Commentary

# Hyperoxic acute lung injury and ventilator-induced/associated lung injury: new insights into intracellular signaling pathways

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Published: 19 April 2007
This article is online at http://ccforum.com/content/11/2/126


*Critical Care* 2007, **11:**126 (doi:10.1186/cc5733)

See related research by Li *et al*., http://ccforum.com/content/11/1/R25

## Abstract

In patients with acute respiratory distress syndrome (ARDS), supportive therapy with mechanical ventilation and oxygen is often life saving. Further acute lung injury however, is an unfortunate consequence of oxygen therapy as well as mechanical injury secondary to ventilator induced/associated lung injury (VI/ALI). In this issue of *Critical Care*, Li *et al*. expand on the intra-cellular signaling pathways regulating interactions between injury cascades resulting from hyperoxia and high tidal volume ventilation. The findings, suggest that interference or cooperation of different signals may have critical consequences as evidenced by indices of increased lung inflammation, microvascular permeability, and lung epithelial apoptotic cell death.

Every patient with acute respiratory distress syndrome (ARDS) is hypoxemic by definition. In these patients, mechanical ventilation (MV) is often life-saving. Repetitive cyclic stretch however, results in regional overdistension or/and derecruitment which is associated with a number of severe complications termed ventilator-induced/associated lung injury (VI/ALI) [1]. The attributable mortality of VI/ALI has been estimated to be at least 9% [2], and despite evidence that high concentrations of oxygen (fractional inhaled concentrations of oxygen [$FiO_2$] greater than 50%), can lead to hyperoxic acute lung injury (HALI), oxygen therapy remains a cornerstone of management. Little is known about "permissive hypoxemia" and for the most part, clinicians will optimize positive end expiratory pressure (PEEP) to enable reductions in $FiO_2$, accepting oxygen saturations in the mid to high 80's. In the first three ICU days, most ARDS patients are ventilated with average FiO2 > 59% (mean FiO2 delivered on day 1 = 70%) [3], but it is not uncommon for the most severely ill to require much higher $FiO_2$ concentrations (100%) for prolonged periods or frequent intervals.

In a previous issue of *Critical Care*, Li and colleagues elucidate the potential mechanisms regulating interactions between injury cascades resulting from hyperoxia and high tidal volume ventilation [4]. Using gene-deficient models and specific inhibitors of intracellular signaling pathways, this author group demonstrate that the combination of hyperoxia and high tidal volume ventilation results in augmented lung injury, evidenced by indices of increased lung inflammation, microvascular permeability, and lung epithelial apoptotic cell death. The combined detrimental effect of oxygen and repetitive cyclic stretch was shown to result in the activation of specific intracellular signaling pathways. The paper by Li and colleagues is part of a growing body of literature suggesting that the response of the mechanically ventilated lung to biochemical or biomolecular stimuli is profoundly altered by the coexistence of injurious stimuli [5,6] that synergize at the cellular level [7] as well as at the tissue level [8]. More importantly, the findings suggest that interference or cooperation of signals may have critical physiological consequences such as activation of death pathways.

Studies on various model systems have shown that a relatively small number of transcription factors can set up strikingly complex spatial and temporal patterns of gene expression. This pattern creation is achieved mainly by means of combinatorial or differential gene regulation; that is, regulation of a gene by two or more transcription factors simultaneously or under different conditions. Li and colleagues offer insight into the specific molecular details of the mechanisms of combinatorial regulation of hyperoxia and high tidal volume. In their model, mitogen-activated protein kinase ERK1/2, c-Jun $NH_2$-terminal kinases, and downstream binding of the transcription factor AP-1 were responsible for

$FiO_2$ = fractional inhaled concentration of oxygen; HALI = hyperoxic acute lung injury; IL = interleukin; NF = nuclear factor; TNF = tumor necrosis factor; VI/ALI = ventilator-induced/associated lung injury.

orchestrating the molecular response and cellular physiological consequence of HALI plus VI/ALI – whilst lung stretch alone is dependent on activation of the JNK pathway, high volume plus hyperoxia mediated its detrimental effect via JNK and ERK 1/2 activation.

Despite a historical emphasis on NF-κB-dependent inflammation-related genes as mediators of injury, Li and colleagues' paper suggests that the augmented response seen when high volume and hyperoxia coexist appears to be NF-κB independent. The molecular implication from their paper is that individual stimuli exert intracellular effects via independent signaling pathways that may converge or diverge at specific molecular 'nodes' or 'hubs' – critical control points and potential targets for therapy. Moreover, molecules that were previously perceived as reflecting redundancy in the response represent a sophisticated system that probably depends on the 'message' carried rather than the messenger. The clinical implications of deciphering injury specific intra-cellular signaling is that it provides novel insight into the potential for future molecular treatment of injury-specific stimuli.

Exposure to hyperoxia is a well-established model of lung injury characterized by the development of pulmonary edema and inflammation. The development of hyperoxic lung injury was until recently thought to require the generation of reactive oxygen species, which leads to alveolar epithelial and endothelial cell death by both apoptosis and necrosis [6]. Disturbance of cell-death pathways, either local (pulmonary) or distal (kidney and intestines), has also been implicated in the pathogenesis of VI/ALI and ensuing MOF [9], and this disturbance is a key feature of the alveolar remodeling process during recovery from injury. In contrast to the literature on VI/ALI, where increased expression of cytokines and chemokines has been thought to be related to increase epithelial cell apoptosis [10], in studies of HALI, overexpression of cytokines or chemokines (for example, TNF-α, IL-1β, IL-6, CXC-chemokine receptor 2, and IL-11), growth factors (for example, insulin growth factor and keratinocyte growth factor [KGF]), or the β subunit of the Na,K-ATPase have been shown to protect animals from hyperoxia by attenuating death signals [11]. Moreover, this effect appears to be independent of potential antioxidant effects, since antioxidants by themselves do not reverse or prevent all of the manifestations of HALI and since the ability of certain cytokines to inhibit hyperoxia-induced cell death is independent of major alterations in lung antioxidants [12]. This evidence raises crucial questions about how different injury signal components are integrated; what are the morbidity and mortality defining manifestations of VI/ALI and/or HALI and which, where and when should "outcome-defining" pathways be blocked.

## Competing interests

The author declares that they have no competing interests.

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