Netherlands
The Journal of Medicine

REVIEW

Cytokines and biotrauma in ventilator-induced lung injury: a critical review of the literature

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ABSTRACT

Background: Mechanical ventilation is known to induce and aggravate lung injury. One of the underlying mechanisms is biotrauma, an inflammatory response in which cytokines play a crucial role.
Objective: To review the literature on the role of cytokines in ventilator-induced lung injury (VILI) and multiple organ dysfunction syndrome (MODS).
Material and methods: 57 English written, peer-reviewed articles on cytokines in *in-vitro* settings (n=5), *ex-vivo* models (n=9) *in-vivo* models (n=19) and clinical trials (n=24).
Results: Mechanical ventilation (MV) can induce cytokine upregulation in both healthy and injured lungs. The underlying mechanisms include alveolar cellular responses to stretch with subsequent decompartimentalisation due to concomitant cellular barrier damage. The cytokines involved are interleukin (IL)-8 and CXC chemokines, and probably IL-6, IL-1β, and tumour necrosis factor (TNF)-α. Cytokines are important for signalling between inflammatory cells and recruiting leucocytes to the lung. There is strong circumstantial evidence that the release of cytokines into the systemic circulation contributes to the pathogenesis of MODS. Multiple studies demonstrate the relation between elevated proinflammatory cytokine concentrations and mortality.
Conclusion: Cytokines are likely to play a role in the various interrelated processes that lead to VILI and other MV-related complications, such as MODS and possibly ventilator-associated pneumonia. Cytokines are good surrogate endpoints in exploring the pathogenesis and pathophysiology of VILI in both experimental and clinical studies.

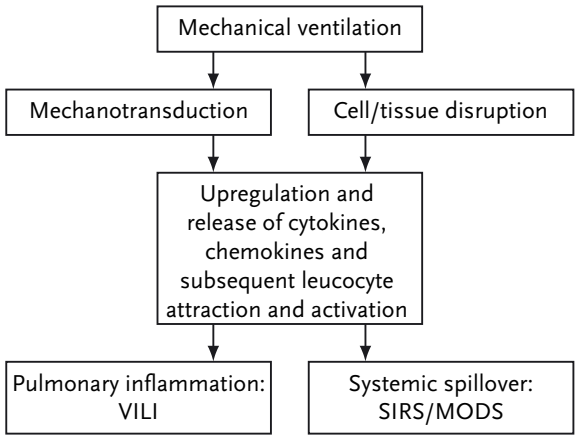
KEYWORDS

Cytokines, mechanical ventilation, ventilator-induced lung injury

INTRODUCTION

Mechanical ventilation (MV) is one of the cornerstones of ICU treatment. Despite its lifesaving effects, MV may lead to serious damage in both previously healthy and diseased lungs, a process called ventilator-induced lung injury (VILI; *figure 1*). In 1974, Webb en Tiernay demonstrated that MV with high peak airway pressures resulted in lung oedema, alveolar disruption, capillary leakage and death.[1] Further studies revealed that the end-inspiratory volume and not the end-inspiratory pressure was the main determinant (volutrauma). Subsequent studies showed that cyclic opening and collapse of alveoli, even at low inspiratory pressures and low inspiratory volume, increases stretch and shear forces resulting in lung injury and surfactant dysfunction.[2,3] This atelectrauma could be attenuated by increasing positive end-expiratory pressure (PEEP) and outweighed the concomitant increase in inspiratory pressure.[1,4] Recent studies have shown that MV upregulates pulmonary cytokine production, which may result in an inflammatory reaction aggravating lung injury (biotrauma). This inflammatory reaction is not confined to the lungs but also involves the systemic circulation and has its effects on distal end-organs, which offers an explanation for the observation that most adult respiratory distress syndrome (ARDS) patients do not die

Figure 1 *Presumed mechanism in mechanical ventilation*



VILI = ventilator-induced lung injury; SIRS = systemic inflammatory response syndrome; MODS = multiple organ dysfunction syndrome.

from respiratory failure but from multiple organ dysfunction syndrome (MODS).[5]

In this review we will discuss the role of cytokines in VILI and relate these findings to the clinical setting.

Inflammatory response to mechanical ventilation

Pulmonary injury and inflammation is a complex process in which cytokines play an important role. Cytokines are low-molecular-weight soluble proteins that transmit signals between the cells involved in the inflammatory response.[6] They are produced by bronchial, bronchiolar and alveolar epithelial cells[7] but also by alveolar macrophages and neutrophils.[8] The balance between the proinflammatory cytokines tumour necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-8 and anti-inflammatory cytokines such as IL-10 is essential for directing the immune response.[9] Some of the cytokines have natural antagonists, for example IL-1ra which makes an interpretation of the net effect cumbersome.[10,11] TNF-α and IL-1 induce NF-κB activation, a critical step in the transcription of genes necessary to perpetuate the innate immune response that ultimately results in activation and extravasation of polymorphonuclear leucocytes (PMNs) and other immune active cells, a process that starts within minutes after commencing mechanical ventilation.[12] Leucocytes are predominantly activated and attracted to the lungs by CXC chemokines and IL-8.[13] However, alveolar recruitment of PMNs by instilling a chemoattractant (LTB4) does not result in lung injury,[14] indicating that other factors, possibly cytokines, are necessary to activate them. This activation and attraction of leucocytes is a very important feature in biotrauma. Experimental studies using PMN-depleted animals demonstrate a significantly reduced degree of VILI.[15] Also, leucocyte apoptosis appears to be delayed in adult acute lung injury (ALI) and neonatal chronic lung disease (CLD).[16,17] contrary to pulmonary epithelial cells[18,19] and other end-organs that exhibit increased apoptosis.[20] Incubation of normal PMNs in bronchoalveolar lavage (BAL) fluid derived from ARDS patients results in delayed apoptosis compared with those incubated in normal BAL fluid.[21] Inhibition of neutrophil apoptosis seems mediated by soluble factors, such as the proinflammatory cytokines, possibly IL-8 and IL-2,[22] granulocyte colony-stimulating factor and granulocyte/macrophage colony-stimulating factor (GM-CSF), and levels of soluble Fas-ligand appear to be higher in BAL fluid derived from ARDS nonsurvivors than in that of survivors.[21] Similarly, Fas, Fas-ligand and Caspase-3 are more prevalent in alveolar walls of patients succumbing to ARDS than in those who died without this diagnosis, and soluble recombinant human Fas ligand infusion in the experimental setting results in increased alveolar apoptosis and injury.[23]

Another important pathophysiological relation in VILI is that between cytokines and surfactant. Surfactant dysfunction or deficiency is one of the prominent features of lung injury. Inflammation and more specifically cytokines such as TNF-α and IL-1 are thought to decrease surfactant components either directly[24] or indirectly by inducing alveolar leakage of proteins that subsequently inhibit surfactant function.[25]

There are several mechanisms by which mediator release may occur during mechanical ventilation: alterations in cytoskeletal structure without ultrastructural damage (mechanotransduction); stress failure of the alveolar barrier (decompartimentalisation), stress failure of the plasma membrane (necrosis), and effects on the vasculature independent of stretch or rupture.

Mechanotransduction

One of the most intriguing mechanisms of ventilation-induced cytokine release is mechanotransduction. Transmembrane receptors such as integrins, stretch-activated ion channels and the cytoskeleton itself are identified as the key structures in mechanosensing that start various intracellular processes.[26,27] Mechanotransduction, the stimulation of gene transcription following mechanosensing, is most likely signalled by mitogen-activated protein kinase (MAPK).[28,29] Most alveolar cells are capable of producing pro- and anti-inflammatory mediators such as TNF-α, IL-1β, IL-6, IL-8, and IL-10[8,28,30-34] when stretched *in vitro*[8,32,33,35] or when ventilated with a large tidal volume (Vt) in *ex-vivo* and *in-vivo* experiments (*tables 1* and *3*).

In premature neonates, cytokine production appears to be related to gestational age, with a delayed maturation of the anti-inflammatory response.[36] Injurious MV also induces upregulation of genes responsible for c-fos which

Table 1 *Experimental in-vitro studies*

Author, reference	Study subject	Study design	Studied variables	Results
Pugin[8]	Human alveolar macrophages	A: Static B: Cyclic stretch C: LPS static D: LPS + cyclic stretch	TNF-α, IL-6, IL-8, NF-κB activation	IL-8: A < C < B < D TNF-α, IL6: A/B = 0, C < D Dexamethasone blocks increase of TNF-α, NF-κB
Vlahakis[33]	Alveolar epithelium	A: Cyclic stretch B: Static stretch	IL-8	A > B
Blahnik[36]	Neonatal lung macrophages	LPS stimulation of lung macrophages: A: preterm B: term	TNF-α, IL-10	TNF-α: A = B IL-10: A < B
Li[85]	Neonatal lung macrophages	rIL-10/dexamethasone administration	IL-6, TNF-α	Decrease
Mourgeon[32]	Foetal rat lung cells	Stretch 0-5% ± LPS	MIP-2	Increase with higher stretch levels especially after LPS
Grembowicz[35]	Endothelium	Stretch	c-fos, NF-κB	Increase after plasma membrane disruption

in turn activates transcription for cytokine synthesis,[35] cyclo-oxygenase production and intercellular adhesion molecule (ICAM)-1 expression.[35]
NF-κB, a DNA-binding protein, plays a central role as a common messenger in cytokine regulation and inflammation. In experimental models, blockage of NF-κB decreases VILI.[8,37-40] However, its exact role in mechanotransduction is not completely clear yet.[27]

Translocation and decompartimentalisation
Besides mechanotransduction, direct trauma to the plasma membrane of alveolar cells and loss of cell integrity leads to the release of intracellular cytokines to the interstitium and decompartimentalisation into both the alveolar space and the systemic circulation.[41] Experiments by Haitsma *et al.* have demonstrated that in healthy animals ventilated without positive end-expiratory pressure (PEEP), endotracheal instillation of lipopolysaccharide (LPS) to induce local TNF-α production results in elevated serum concentrations of TNF-α, and conversely intraperitoneal LPS injection resulted in TNF-α in BAL fluid.[42]

Cytokines in VILI
Experimental studies
Experimental studies consist of both *in-vitro*, *ex-vivo* and *in-vivo* models, using different species and applying various techniques, which probably explains some of the observed inconsistencies in cytokine response (*tables 1* to *3*).[43] In almost all studies, cyclic overstretch increases alveolar levels of IL-8 or its rodent equivalent macrophage inflammatory protein (MIP)-2. MIP-2 is the most potent leucocyte chemoattractant and its role in the pathogenesis of VILI is very important. Neutrophil depletion attenuates the increase of IL-8 in the lungs and results in less severe VILI.[15,38] Activation of neutrophils in VILI occurs primarily in the alveolar space after migration. Subsequent lung damage is partly mediated by the interaction of the CXC chemokine receptor 2 ligand in lung tissue with its receptor on neutrophils.[44] Other proinflammatory cytokines such as IL-1β and IL-6 are elevated in most but not all studies. Recombinant IL-1 receptor antagonist attenuates neutrophil recruitment in a lung lavage model.[45] The involvement of another potent proinflammatory cytokine TNF-α in the pathogenesis of VILI is still under debate. Increased TNF-α levels after MV were found in most but not all uninjured lung models, surfactant depletion and ALI models, and sepsis models (*tables 2* and *3*). Endotracheal instillation of anti-TNF-α antibody attenuates VILI in both the previously uninjured and injured lung, suggesting a role for TNF-α.[46,47] However, lack of TNF-α signalling (TNF-α receptor -/- mice) does not show diminished VILI.[46] In general, most of the reviewed studies show a more pronounced increase in cytokine levels with larger tidal volumes or absent PEEP or when animals are concomitantly subjected to other injurious strategies such as hyperoxia.[48] The observed proinflammatory response usually parallels the observed histopathology. The injured lung appears to be far more susceptible for VILI than the healthy lung (two-hit model).

Human studies (table 4)
Both short-term and long-term clinical studies have shown that ventilator settings influence pulmonary cytokine levels. Plotz *et al.* demonstrated that two hours of lung-protective MV (Vt 10 ml/kg, 4 cm H_2O PEEP, FiO_2 0.4) in healthy infants anaesthetised for cardiac catheterisation

Table 2 *Experimental ex-vivo studies*

Author, reference	Study subject	Study design	Studied variables	Results
Tremblay[31]	Isolated rat lung, n=55	A: MV Vt 7/PEEP 3 B: MV Vt 15/PEEP 10 C: MV Vt 15/PEEP 0 D: MV Vt 40/PEEP 0 NaCl 0.9% *vs* LPS	TNF-α, IL-β, IFN-γ, IL-6/10, MIP-2, c-fos mRNA in BAL	A < B < C < D TNF-α/MIP2/c fos: LPS > NaCl 0.9%
Tremblay[7]	Isolated rat lung, n=24	A: MV Vt 7/PEEP 3 B: MV Vt 15/PEEP 10 C: MV Vt 15/PEEP 0 D: MV Vt 40/PEEP 0 NaCl *vs* LPS	TNF-α, IL-6, mRNA, in lung, homogenate, BAL	C and D > A Time-dependent response, peak at T = 30 min
Whitehead[86]	Isolated rat lung, n=70	A: MV Vt 7/PEEP 3 B: MV Vt 15/PEEP 3 C: MV Vt 15/PEEP 0 D: MV Vt 40/PEEP 0 NaCl *vs* LPS	TNF-α, IL-β, MIP-2, in BAL	*NaCl*: TNF-α, IL-β: A < D *LPS*: TNF-α, MIP-2 A > D
Chu[87]	Isolated rat lung, n=88	A: MV Vt 7 PEEP 5 B: MV Vt 7 PEEP 0 C: MV Vt 0 PEEP 0 D: MV PIP 50 PEEP 8 E: MV Vt 0 PEEP 50 F: MV Vt 0 PEEP 31	TNF-α, IL-6, MIP-2, in BAL	*TNF*-α: B > C = A; D = E > F *IL-6*: B > C = A; D > F = E *MIP-2*: B > C = A; D = E = F
Ricard[88]	Isolated rat lung, n=38	A: MV Vt 42 B: MV Vt 7 C: CPAP ± LPS	TNF-α, IL-1β, MIP-2, in serum and BAL	*Before LPS:* *Serum: A,B* - *BAL:* MIP-2/IL-1β: A > B = C *TNF*-α: - *After LPS*: *Serum*: TNF-α, IL-1β, MIP-2: increase B, C, D *BAL*: TNF-α, IL-1β, MIP-2: B = C > D
Bethmann[34]	Isolated mouse lung, n=27	A: MV ΔP 10 B: MV ΔP 25 Positive or negative pressure MV	TNF-α, IL-6, mRNA	A < B in both positive and negative pressure ventilation
Cheng[89]	Isolated mouse lung, n=nd	A: MV Vt 7 ZEEP 0 B: MV Vt 7 NEEP -7.5 C: MV Vt 7 NEEP –15	TNF-α, MIP-1, lung dynamics	C > A/B C < B/A
Bailey[48]	Isolated mouse lung, n=106	A: FiO_2 0.21 B: FiO_2 1.0 ± MV Vt 20	TNF-α, IL-6 in BAL	*TNF*-α: B + MV > B – MV *IL-6*: B > A ± MV
Held[40]	Isolated mouse lung, n=31	A: MV Vt 9 ΔP 10 B: MV Vt 32 ΔP 25 C: LPS	MIP-2, MIP-1α, NF-κB in BAL and Serum	*BAL/serum*: B = C > A Attenuation by dexa-methasone

resulted in elevated alveolar IL-6 levels.[49] Stuber *et al.* showed that increasing Vt from 6 to 12 ml/kg in ARDS patients increases cytokine levels in both BAL fluid and plasma within one hour.[50,51] These findings are consistent with both the results of Ranieri *et al.* who found lower cytokine levels in BAL fluid of patients ventilated with low Vt[52] and those of the ARDS network trial in 2000 that found lower plasma IL-6 levels in the low Vt group.[51]

In accordance with experimental data, previously injured lungs may be more susceptible for VILI. Wrigge *et al.* found elevated cytokine levels after elective surgery in patients with normal lungs, but there was no difference between patients ventilated with Vt 15 ml/kg and those with Vt 6 ml/kg.[53,54]

In longitudinal studies in both adults and neonates,[55-59] elevated proinflammatory cytokine levels are associated

Table 3 *Experimental in-vivo studies*

Author, reference	Study subject	Study design	Studied variables	Results
Wilson[90]	Mouse, n=29	A: MV Vt 9 B: MV Vt 35	TNF-α, MIP-2 in BAL	A < B
Wilson[46]	Mouse, n=15	A: MV Vt 10 B: MV Vt 44 TNF receptor knock out Anti-TNF e.t. wild mice Anti-TNF i.v. wild mice	MIP-2 in BAL Pulmonary PMN influx Lung injury	A < B in all mice PMN influx less in knock-out and anti-TNF e.t. mice, *not* in anti-TNF i.v. mice
Belperio[44]	Mouse, n=30	A: MV PIP 20 B: MV PIP 40 C57B6 *vs* $CXCR2^{-/-}$	KC/CXCL1, MIP-2/CXCL2/3 in lung tissue	A < B Less in $CXCR2^{-/-}$ mice
Gurkan[91]	Rat, n=26	A: MV Vt 6 B: MV Vt 17 NaCl 0.9 *vs* HCL e.t.	Il-6, TNF-α, VEGF in BAL	*NaCl*: A = B = 0 *HCl*: IL-6, VEGF: A < B
Chiumello[64]	Rat, n=40	A: MV Vt 16 PEEP 0 B: MV Vt 16 PEEP 5 C: MV Vt 9 PEEP 0 D: MV Vt 9 PEEP 5 E: MV Vt 9 PEEP 5 + RM HCl e.t.	TNF-α, MIP-2 in serum and BAL	*BAL TNF*-α: A > D > B > E *Serum TNF*: A > B = D = E *BAL MIP-2*: A > B = D = E *Serum MIP*: A > B > D = E
Caruso[92]	Rat, n=30	A: spontaneous ventilation B: MV Vt 6 C: MV Vt 24	IL-1β mRNA in lung tissue L infiltration	A < B = C
Copland[93]	Rat, n=nd	MV Vt 25 PEEP 0	HSP-70, IL-1β in lung tissue	Increase after 90 min MV
Copland[94]	Rat, n=18	A: MV Vt 25 B: MV Vt 40 Adult *vs* neonatal rats	mRNA IL-1β, IL-6, IL-10 TNF-α, MIP-2 in lung tissue	A/B: all parameters: adult > neonatal
Imanaka[95]	Rat, n=23	A: MV PIP 45 PEEP 0 B: MV PIP 7 PEEP 0	TNF-α mRNA, TGFβ1 mRNA PMN ICAM PaO_2	No increase A = B A < B B < A
Verbrugge[96]	Rat, n>100	Lung lavage model A: MV + Surfactant B: Partial liquid vent C: MV PEEP 16 D: MV PEEP 8 E: MV PIP 32/6	TNF-α, protein in BAL	*TNF*-α: A = B = C = D = E *Protein*: A = B = C < D = E
Quinn[97]	Rat, n=35	A: MV FiO_2 0.21 B: MV FiO_2 1.0	MIP-2, WBC in BAL Lung weight	B > A B > A
Bueno[98]	Rat, n=33	A: Vt 7 B: Vt 21 C: Vt 42	TNF-α in plasma PaO_2, lung weight	C > A/B (ns) *PaO2*: C < A/B *Lung weight*: A/B < C
Haitsma[99]	Rat, n=85	A: MV P 13/3 B: MV P 32/6 C: MV P 32/0	IL-6, MIP-2 in BAL and serum	A/B/C: increase MIP-2 in BAL B/C: increase MIP-2 in serum C: increase IL-6 in serum,
Haitsma[41]	Rat, n=85	A: MV P 45/0 B: MV P 45/10 LPS et/IP *vs* NaCl	TNF-α in serum and BAL	A > B LPS > NaCl
Lin[76]	Rat, n=50	A: MV Vt 7 PEEP 5 1h/day B: MV Vt 21 PEEP 0 1h/day Bacterial installation e.t.	MIP-2, TNF-α Blood cultures	A > B A < B positive

Table 3 *Continued*

Author, reference	Study subject	Study design	Studied variables	Results
Herera[100]	Rat, n=125	A: MV Vt 6 B: MV Vt 20 PEEP vs ZEEP	IL-1β, IL-6, TNF-α serum, mRNA in lung tissue	B ZEEP > A ZEEP > A PEEP
Takata[101]	Rabbits, n=13	MV P 28/5	TNF-α mRNA in lung lavage cells	Increase
Imai[47]	Rabbits, n=25	A: MV Anti-TNF-α e.t. B: MV IgG e.t. C: MV NaCl e.t.	WBC in BAL	A < B = C
Narimanbekov[45]	Rabbits	A: FiO_2 0.21 low PIP B: FiO_2 1.0 high PIP C: B + rIL-1 antagonist	WBC in BAL	A, C < B

Table 4 *Human studies*

Author, reference	Study subject	Study design	Studied variables	Results
Ranieri[52]	ARDS, n=44	A: Vt 11 PEEP 6.5 B: Vt 7.5 PEEP 14.8	TNF-α, IL-1β, IL-6, IL-8, IL1-RA, in BAL/serum	Most variables A > B
Stuber[50]	ALI, n=12	A1: Vt 5 PEEP 15 (6H) A2: Vt 12 PEEP 5 (6H) A3: Vt 5 PEEP 15 (6H)	TNF-α, IL-1β, IL-6, IL-10, IL1-RA, in BAL/serum	Serum A1 = A3 < A2 BAL A1 < A2 < A3
Wrigge[53]	Elective surgery, n=39	A: Vt 15 PEEP 0 B: Vt 6 PEEP 0 C: Vt 6 PEEP 10	TNF-α, IL-6, IL-10, IL1-RA	A = B = C
Wrigge[54]	Thoracotomy/ laparotomy, n=34/30	A: Vt 12-15 PEEP 0 B: Vt 6 PEEP 10	TNF-α, IL-1, 6, 10, 12	A = B = C
ARDS network[51]	ARDS, n=861	A: Vt 6 B: Vt 12	IL-6 Mortality	A < B A < B
Meduri[60]	ARDS, n=27	A: survivors B: nonsurvivors	TNF-α, IL-1β, IL-6, IL-8	A < B
Meduri[102]	Persistent ARDS, n=17	A: R/methylprednisolone B: R/-	TNF-α, IL-1β, IL-6 IL-10 mRNA in cells primed with plasma	A < B A > B
Headley[73]	ARDS, n=43	A: survivors B: nonsurvivors	TNF-α, IL-1β, IL-6, IL-8	A < B
Douzinas[63]	Sepsis/ARDS, n=8	Mechanical ventilation	TNF-α, IL-6,	Arterial > venous
Park[9]	ARDS, n=69	A: patients at risk for ARDS B: patients developing ARDS	TNF-α, TNF-α R I & II, IL-1β, IL1-RA, sol IL-1β r II, IL-6, sol IL-6 r, IL-8	Anti-inflammatory cytokines/ pro-inflammatory cytokines A > B, both > 1
Parsons[70]	ALI, n=861	A: Vt 6 B: Vt 12	IL-6, IL-8, IL-10	IL-6, IL-8 : A < B Mortality and morbidity related with IL-6, IL-8
Parsons[71]	ALI, n=95	A: Vt 6 B: Vt 12	Sol TNF receptor I	A < B
Plotz[49]	Infants, n=12	Vt 10 PEEP 4 Anaesthesia for cardiac catheterisation	TNF-α, IL-6	Increased after 2 hours
Yoon[103]	Neonates, n=69	Intrauterine infection	IL-6, CLD	IL-6 related to CLD
Wang[104]	Neonates, n=34	Mechanical ventilation	IL-16 in BAL	Detectable Associated with increased BAL L

Table 4 *Continued*

Author, reference	Study subject	Study design	Studied variables	Results
Kwong[105]	Premature neonates, n=15	Mechanical ventilation	IL-1β, IL-8, IL-10 in BAL	IL-10 undetectable IL-10 inhibits IL-1β, IL-8 in BAL derived macrophages
Mc Colm[106]	Preterm neonates, n=17	Mechanical ventilation	IL-1β, IL-8, IL-10 in BAL	IL-10 detectable in CLD, elevated IL-1β, IL-8
Oei[59]	Neonates, n=48	Mechanical ventilation	IL-10 in BAL	IL-10 increases with GA Low IL-10 in CLD
Schultz[107]	Neonates, n=20	RDS	IL-10 in BAL	Elevated pro-inflammatory cytokines, stable IL-10
Groneck[55]	Neonates, n=59	Follow-up infants with prolonged MV need	IL-8 in BAL	Increased IL-8 levels
Hitti[56]	Neonates, n=136	A: RDS B: no RDS	TNF-α in BAL	A > B
Jonsson[57]	Neonates, n=28	A: CLD B: no CLD	IL-1β, IL-6, IL-8 in BAL	A > B
Munshi[58]	Neonates, n=56	A: RDS progress to BPD B: RDS resolving	IL-6, IL-8 in BAL	A > B

with more severe lung injury and worse outcome, supporting the concept that lung injury is partly the result of a massive proinflammatory response.[60-62]

Cytokines and multiple organ dysfunction syndrome

In patients with ARDS the highest cytokine concentrations are found downstream from the lung.[63] Thus biotrauma is not only confined to the lungs but may also result in a systemic inflammatory response syndrome (SIRS)[52,61,62,64] and distant organ apoptosis,[20] both leading to MODS and death. This offers an explanation for the observation that most patients with ARDS do not die from respiratory failure but from MODS.[5] The presumed causal relation between a ventilation-induced increase in systemic cytokine levels and subsequent MODS is an interesting hypothesis.[37,61,62,65-69] Several studies have found plasma cytokine levels to be higher during large tidal volume ventilation.[51,52,70,71] and associated with the development of MODS,[72] and persistent cytokine elevation in turn is associated with a poor outcome in patients with ARDS.[60,73] Another important mechanism contributing to the development of MODS is the ventilation-induced enhancement of local dissemination of bacteria[74] and decompartimentalisation of bacteria and endotoxins from the alveolar space into the circulation.[75-77] Bacteria derived from BAL fluid from ARDS patients with persistent local inflammation exhibit enhanced growth capacity when incubated with proinflammatory cytokines.[78] Kanangat *et al.* showed that the induction of cytokines by LPS diminished the bacterial killing capacity of monocytes.[79] This supports the theory that a persistent local proinflammatory reaction may be a risk factor for developing a ventilator-associated pneumonia (VAP).[80] *In-vitro* corticosteroids block these increased bacterial growth capacities in the presence of high pro-inflammatory cytokine concentrations.[81] If confirmed this may be an interesting new strategy in preventing VAP in certain selected patient groups.

The role of immunomodulation on the clinical course of VILI and MODS needs further investigation. In neonatal RDS, early treatment with corticosteroids has significantly decreased the inflammatory response,[82] diminished CLD and dramatically improved survival, the contribution of corticosteroids in (late) adult ARDS is still controversial.[83]

CONCLUSIONS

There is a growing body of evidence that mechanical ventilation may sensitise the innate immune system and that in turn the innate immune system may sensitise the lungs to the effects of mechanical ventilation. This explains the exaggerated ventilation-induced inflammatory response in preinjured lungs and is of great clinical importance.[84] Cytokines play an important role in the various interrelated processes that lead to ventilator-induced lung injury and other related systemic complications, such as multiple organ dysfunction syndrome and possibly ventilator associated pneumonia.

ABBREVIATIONS

ΔP = PIP-PEEP difference
ALI = actual lung injury
ARDS = adult respiratory distress syndrome
BAL = bronchoalveolar lavage
BPD = bronchopulmonary dysplasia
CLD = chronic lung disease
CPAP = continuous positive airway pressure
e.t. = endotracheal
FiO_2 = fractional inspired oxygen
HSP = heat shock protein
ICAM = intercellular adhesion molecule
IL = interleukin
i.v. = intravenous
LPS = lipopolysaccharide
MIP = macrophage inflammatory protein
MV = mechanical ventilation
nd = not documented
NEEP = negative end-expiratory pressure (in cm H_2O)
PaO2 = pulmonary artery oxygen
PEEP = positive end-expiratory pressure (in cm H_2O)
PIP = peak inspiratory pressure (in cm H_2O)
PMN = polymorphonuclear leucocytes
RA = receptor antagonist
RDS = respiratory distress syndrome
rIL = recombinant interleukin
RM = recruitment maneuver
SOL = soluble
TNF = tumour necrosis factor
VEGF = vascular endothelial growth factor
Vt = tidal volume (in ml/kg)
WBC = white blood cells
ZEEP = zero end-expiratory pressure

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