Intensive Care Med (2002) 28:383–385
DOI 10.1007/s00134-002-1226-5

EDITORIAL

P.M. Suter

# MV causes lung inflammation and systemic immune depression

## A balance of fire and ice

Received: 27 December 2001
Accepted: 28 December 2001
Published online: 9 February 2002


P.M. Suter (✉)
Surgical intensive care, University Hospitals,
1211 Genève 14, Switzerland
e-mail: peter.suter@hcuge.ch

The lung is a unique immunologic organ, responding to infectious, antigenic or toxic insults with specific humoral, cellular, and tissular mechanisms while maintaining its primary biologic functions [1]. It has been recognized more recently that other types of aggression lead to a significant activation of inflammatory mechanisms within the lung. For instance, direct or indirect severe trauma results in acute inflammation of the pulmonary parenchyma in a significant proportion of patients. These changes are characterized by massive leukocyte segregation in lung capillaries and interstitial space, as well as a marked leak of plasma and blood cells into the interstitium. This inflammatory reaction is associated with significant changes in pro- and anti-inflammatory cytokine levels in bronchoalveolar lavage (BAL) fluid [2]. These mediators seem to play essential roles in the lung tissue changes, as their local concentrations are significantly higher than in the systemic circulation. A few exceptions exist, however: in ARDS secondary to septic shock due to an extrapulmonary infection, for instance, serum levels of proinflammatory cytokines can increase as much as intrapulmonary values [3]. The inflammatory tissue reaction can be of short duration and self-limiting, probably due to a subtle autoregulation and balance between pro- and anti-inflammatory mediators and repair mechanisms. The resulting features of cellular infiltration, tissue remodelling, and healing seem to be quite similar to other types of wounds and their healing [4]. In relatively rare cases, lung inflammation can persist for weeks, even without clear-cut superinfection, and persistently high BAL and/or plasma levels of proinflammatory cytokines seem to indicate a poor outcome [5].

The latest addition to the list of identified agents capable of inducing significant inflammatory lung injury is mechanical ventilation (MV), above all if higher tidal volumes and lower positive end-expiratory pressure (PEEP) levels are used [6, 7]. Although it has been known for a long time that damage to pulmonary tissue and airways can occur during prolonged MV, it has only become clear during recent years that not only are mechanical forces responsible for alveolar rupture and airway dilatation, but also acute inflammation is involved.

MV with “normal” or high tidal volumes leads to activation of leukocytes such as macrophages, monocytes, and polymorphonuclear cells, but possibly also to stimulation of alveolar pneumocytes I and airway epithelial cells, with a consecutive production of cytokines of the TNFα, IL-1β, IL-6 or IL-8 type, and a number of others. Stretching cultured human macrophages in a plastic chamber by positive pressure ventilation results in a significant production of pro-inflammatory cytokines when endotoxin is present [8]. MV of isolated perfused lungs produces increased pulmonary cytokines and translocation of nuclear factor-κB, which are effects similar to these observed after endotoxin infusion [7, 9].

From earlier work in humans, i.e., critically ill patients requiring MV, it seems clear that marked changes in cytokine levels and leukocyte count can be observed in BAL over a time period of 1–3 days [10]. Less is known about shorter periods of MV, both in terms of lung injury and inflammatory changes.

This gap in knowledge is beginning to be filled by work such as the one published in this issue of *Intensive Care Medicine* by Frans B. Plötz and his colleagues [11]. These authors have studied twelve infants undergoing diagnostic cardiac catheterization. The short-term effects of MV using a $V_T$ of 10 ml/kg and a PEEP of 4 $cmH_2O$ on intrapulmonary levels of pro- and anti-inflammatory

mediators were assessed, as well as the associated changes in the capacity of leukocytes collected from the systemic circulation to produce interferon IFNγ, TNFα, and IL-6, and finally the killing activity of systemic natural killer (NK) cells. The authors observed an increase in TNFα and IL-6 levels in BAL, but no significant changes in IL-8 and the anti-inflammatory cytokines IL-10 and IFNγ. In systemic blood, the capacity of lymphocytes to produce IFNγ was decreased and, after LPS stimulation, monocytes released less IL-6 and TNFα; in addition, the killing activity of NK cells was decreased.

How do these findings fit into the concept of the response of the lung tissue to insults such as trauma or MV? First, the results reported by Plötz et al. confirm the early inflammatory reaction to positive pressure ventilation seen in isolated lungs [7, 9], experimental animals subjected to high $V_T$ and low PEEP ventilation [12], and ICU patients [10]. Second, the data presented indicate that 2 h of MV is sufficient in these children to initiate significant changes in the local and systemic immune status. Third, their work suggests that further studies in children and adults are warranted – not only to confirm the results reported here, but also to define if different techniques of MV (e.g., lower tidal volume, higher PEEP) lead to a different pulmonary and systemic immune response. In addition, the specific roles of MV, anesthesia, and other interventions such as surgery should be investigated further.

There is another important consideration which should be included in this discussion. Indeed, the effects of a local inflammatory reaction on systemic immune status are not well explored. On the one hand, an overflow or a translocation of mediators and activated cells from the site of inflammation into the systemic circulation and to distant organs have been observed, inducing systemic signs of inflammation such as fever, hyperdynamic cardiovascular state, and leukocytosis as well as vital organ dysfunctions [13]. On the other hand, it has been suggested that local inflammation could be coordinated with systemic antiinflammation, thereby allowing the body to localize activated leukocytes at the injured local site [14]. This reaction could protect uninvolved organs and tissues from the damaging effects of mediators and activated cells, but it may also be immunosuppressive.

There are some data confirming a strong local proinflammatory activity in acute lung injury, assessed by BAL, whereas no such activity was detected in systemic blood [15]. Another clinical example of systemic immunosuppression (also called immune paralysis) occurs in the trauma patient: lymphocyte function can be impaired and these patients are at increased risk for infection, sepsis, and death [16]. In critically ill patients undergoing non-protective methods of MV and presenting with increased signs of intrapulmonary inflammation as assessed by BAL fluid, higher plasma levels of IL-6 (a cytokine considered to have significant antiinflammatory characteristics), more vital organ dysfunctions and a higher mortality have been observed [17, 18].

Any therapeutic consequences? If confirmed, the data of the present [11] and further studies could change the methods and techniques of MV used to allow short- or longer-term diagnostic or therapeutic interventions under anesthesia. It could be possible that even short-term MV should be conducted using a lung-protective strategy. On the other hand, millions of patients undergo MV during general anesthesia each week around the world, and little clinical evidence is available suggesting this is harmful for subsequent respiratory and other organ function. Recently, a clinical study did not reveal an increase in plasma levels of pro- or antiinflammatory cytokine levels after 1 h of mechanical ventilation with 15 or 6 ml/kg bw tidal volume [19].

However, the absence of clinically visible harmful effects of MV with normal tidal volume should not stop clinical investigators from looking into mechanisms producing acute lung inflammation and systemic depression of immune defences, because superinfection is a well-recognized complication after this type of intervention. The susceptibility and mechanisms of infection have been clarified to some extent, but more work must be done to improve our understanding, and thereby the means for prevention.

In conclusion, Plötz et al. report important changes in the immune response in children after only 2 h of MV – fire in the lung and icy peripheral leukocytes – a confirmation of a systemic immunosuppression in response to acute lung inflammation?

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