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Biotrauma and Ventilator Induced Lung Injury: Clinical implications

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Abreviations: VILI = Ventilator Induced Lung Injury; PEEP = Positive End Expiratory Pressure; TNF = Tumour Necrosis Factor; IL = Interleukin; mRNA = messenger ribonucleic acid; Vt(s) = Tidal Volume(s); TNFR1 = Tumour Necrosis Factor Receptor 1; CT = computed tomography, PBW = Predicted Body Weight; CRS = compliance of the respiratory system; ARDS = Acute Respiratory Distress Syndrome; Pplat = Plateau Airway Pressure; Pes = Esophageal Pressure; Paw = airway opening pressure; Ppl = pleural pressure; PaO_2/FiO_2 = Partial Pressure of Arterial Blood Oxygen/Fraction of Inspired Oxygen; $ECCO_2R$ = Extra-corporeal Carbon Dioxide Removal; ECMO = Extracorporeal Membrane Oxygenation; RAGE = Receptor for Advanced Glycation Endproducts; AEC = Alveolar Epithelial Cell; CCL20 = Chemokine (C-C Motif) Ligand 20.

Abstract

The pathophysiological mechanisms by which mechanical ventilation can contribute to lung injury – termed ventilator induced lung injury (VILI) – is increasingly well understood. "Biotrauma" describes release of mediators by injurious ventilatory strategies, which can lead to lung and distal organ injury. Insights from preclinical models demonstrating that traditional high tidal volumes drove the inflammatory response helped lead to clinical trials demonstrating lower mortality in patients ventilated with a lower tidal volume strategy. Other approaches that minimize VILI, such as higher PEEP, prone positioning and neuromuscular blockade have each been demonstrated to decrease indices of activation of the inflammatory response. This review examines the evolution of our understanding of the mechanisms underlying VILI, particularly with regard to biotrauma. We will assess evidence that ventilatory and other 'adjunctive' strategies that decrease biotrauma offer great potential to minimize the adverse consequences of VILI, and to improve the outcomes of patients with respiratory failure.

Introduction

Mechanical ventilation is an indispensable component of advanced life support strategies; however, mechanical ventilation can damage the lung, a process that has been termed Ventilator Induced Lung Injury (VILI). The physical mechanisms whereby ventilation contributes to lung injury are increasingly well understood.[1,2] In particular, VILI is caused by over-distension at high lung volumes, and collapse/re-opening of airway units at low lung volumes.[3] In addition, mechanical stretch can cause release of mediators associated with activation of the immune response, further adding to injury, and potentially causing remote injury to other organs – this is termed 'biotrauma'.

This review will address the evolution of our understanding of VILI, focusing on biotrauma as well as the clinical implications of VILI. Although the term used throughout this review is Ventilator-Induced Lung Injury (VILI), the mechanisms of injury are related to changes in lung volume (e.g. overdistension) which can also occur during spontaneous ventilation[4], and hence a better term might be Ventilation-Induced Lung Injury.

VILI – early insights and concepts

The potential harm from mechanical ventilation has been a matter of concern since at least the 1950's polio epidemic. In 1967 the term "respirator lung syndrome"[5] was used to label the injury observed postmortem in ventilated patients, although the major factor causing injury was thought to be the high fractional concentrations of oxygen used in many ventilated patients.[6] Webb and Tierney conducted one of the first comprehensive studies in intact

animals, unambiguously demonstrating that mechanical ventilation can cause pulmonary edema.[7] Profuse edema and alveolar flooding developed within 35 min in rats ventilated with a peak airway pressure of 45 cmH_2O.

Barotrauma, Volutrauma and Atelectrauma

Ventilation at high airway pressures can lead to barotrauma, manifest for example as pneumothorax or subcutaneous emphysema. The term barotrauma is really a misnomer, since the high airway pressures per se do not cause VILI unless they are associated with high lung volumes.

Another type of injury caused by ventilation at high lung volumes is volutrauma. In one study, rats subjected to high peak airway pressures ($45cmH_2O$) associated with high tidal volumes, developed increased lung permeability and pulmonary edema.[8] However, rats ventilated with the same high peak airway pressures but who received low tidal volumes because of thoracoabdominal strapping, had no edema. These findings have been replicated in several species using different approaches[9-11]. The dependence of the injury on lung volume rather than airway pressure led to the term volutrauma for this type of injury.

Webb and Tierney[7] demonstrated that some of the detrimental effects of high peak inspiratory pressure of 45 cmH_2O edema could be abrogated by the application of 10 cmH_2O PEEP. Later studies demonstrated less epithelial injury in lungs ventilated with higher PEEP levels compared to zero end-expiratory pressure.[12] PEEP helped reverse atelectasis, thus mitigating injury due to repetitive opening and closing of terminal units – a mechanism of injury termed atelectrauma.[13]

The Concept of "Baby Lung" and Lung Heterogeneity

Injured lungs are particularly susceptible to volutrauma and atelectrauma because the number of aerated and recruitable lung units is decreased ("baby lung concept").[14] Within the "baby lung", both fully aerated and nonaerated respiratory units exist in close proximity.[15] The preferential distribution of ventilation to the less injured units, as well as the heterogeneities at the interfaces between aerated and atelectatic regions places these units at a high risk for injury **(Figure 1A-B)**.[16]

Biotrauma

The concepts of VILI discussed above are based on the biophysical injury induced when applied forces cause mechanical destruction of the anatomical lung structure. Alveolar overdistension, lung strain (the associated deformation of a structure to an external load in relation to its resting state), and atelectasis are key inciting features of VILI. However, numerous studies over the past 20 years have demonstrated that there can be a more subtle form of injury with release of various mediators into the lung, pulmonary recruitment of leucocytes, and local initiation of inflammatory processes. This biological response to mechanical forces has been called biotrauma.[17] The biotrauma hypothesis postulates that the circulating mediators can cause local lung injury, and if they translocate into the systemic circulation, they may lead to distal organ dysfunction and death **(Figure 1C)**.[18]

Tremblay and colleagues[19] found that isolated, non-perfused rat lungs ventilated for 2 hours with large tidal volumes without PEEP had large increases in lavage concentrations of TNF-α, IL-1β, IL-6, and macrophage inflammatory peptide-2. High tidal volume ventilation also increased

expression of c-fos mRNA, a transcription factor important in the early stress response.[19]

The potential for ventilation-induced inflammation in humans was examined in 44 patients with ARDS who were randomized to receive traditional or lung protective ventilation.[20] Bronchoalveolar lavage (BAL) and plasma concentrations of several proinflammatory cytokines were lower in patients receiving protective ventilation, as were other indices of plasma and alveolar fluid inflammation, compared to patients receiving traditional tidal volumes and lower PEEP.

Implications for Current Clinical Practice

Lung Protective Ventilation

Injured Lungs: The fact that mechanical ventilation can worsen lung injury is clearly proven.[21] The importance of VILI is underscored by the fact that ventilation strategies that reduce lung stretch save lives.[22,23] In 2000, a landmark, randomized controlled trial demonstrated a ~9% absolute mortality reduction using a strategy of low tidal volume [6ml/kg predicted body weight (PBW), Formulae: PBW in males (kg) =50 + 0.91 (centimeters of height - 152.4)); PBW in females (kg) = 45.5 + 0.91 (centimeters of height - 152.4)], and limitation of plateau pressure (30 cmH_2O).[22] A statistically significant decrease in nonpulmonary organ failure days (15 vs 12) was also observed. The lower tidal volume strategy led to lower concentrations of plasma IL-6, IL-8, and TNFR1 over the first 1–3 days,[22] underlining the potential contribution of reduced biotrauma to decreased mortality.

Since the first description of ARDS, PEEP has been used to combat hypoxemia and atelectasis.[24] PEEP helps prevent end-expiratory collapse of unstable lung units, and should lessen atelectrauma. In addition, in pre-clinical studies PEEP has been shown to prevent pulmonary de--compartmentalization with release of pro-inflammatory cytokines.[25,26] Three large multicentre randomized trials that tested higher *versus* lower levels of PEEP were negative.[27-29] However, an individual patient-based meta-analysis[30] combining these data found a modest but significant reduction in mortality for patients with moderate and severe ARDS assigned to higher PEEP.

Previously Healthy Lungs: The potential for mechanical ventilation to worsen outcomes in patients with previously healthy lungs is emerging. Normal lungs are probably no longer "healthy" during and after prolonged general anesthesia. Atelectasis develops in about 90% of anesthetized patients, irrespective of ventilatory control (spontaneous or mechanically supported) and of the type of anesthesia.[31] Excessive crystalloid use increases capillary hydrostatic pressure and promotes interstitial/alveolar edema particularly when lymphatics are disrupted. Additionally, tissue trauma, ischemia-reperfusion, blood transfusion and exposure to extracorporeal devices may all combine to result in regional heterogeneities that make the lung more vulnerable to VILI. In a French multicenter trial, protective ventilation in non-obese patients undergoing major abdominal surgery resulted in fewer post-operative pulmonary complications and shorter hospital length of stay.[32] Another study comparing PEEP <2 cm H_2O with PEEP 12 cm H_2O in 900 patients demonstrated that postoperative pulmonary complications

were equally high (~40%) in both groups while high PEEP resulted in some circulatory impairment requiring more fluid and vasoactive drugs.[33] Finally, in a recent meta-analysis examining 3,365 abdominal or thoracic surgery patients, the incidence of postoperative pulmonary complications was higher in patients who had received a high tidal volume and a lower PEEP intra-operatively.[34] The mechanisms underlying these effects are unclear, but a Dutch study conducted in 150 critically ill patients without ARDS demonstrated that mechanical ventilation with conventional tidal volume (n=74) was associated with increased plasma concentrations of cytokines compared to patients ventilated with low tidal volumes (n=76), suggesting that biotrauma may have played a role.[35]

Prone Positioning

Prone positioning improves survival in patients with severe ARDS **(Figure 2)**, as demonstrated in a recent clinical trial[36], a result that is consistent with a previous meta-analysis.[37] Although the initial rationale for prone positioning in ARDS was to improve oxygenation as observed in ~66 to 75% of patients[38], it likely improves survival by preventing ventilator-induced lung injury (VILI)[39], including biotrauma. Studies in several species have demonstrated less VILI when animals are ventilated in the prone position.[39,40] CT scan studies in animals[40] and humans demonstrated a reduction in atelectrauma and overdistension in the prone position.[41] This lung protective affect also appears to result in a reduction in biotrauma. Papazian et al.[42] found lower concentrations of pro-inflammatory cytokines in the bronchoalveolar lavage fluid of patients with ARDS after 12 hours in the prone compared to the supine position.

Neuromuscular blockade

A multicentre randomized controlled trial[43] in 340 patients with moderate-to-severe ARDS demonstrated that early administration of the neuromuscular-blocking agent cisatracurium reduced adjusted 90-day mortality. The mechanism mediating this effect is unclear. It may be a consequence of a reduction in patient ventilator asynchrony, leading to decreased biotrauma; this could potentially explain the observation that the mortality benefit was not apparent for at least 2 weeks.[44] It is also possible that cisatracurium may have important anti-inflammatory properties by blockade of nicotinic acetylcholine receptor α1(nAChRα1) signaling (**Figure 2**).[45]

Implications for Future Clinical Practice: Precision Ventilation

Individualized tidal volumes using driving pressure

Protective ventilation strategies generally use tidal volumes adjusted to the patient's predicted body weight (PBW), as assessed from the patient's height and gender. The rationale underlying this approach is that PBW is a better surrogate than measured weight to adjust for variations in lung size. This may be useful in patients with normal lungs, but in patients with ARDS, as described above, a variable portion of the lung is not available for ventilation. Indeed in the ARDS Network trial of low tidal volume ventilation, adjustment for PBW was an initial strategy for setting tidal volume, but if plateau airway pressure was > 30 cmH_2O, further reductions in tidal volume to 5 or 4 ml/kg PBW were recommended.

An alternative mechanical ventilation strategy would normalize Vt to the size of the injured lung.[46] Recently, a post hoc analysis of 3,562 patients with ARDS enrolled in nine randomized trials examined whether Vt normalized by

respiratory system compliance (CRS) was a better predictor of mortality than tidal volume normalized to PBW.[47] This ratio (Vt/CRS=Pplat-PEEP), termed the driving pressure (ΔP), performed considerably better than tidal volume or PEEP, suggesting that compliance — an indicator of lung size — is a better surrogate than PBW in setting tidal volume. A similar strategy applied experimentally was shown to reduce biotrauma.[48] The use of driving pressure to set the ventilatory strategy in patients with ARDS has a clear and compelling rationale, but requires confirmation in prospective randomized trials.

Individualized PEEP

Higher PEEP may reduce alveolar stress and improve gas exchange if it recruits lung tissue; however, higher levels may be harmful by causing regional lung over-distension or hemodynamic depression. Setting the appropriate PEEP is challenging because of the heterogeneity in response, related to the variability in recruitable lung in patients with ARDS.[49,50] Assessing individual recruitability may be essential for individualising PEEP settings. One technique relies on titration of PEEP guided by transpulmonary pressures, where esophageal pressure (Pes) is used as a surrogate for pleural pressure. The variable most closely linked with VILI is the alveolar distending pressure, best estimated by the transpulmonary pressure (Ppl), defined as airway opening pressure (Paw) minus pleural pressure (Ppl).[51] Proof of concept for using Pes to guide PEEP therapy in ARDS has been shown.[52] Patients who had PEEP titrated to ensure a positive end-expiratory transpulmonary pressure (0-10cmH_2O) had higher PaO_2/FiO_2, better

respiratory system compliance and a trend towards reduced 28-day mortality. A more definitive study is currently underway.[53]

Extra-corporeal Strategies

The recent LUNG SAFE study demonstrated that many clinicians use higher than recommended tidal volumes in ARDS patients[54], perhaps because of limited clinician tolerance of hypercapnia. In addition, there is growing evidence that our current lung protection strategies are not protective enough, and that further reduction in mechanical stresses may improve outcomes. Tidal volume reduction to 3–4 mL/kg in animals reduces lung edema and preserves, at least in part, alveolar epithelial and endothelial integrity.[55,56]

Extra-corporeal CO_2 removal ($ECCO_2R$) may facilitate targeting of lower tidal volumes by lowering arterial $PaCO_2$. Following the original concept developed by Kolobow et al[57], several new devices and technical approaches have been implemented to perform extracorporeal CO_2 removal. A few small studies have been conducted in patients and have concluded that lower tidal volumes are associated with a reduced pro-inflammatory, biotrauma response.[58,59]

Extracorporeal membrane oxygenation (ECMO) has a long history in the management of ARDS, although early studies had very high complication rates resulting in poor outcomes.[60,61] Recent advances in technology have resulted in a more favorable risk-benefit profile, with data suggesting improved survival rates.[62] The only controlled clinical trial of ECMO for ARDS using relatively modern technology is the CESAR trial.[63] Although this study demonstrated a reduction in the composite endpoint of death or severe

disability at six months in patients randomized to the ECMO group, all these patients were treated in a single expert center. In contrast, patients randomized to control were treated at multiple hospitals, which were not required to use lung protective ventilation. Thus, the results may have been biased in favor of the treatment arm. As extracorporeal technology continues to evolve, there is potential to have a greater impact on the management of ARDS by both facilitating and enhancing lung-protective ventilation strategies, and minimizing VILI and biotrauma (**Figure 2**). The EOLIA study (Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome, NCT01470703), a multicenter, international, randomized, controlled trial of ECMO, instituted early after the diagnosis of very severe ARDS (P/F ratio < 80), is currently completing recruitment, and the results should be available in the near future.

Biomarkers and Pharmacologic Strategies

Biomarkers have the potential to identify patients at high-risk for VILI or to identify patients most likely to benefit from a specific intervention, such as ultra-low tidal volume, lung protective ventilation (**Figure 2**). At present, the most promising plasma biomarker for estimating endothelial injury during ARDS is angiopoietin-2[64], while the receptor for advanced glycation end products (RAGE) may provide the best assessment of the extent of lung epithelial injury.[65]

In the future, a biomarker-driven approach could guide ventilator management. In the ARDS Network low tidal volume study, lower tidal volumes led to lower levels of plasma IL-6, IL-8, and TNFR1 over the first 1–3 days.[27] Stuber and colleagues[66] found increases in IL-6 within one hour of

switching from a lung protective strategy to a less protective strategy; 5 hours later the patients were returned to the lung protective strategy, and IL-6 decreased one hour thereafter. Similarly, changes in plasma RAGE levels occurred within 1 hour of a recruitment maneuver in patients with diffuse ARDS.[67] Given their responsiveness during alterations of ventilator settings, bedside point-of-care testing of circulating mediators could potentially be used to guide ventilator management.

Animal models have demonstrated the efficacy of therapies aimed at mitigating biotrauma. In Sprague-Dawley rats, Hoegl and colleagues demonstrated that prophylactic, inhaled IL-10 improved survival and reduced lung injury in a model of VILI induced by high airway pressures.[68] They concluded that these results may be due to inhibition of biotrauma. In a rat model, Guery et al. observed that intravenous delivery of anti-TNF antibodies decreased lung edema due to high pressure ventilation, as well as reducing the ventilation-associated increase in gut permeability.[69] An advantage of such anti-biotrauma therapies is that they could be administered prior to the inciting stimulus – endotracheal intubation and mechanical ventilation.

One promising therapeutic strategy with the potential to impact on inflammation (and hence biotrauma) and augment tissue repair is the use of mesenchymal stem cells.[70,71] A phase I study of MSCs in ARDS has been completed[72] and a phase II study is underway[73].

The link between Biotrauma and Ventilogenomics

Genetic factors that contribute to susceptibility and severity of VILI (Ventilogenomics) have emerged as a major research focus. Recent literature has seen the application of microarray-based approaches to animals and *in*

vitro models of VILI. Copland and colleagues[74] ventilated mice with large tidal volumes, and identified genes that were highly up-regulated, including the immediate-early response genes Nur77, Egr1, Btg2, and c-Jun. Dos Santos *et al* studied the effect of cyclic stretch on gene expression in alveolar epithelial cells (AECs) *in vitro*.[75] Cyclic stretch of AECs (20% elongation) alone caused no significant differences in their gene expression whereas TNF-α treatment led to 40 genes that were differentially regulated. The combination of cyclic stretch of AECs with TNF-α pre-treatment resulted in augmented expression of 16 genes, including the chemokine CCL20. These and other studies[76] will help us understand the signaling pathways by which mechanical ventilation alters and augments the transcriptional response to lung injury, and will provide further insights and strategies to disrupt this interaction.

Conclusions

The biotrauma concept, namely that mechanical ventilation results in the release of mediators, which cause or worsen lung injury and perhaps lead to systemic organ failure, remains a central component of our understanding of the pathophysiology of VILI. Understanding the impact of biotrauma has contributed to our understanding of various advances in ventilation, particularly lower tidal volume, higher PEEP, prone positioning, and neuromuscular blocking agents, as well as the identification of promising biomarkers to detect subclinical injury. Evolving molecular approaches[77,78] – that examine the cellular response to stretch and injury - may facilitate an even greater understanding of the contribution of biotrauma during critical illness, including identification of novel candidate mediators. Further

refinements in bedside ventilator management, together with development and testing of mediator-directed therapy has the promise to dramatically improve outcomes.

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Figure Legends

FIGURE 1: The normal alveolus **(Panel A)** and the alveolus injured by ventilation **(Panel B)**. Mechanical ventilation with high tidal volumes induces tensile strain and shear forces in the lung. Pre-existing lung injury leads to lung endothelial and epithelial injury, flooding of the airspace with protein-rich pulmonary edema and activation of alveolar macrophages and recruitment of neutrophils. Volutrauma (overexpansion of regional lung units) and atelectrauma (repetitive opening and closing of lung units) **(Panel B)** during mechanical ventilation result in further disruption of the alveolar–capillary barrier and increased permeability, a hallmark of experimental VILI. Intra-alveolar accumulation of neutrophils, other leukocytes, and erythrocytes is also associated with altered endothelial and epithelial barrier function.

Mechanical forces also induce an increase in the concentrations of proinflammatory mediators (including IL-1β, tumor necrosis factor alpha, IL-8 and IL-6) in the distal airspaces of the lung **(Panel C).** The loss of compartmentalization in the lung results in the release of these mediators into the systemic circulation where they may play a role in end organ dysfunction.

FIGURE 2: A protective ventilatory strategy (low-stretch ventilation) can limit further lung endothelial and epithelial injury, allowing endothelial and epithelial repair to occur and reduce the release of proinflammatory cytokines **(Panel A)**. Prone positioning, neuromuscular blockade and PEEP have all been demonstrated to lessen biotrauma and improve outcomes in patients with ARDS **(Panel A)**. In the future, a more individualized approach **(Panel B)** could see tidal volumes and PEEP adjusted using driving pressures or

esophageal pressures. Extra-corporeal technologies could facilitate ultra-low tidal volumes which could reduce the impact of biotrauma even further, while biomarkers or gene expression patterns could identify patients at high risk of VILI, biotrauma and multi-organ failure prior to intubation and mechanical ventilation.

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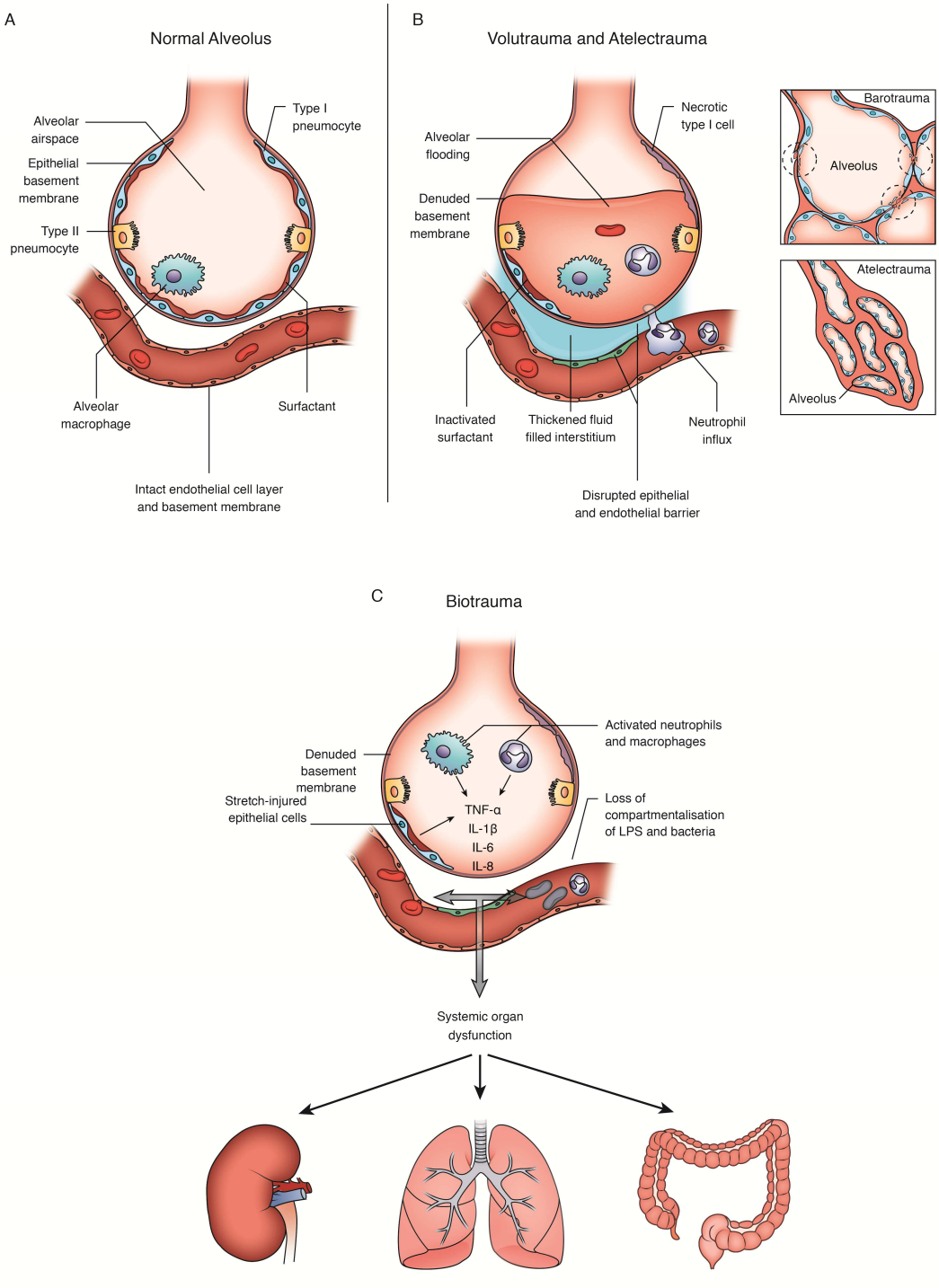

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