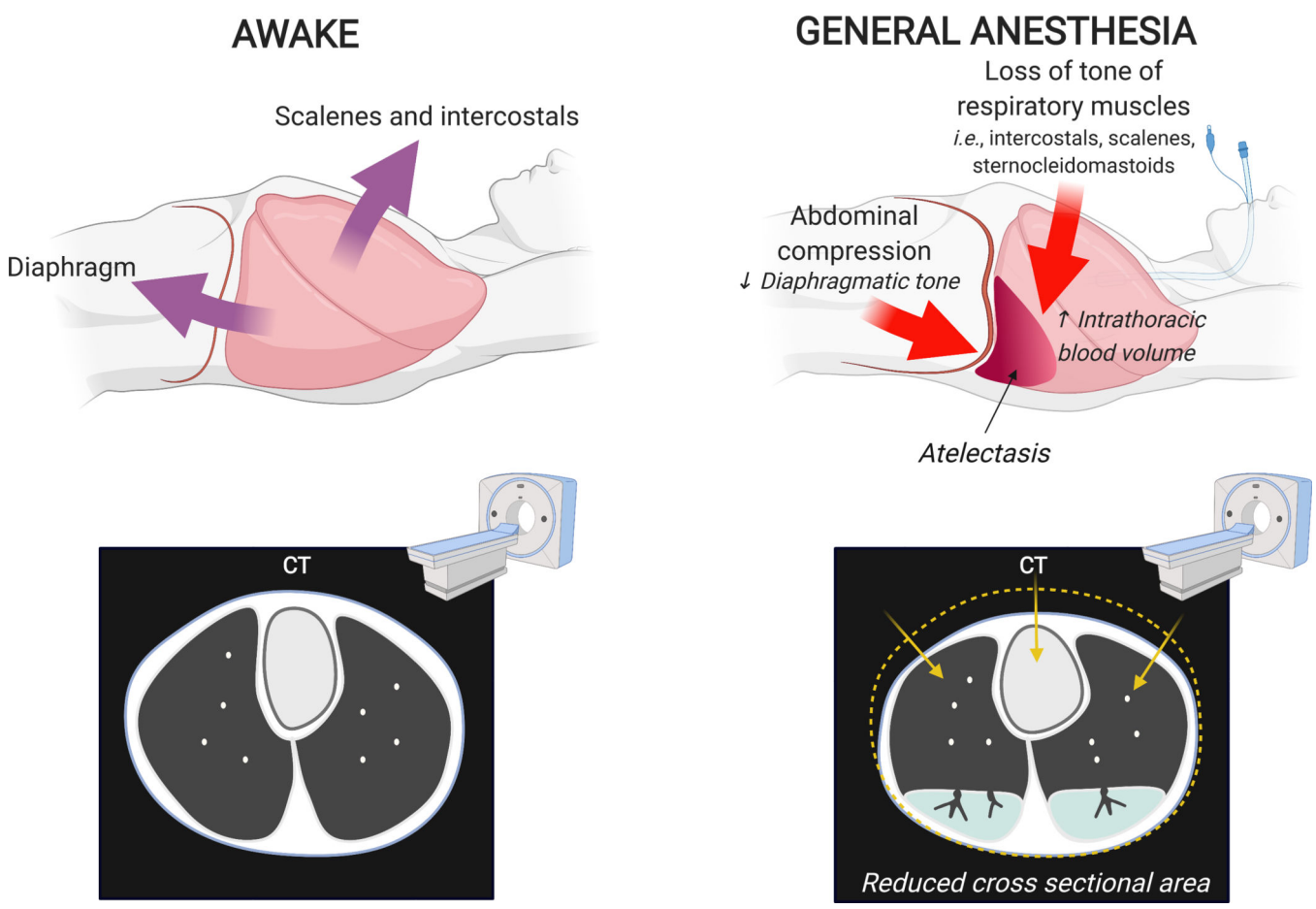

Fig. 3: Changes in chest wall shape due to general anesthesia in a supine patient.

During awake spontaneous breathing, contraction of diaphragm and accessory muscles of respiration maintain lung expansion. Loss of muscular tone during anesthesia is associated with cephalad motion of the dependent diaphragm, reduction in cross-sectional chest area, and generation of non-gravitational compressive forces (*i.e.*, cephalocaudal gradients). Together with gravitational forces and potential increase in intrathoracic blood volume, these factors contribute to reduction of lung volume and lung collapse particularly on the dorsal and basal lung regions.

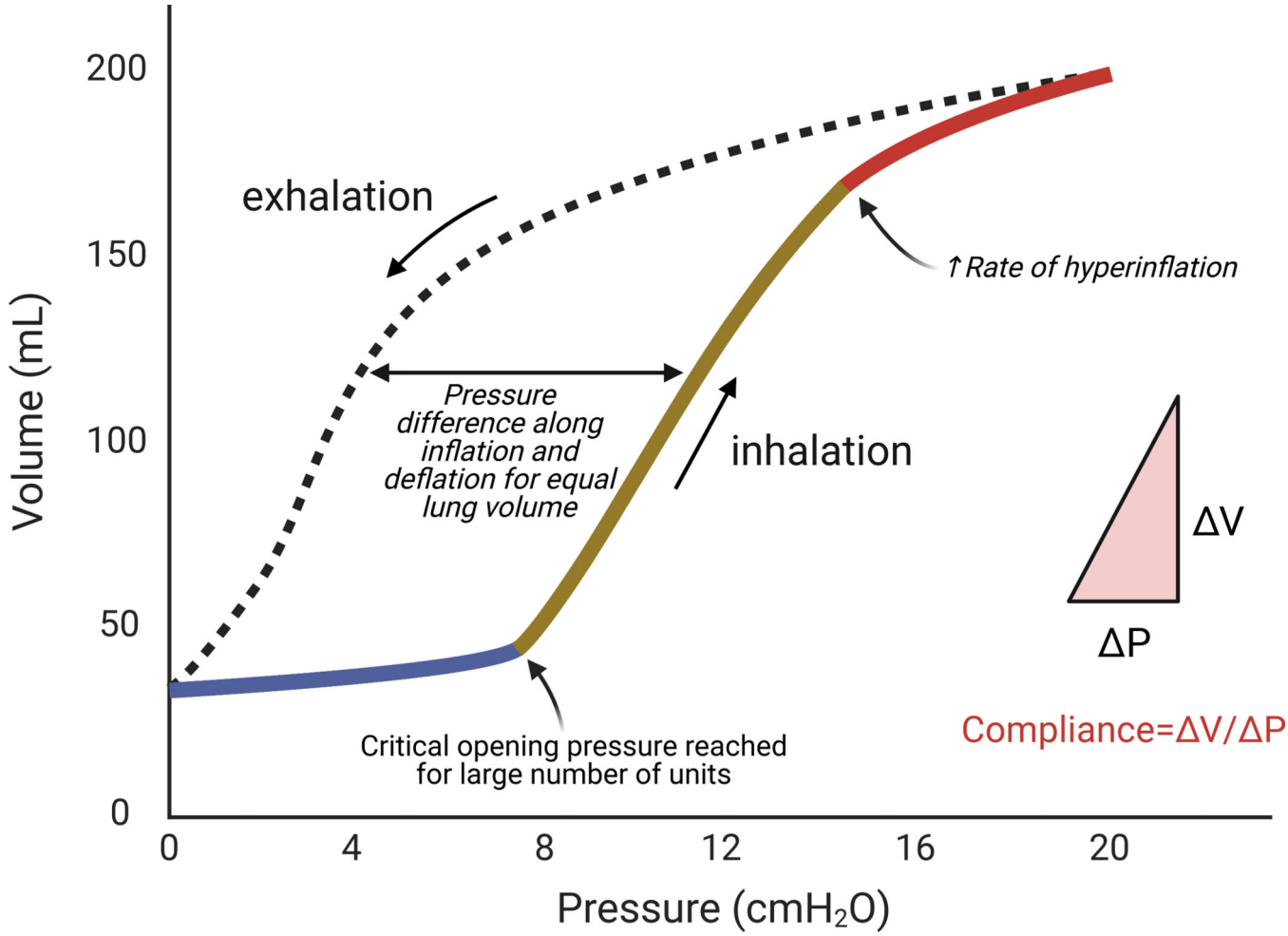

Fig. 4: Pulmonary pressure-volume curve during inhalation and exhalation showing lung hysteresis.

The shape of the lung pressure-volume curve is sigmoidal. There are three main portions of the curve. The initial portion (blue) of lung recruitment at low pressures and volumes is related to low compliance (i.e., the change in volume divided by the change in pressure is low). This is followed by a portion with linear relationship between volume and pressure (ochre) with higher compliance. Finally, hyperinflation ensues at high pressures and volumes with return of lower compliance (red). The transition between the first and second portions indicate that critical opening pressures for a large number of bronchoalveolar regions has been reached (lower inflection point). Note the higher pressure to reach the same lung volume during inhalation than exhalation. Modifed from Radford EP Jr.[66]

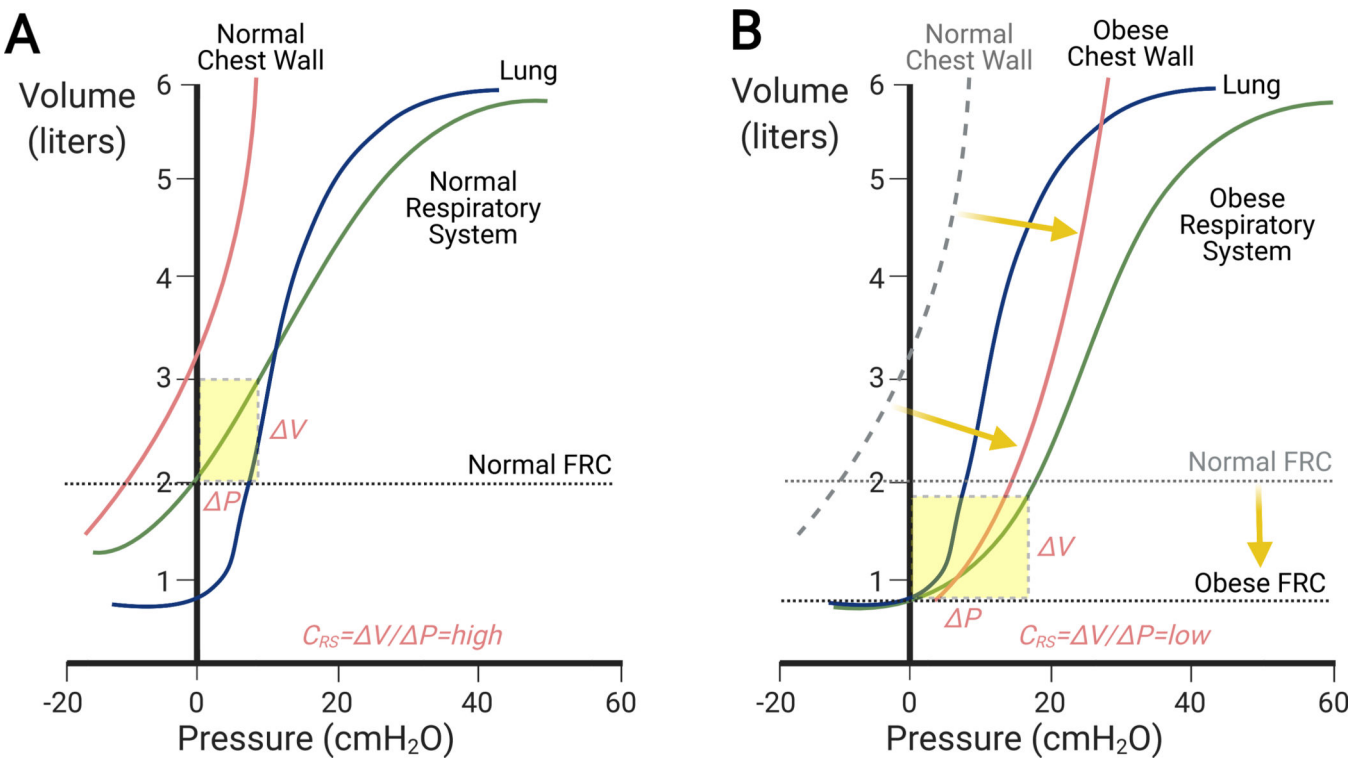

Fig. 5: Pressure-volume relationship for the chest wall, lungs and their combination (respiratory system) in normal (A) and obese (B) subjects in supine positions.

(A) The shape of the respiratory system pressure-volume curve reflects the balance of the forces from the chest wall and lung parenchyma. In normals, functional residual capacity is reduced as compared to the upright position but large enough to locate an operating range of the respiratory system pressure-volume curve within a region of high compliance (dashed yellow rectangle). (B) In obese subjects, increased weight of the chest wall and abdomen shift the chest wall pressure-volume curve to the right at similar chest wall compliances. Combined with the substantial reduction of functional residual capacity (FRC), the operating range of the respiratory system pressure-volume curve moves to a region of low compliance (dashed yellow rectangle). This occurs even in the presence of the same normal pressure-volume curve of the lungs. Modifed from Behazin *et al.*[104]

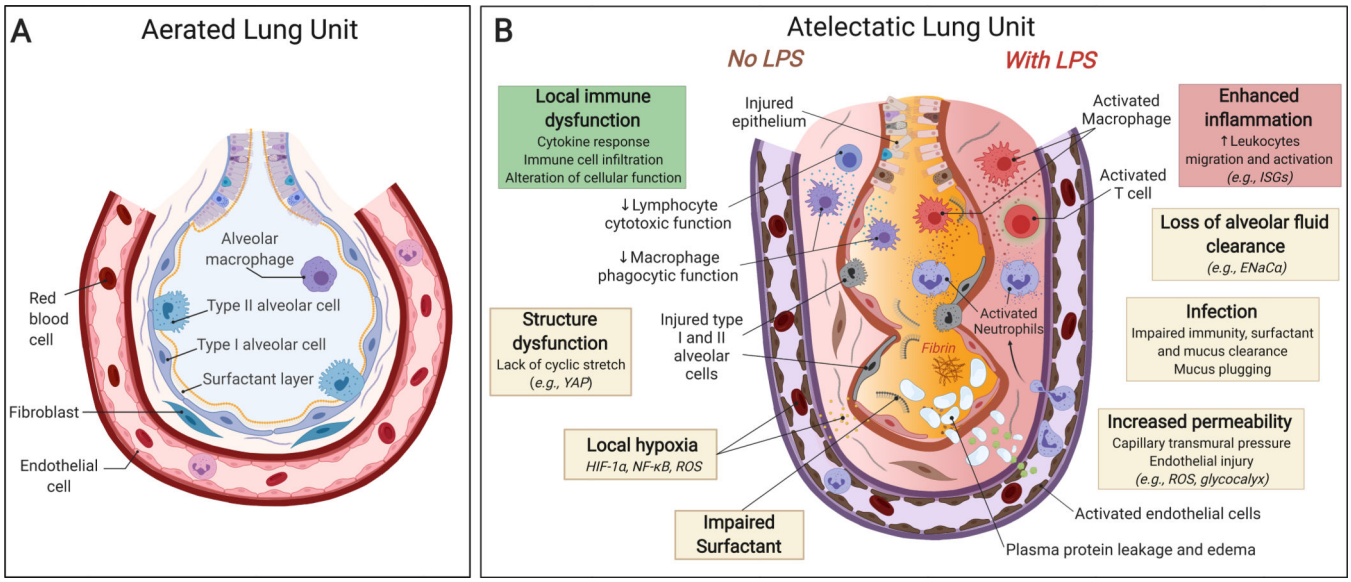

Fig. 6: Atelectasis-associated regional biological injury.

(A) Normally aerated lung. (B) Atelectatic Lung. There is local immune dysfunction with dysregulated cytokine secretion and impaired function of immune cell and surfactant, in part associated with local hypoxia and lack of cyclic stretch. Endotoxemia (=systemic lipopolysaccharide, LPS) enhances inflammatory responses characterized by marked immune cell infiltration and activation. In addition, atelectasis leads to structure dysfunction accompanied by loss of alveolar fluid clearance and increased protein permeability, flooding of the airspace with protein-rich pulmonary edema fluid, and potentially increased susceptibility to infection.

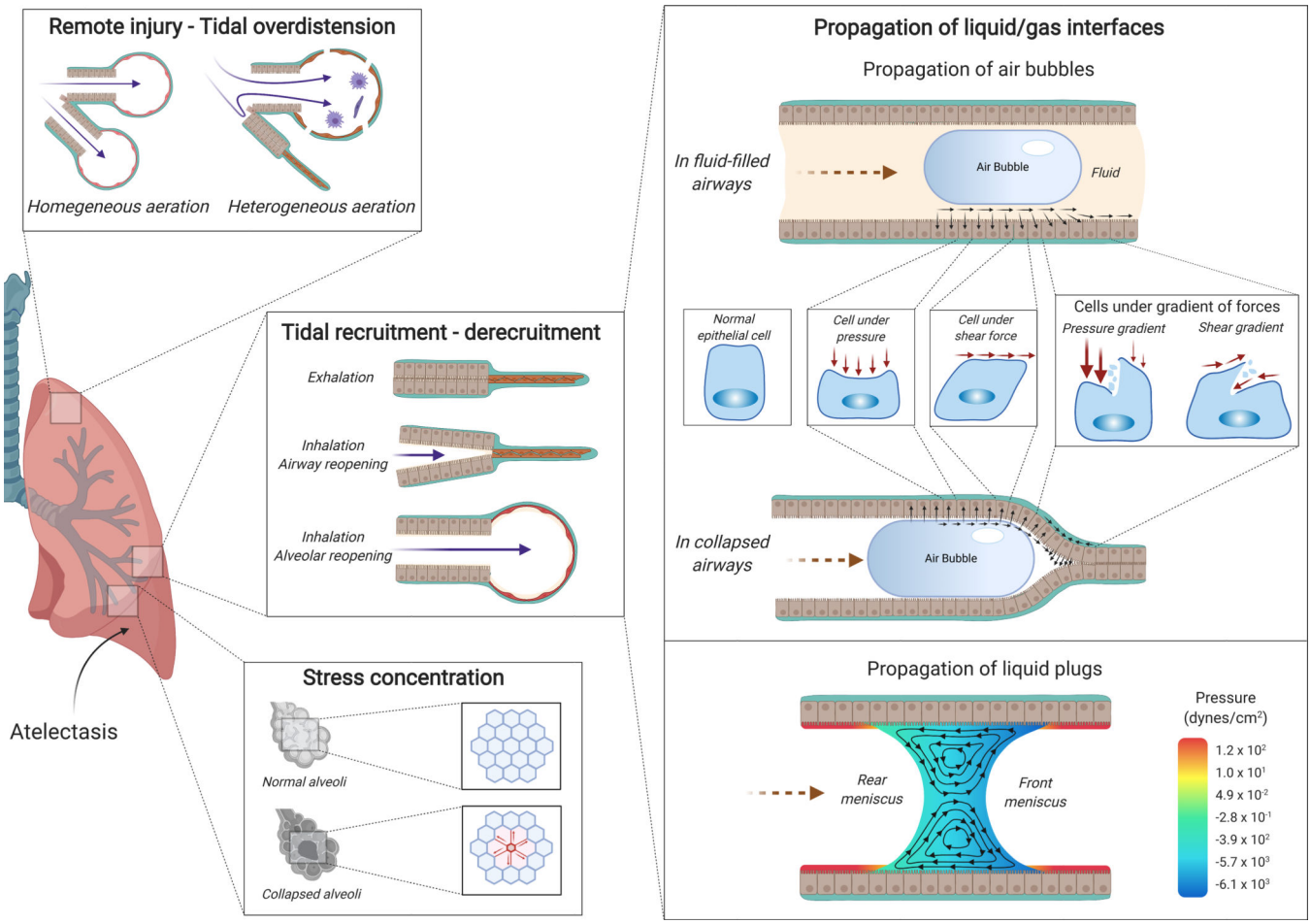

Fig. 7: Atelectasis-associated regional mechanical injury.

Airway or alveolar injury can occur during tidal recruitment-derecruitment. Propagation of gas-liquid interfaces is a potential mechanism. During inhalation, air propagates into a fluid-filled airway (right upper panel) or a collapsed airway (right middle panel) generating mechanical forces at the interface of air bubble and airway with resulting cell deformations due to normal pressure, shear stress, and their gradients. The pressure gradient is likely the major determinant of injury. Propagation of liquid plugs and rupture of the liquid menisci also generate abnormally large mechanical forces in the area of smallest film thickness where the front meniscus converges to a precursor film (right lower panel). Stress concentration (left bottom panel) is another potential mechanism for atelectasis-related lung injury. In normally expanded lungs, the alveoli are ventilated homogeneously. During atelectasis, however, collapsed areas may result in stress concentration, locally multiplying the stress around the atelectatic regions. Atelectasis also leads to the redistribution of tidal volume from atelectatic to aerated areas resulting in remote tidal overdistension (left upper panel).

Table 1.

Atelectasis associated inflammatory response in clinical and animal studies.

Inflammatory response	Subject	Model/Design	Mechanical ventilation	Samples	Results	Reference
Cytokine production	C57BL/6 mice	Ex vivo IPL model	V_T=7 mL/kg, PEEP=0 cmH_2O, no recruitment	BALF	↑ KC	Wakabayashi *et al.* 2014[148]
	Sprague-Dawley rats	OLV model	V_T=8 ml/kg, PEEP=4 cmH_2O, TLV and OLV	Lung homogenates	↑ MPO ↓ CCL-2	Tojo *et al.* 2015[146]
	Patients, lung resection surgery	Prospective, observational	TLV: V_T=8 ml/kg, PEEP=3–5 cmH_2O; OLV: V_T=6 ml/kg, PEEP=5 cmH_2O	BALF	↑ IL-1, IL-2, IL-6, TNF-α, NO, CO and MMP-2	de la Gala *et al.* 2015[143]
	Patients, lung resection surgery	Prospective, observational	V_T=10 ml/kg, RR to maintain normal $PaCO_2$	ELF	↑ IL-8	Komatsu *et al.* 2012[144]
	ICU patients with atelectasis and no cardiopulmonary disease	Prospective controlled study	V_T=9–11 ml/kg with PEEP=3–5 cmH_2O	BALF	↑ PAF	Nakos *et al.* 2003[147]
	Sheep	Left lung collapse and right lung ventilated model with or without systemic LPS	V_T=10 ml/kg with PEEP=2 cmH_2O	Lung tissue mRNA	↓ CXCL-8 and F2RL1 (without systemic LPS) ↑ CXCL-9, CXCL-10, CCL-5, IL-12B, MX1 and MX2 (with systemic LPS)	Zeng *et al.* 2020[154]
Cell infiltration	Dogs	Lobar atelectasis		BALF	↑ Neutrophils	Nguyen *et al.* 1991[149]
	ICU patients with atelectasis and no cardiopulmonary disease	Prospective controlled study	V_T=9–11 ml/kg with PEEP=3–5 cmH_2O	BALF	↑ Neutrophils	Nakos *et al.* 2003[147]
	Wistar albino rats	Pneumothorax model		Lung tissue	↑ Neutrophils	Sivrikoz *et al.* 2002[156]
Cellular function	Sprague-Dawley rats	Left main stem bronchus ligation	V_T=2.5 ml/kg, RR=90 breaths/min	Alveolar macrophages	↑ Activation with increased IL-1 and TNF release	Kisala *et al.* 1993[152]
	Yorkshire swine	Right upper lobe atelectasis		Alveolar macrophages	↓*In vitro* phagocytosis against Pseudomonas aeruginosa	Shennib *et al.* 1984[153]
	Dogs	Lobar atelectasis		Broncho-alveolar lymphocytes	↓ Cytotoxic activity	Nguyen *et al.* 1991[149]

IPL: isolated, buffer-perfused lungs; V_T: tidal volume; KC: keratinocyte-derived chemokine; TNF: tumor necrosis factor; PEEP: positive end-expiratory pressure; BALF: bronchoalveolar lavage fluid; IL: interleukin; NO: nitric oxide; CO: carbon monoxide; MMP-2: matrix metalloproteinase 2; OLV: one-lung ventilation; TLV: two-lung ventilation; RR: respiratory rate; ELF: epithelial lining fluid; ICU: intensive care units; $PaCO_2$: partial tension of carbon dioxide; PAF: platelet-activating factor; CCL: chemokine (C-C motif) ligand; LPS: lipopolysaccharides; CXCL: chemokine (C-X-C motif) ligand; F2RL1: coagulation factor II (thrombin) receptor-like 1; MX: Interferon-induced GTP-binding protein; MPO: myeloperoxidase.