Cytokines, neurokines or both? Mixed mechanisms of mechanical lung injury

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The lung is a dynamic organ, subject to mechanical forces throughout development and adult life. Whilst the changes in shape and size during breathing may be important in regulating the normal physiology of the lung (Wirtz & Dobbs, 2000), the deformations associated with positive pressure mechanical ventilation can cause damage, particularly in the already injured lung.

Is stretch-induced lung injury clinically significant?

The answer is yes. Although positive pressure ventilation is often used to provide respiratory support in critically ill patients, clinical and animal studies have shown that mechanical ventilation can worsen existing lung injury and cause injury in its own right. By limiting lung expansion, using smaller tidal volumes or airway pressures, and by sustaining alveolar volume with positive end-expiratory pressure, the release of pulmonary and systemic inflammatory mediators is reduced, as are organ dysfunction and mortality (Ranieri *et al.* 1999). 'Protective' ventilation is now generally accepted as a means (some would argue the *only* proven means) to reduce mortality in patients with acute lung injury and acute respiratory distress syndrome (ARDS).

What is the mechanism of stretch-induced lung injury?

Mechanical injury to the lung from excessive alveolar distension, high airway pressures and repeated closing and opening of small airways and alveoli, leads to stress failure of the plasma membranes of both endothelial and epithelial barriers (Uhlig, 2002). In addition to direct mechanical injury, lung injury is also caused by cell-mediated inflammation and soluble mediators (Tremblay & Slutsky, 1998). The alveolar macrophage (Pugin *et al.* 1998), the neutrophil (Zhang *et al.* 2002) and the alveolar epithelium (Tremblay *et al.* 2002) have all been implicated, with pro-inflammatory cytokines (e.g. tumour necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and IL-8) playing a central role. Early accounts of acute lung injury concentrated almost exclusively on such mechanisms (Donnelly & Haslett, 1992) and later clinical studies used inflammatory mediators as biomarkers. To date, it could be argued that research into mechanically induced lung injury has remained constrained within this paradigm. However, while cytokine release can be related to the degree of lung stretch (Nakamura *et al.* 2001), and inhibition of cytokine actions reduces lung injury (Imai *et al.* 1999), the mechanisms of stretch-induced injury are more complex, and appear to involve neural as well as simple mechanical and cytokine effects.

Substance P in stretch-induced lung injury

Substance P is the best known of a host of mediators involved in neurogenic inflammation (de Swert & Joos, 2006). Other mediators (prostaglandins, histamine, purines, bradykinin, leukotrienes and proteases) and extrinsic substances that can damage the lung (smoke, ozone, sulphur dioxide and endotoxin) activate the unmyelinated C fibre axon, predominantly through transient receptor potential (TRP) ion channels. Antidromic impulses activate C fibre endings, an important mechanism of inflammation, with release of substance P, neurokinins and calcitonin gene-related peptide, which trigger vasodilatation, oedema, mucus secretion and leukocyte activation. Substance P acts on the TRPV1 receptor, and a variety of irritants such as acrolein and other oxidants are now recognised to act via the TRPA1 receptor. These receptor pathways interact with other recognised inflammatory mediators, for example bradykinin and acetylcholine interact with TRPV1 and TRPA1 (McMahon & Wood, 2006; Woolf & Ma, 2007). In addition, pulmonary nociceptors can also be activated by pro-inflammatory cytokines (Yu *et al.* 2007). The end result of these synergies is amplification of the inflammatory process.

Increased levels of substance P are found in animals with induced acute lung injury and in patients with ARDS. It is also possible that stretch-induced lung injury may be mediated by these mechanisms, because the TRPA channels are also mechanosensors (Tsunozaki & Bautista, 2009). Both selective C fibre denervation by capsaicin administration, and targeted gene deletion of the preprotachykinin-A (PPT-A) gene, can reduce stretch-induced lung injury in mice, with injury to the air–blood barrier continuing long after the discontinuation of injurious ventilation. These findings support the concept that the lung injury induced is neurokinin dependent and not simply the result of mechanical disruption (Chavolla-Calderon *et al.* 2003).

In a recent issue of *The Journal of Physiology*, Brégeon *et al.* (2010) explored the role of substance P in stretch-induced lung injury further. They subjected rats to injurious high airway pressure ventilation and found that measures of lung injury (oxygenation, lung compliance, weight and myeloperoxidase) and increases in lung substance P, interleukin-1β and IL-6 were reduced by specific blockade of the neurokinin-1 receptor or bilateral vagotomy. These results appear consistent with a neurally mediated mechanism in stretch-induced cytokine upregulation and lung injury.

The wider role of neurally mediated lung inflammation

Rapid shallow breathing has long been recognised as a reflex response to pulmonary parenchymal inflammation (Binger & Brow, 1924). Recent evidence of this mechanism is that endotoxin (Lai *et al.* 2005) or irritants such as hydrogen peroxide activate C fibres by a TRPV1-dependent pathway (Ruan *et al.* 2005). C fibre activation causes reflex rapid shallow breathing. The TRPA1 receptor is also involved in C fibre activation (Taylor-Clark *et al.* 2008; Nassenstein *et al.*

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2008). While abnormal breathing patterns commonly occur in patients who have problems in weaning from ventilatory support (Jubran & Tobin, 1997; Bien *et al.* 2004), the intriguing question of whether these abnormal patterns are the result of neurally mediated lung inflammation remains unresolved.

In conclusion, the mechanisms underlying stretch-induced lung injury are incompletely understood, but neurokinins and substance P are clearly implicated in ventilator-induced lung injury. Although stretch can cause extra-neuronal substance P release, for example from leukocytes, release of substance P from C fibres and the effects of vagal section support the concept that stretch-induced lung injury is, at least in part, neurogenically mediated. This concept warrants further investigation. Pharmacological blockade of the neurokinin system may be an option in the treatment or prevention of stretch-induced lung injury. Modulation of the neurokinin system may also reduce abnormal breathing patterns in patients with critical illness and facilitate weaning from mechanical ventilation.

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