Types of Lung Injury

Since its introduction into clinical practice as life-sustaining therapy in the polio epidemic, mechanical ventilation has proved to be an important tool for the treatment of the respiratory failure. One of the main reasons for a patient’s admission into the intensive care unit (ICU) is to receive ventilator support [1]. According to a recent review by Esteban and co-workers [2], 66% of patients who require mechanical ventilation suffer from acute respiratory failure, including acute respiratory distress syndrome (ARDS), heart failure, pneumonia, sepsis, complications of surgery and trauma. The remaining indications include coma (15%), acute exacerbation of chronic obstructive pulmonary disease (13%) and neuromuscular disorders (5%). The aims of mechanical ventilation are primarily to decrease the work of breathing and to reverse life-threatening hypoxaemia or acute progressive respiratory acidosis. However, over the last two decades, research in a number of animal models has shown that mechanical ventilation itself can produce acute lung injury (ALI) [3]. The classical form of iatrogenic lung injury, recognised clinically for many decades, is the well-known barotrauma, defined as radiological evidence of extra-alveolar air [4]. The extra-alveolar accumulation of air has several manifestations, of which the most threatening is tension pneumothorax.

There are also more subtle morphologic, structural and physiologic changes that can be induced by mechanical ventilation. A large number of studies have observed that high end-inspiratory lung stretch can lead to diffuse alveolar damage, increased fluid filtration, epithelial permeability and microvascular permeability, pulmonary oedema [3]. The term volutrauma was coined to indicate that the critical variable causing injury was alveolar distension, namely volume, rather than high proximal airway pressure [5]. However, it is important to point out that alveolar overdistension is due to an increased transpulmonary pressure (alveolar minus pleural pressure), such that volutrauma actually represents a form of barotrauma.

In addition to the injury caused by ventilation at high lung volumes, ventila-
tion at low lung volumes may be harmful. This injury, termed as *atelectotrauma* is related to repetitive opening and closing of lung units [6].

Ventilator-induced lung injury (VILI) is the term coined to define ALI directly induced by mechanical ventilation in animal models [7]. VILI comprises morphological, physiological and radiological features that are indistinguishable from those of the diffuse alveolar damage of ALI/ARDS [7].

Since it is ethically not possible to perform experiments on humans exposed to injurious strategies of ventilation, it is not easy to demonstrate that mechanical ventilation can cause damage to human lungs. Thus, a better term that might be used in human studies is ventilator-associated lung injury (VALI), which is defined as lung injury that resembles ARDS and occurs in patients receiving mechanical ventilation [7].

The types of injury described above are largely thought to be related to the mechanical stress placed on the pulmonary and non-pulmonary structures by mechanical ventilation. In the last few years, there has been increasing evidence that mechanical stresses produced by mechanical ventilation can lead to the up-regulation of an inflammatory response. This new mechanism of injury has been termed *biotrauma* [8]. One hypothesis that has recently been advanced is that activation and/or propagation of the inflammatory cascade, induced by mechanical ventilation, plays a pivotal role in the clinical outcomes of patients with ALI/ARDS and may also lead to the development of a systemic inflammatory response syndrome (SIRS) [8,9] and multiple systemic organ failure [10]. This hypothesis offers a reason why mortality in ARDS remains about 35–65% despite advances in critical care, and most patients with ARDS who die do so from multiple systemic organ failure rather than from hypoxia [11].

**Mechanical Stress and Ventilator-Associated Lung Injury**

Two distinct phenomena have been proposed as responsible for VALI: (1) high lung volume associated with elevated transpulmonary pressure and alveolar overdistension; (2) the continuous recruitment/derecruitment of collapsed alveoli due to low end-expiratory volume [12]. Other factors contribute to or aggravate injury, including pre-existing lung damage, high-inspired oxygen concentration and the local production and systemic release of inflammatory mediators [13]. Therefore, the main determinant of the degree of VALI is the interaction of the ventilator settings with patient-related factors, particularly the condition of the ventilated lung.

**Alveolar Overdistension**

The observation that trumpet players commonly achieve airway pressures of 150 cmH\textsubscript{2}O without the occurrence of air leakage suggests that the degree of lung