CRITICAL CARE

REVIEW

Bench-to-bedside review: Ventilation-induced renal injury through systemic mediator release - just theory or a causal relationship?

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Abstract

We review the current literature on the molecular mechanisms involved in the pathogenesis of acute kidney injury induced by plasma mediators released by mechanical ventilation. A comprehensive literature search in the PubMed database was performed and articles were identified that showed increased plasma levels of mediators where the increase was solely attributable to mechanical ventilation. A subsequent search revealed articles delineating the potential effects of each mediator on the kidney or kidney cells. Limited research has focused specifically on the relationship between mechanical ventilation and acute kidney injury. Only a limited number of plasma mediators has been implicated in mechanical ventilation-associated acute kidney injury. The number of mediators released during mechanical ventilation is far greater and includes pro- and anti-inflammatory mediators, but also mediators involved in coagulation, fibrinolysis, cell adhesion, apoptosis and cell growth. The potential effects of these mediators is pleiotropic and include effects on inflammation, cell recruitment, adhesion and infiltration, apoptosis and necrosis, vasoactivity, cell proliferation, coagulation and fibrinolysis, transporter regulation, lipid metabolism and cell signaling.
Most research has focused on inflammatory and chemotactic mediators. There is a great disparity of knowledge of potential effects on the kidney between different mediators. From a theoretical point of view, the systemic release of several mediators induced by mechanical ventilation may play an important role in the pathophysiology of acute kidney injury. However, evidence supporting a causal relationship is lacking for the studied mediators.

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Introduction

Acute kidney injury (AKI) is a common problem in critically ill patients and carries significant morbidity and mortality. Based on a recent multinational study, the incidence of AKI is estimated to be 5.7%, with a mortality of 60% [1]. AKI rarely occurs in isolation but usually develops in the context of multiple organ failure. Despite advances in dialysis technology and supportive care, mortality resulting from AKI has remained unchanged over the past years and is as high as 80% when associated with respiratory insufficiency [1,2]. An observational study recently found that 75% of all patients with acute respiratory failure required some form of renal replacement therapy [1].

Mechanical ventilation (MV) is an independent risk factor for the development of AKI and can contribute to its development by three proposed mechanisms: blood gas disturbances leading to hypoxemia or hypercapnia and subsequent neurohumoral-mediated effects on renal blood flow during MV; changes in cardiac output, redistribution of intra-renal blood flow and stimulation of hormonal and sympathetic pathways may affect systemic and renal hemodynamics, thereby decreasing renal blood flow; and MV-induced biotrauma, defined as a pulmonary inflammatory reaction to MV with pulmonary mediator release [1,3]. Subsequent spill-over of these mediators into the systemic circulation may contribute to AKI [4].

Although various processes play significant roles in the pathophysiology of AKI, this review focuses specifically on the potential role of plasma mediators released as a result of MV in the pathogenesis of AKI. First, we review the current clinical and experimental literature describing mediators that are systemically released during MV and their effect on the kidney. The causality of the relationship between systemically released mediators and AKI will be explored. Second, we identify mediators whose release is attributable to MV and discuss the potential effects of these mediators on the kidney. This will provide a framework for future research on ventilation-induced renal injury through systemic mediator release.

Methods

We performed an extensive literature search in PubMed using medical subject headings and text words, supplemented by scanning the bibliographies of the recovered articles. We combined 'acute renal failure' and 'acute kidney injury' using the term 'OR'. This search was subsequently combined with 'mechanical ventilation' using the Boolean operator 'AND'. Using a similar search strategy, using 'mediator' and 'cytokine' we identified 19 different plasma mediators that increased during MV. We included only *in vivo* studies in which the increase in plasma mediator levels was exclusively attributable to MV. We excluded neurohumorally increased mediators, mediators increased in renal tissue samples and mediators derived from *in vitro* experiments exposing cell cultures to mechanical stretch. Each mediator was searched in PubMed, also including alternative names and abbreviations. We combined these results with the terms 'glomerular', 'glomerulus', 'tubular', 'mesangial', 'mesangium', 'podocyte', 'acute renal failure' and 'acute kidney injury'. To delineate the potential effects of these mediators on the kidney, we limited the articles to studies that solely studied effects on the kidney or on different kidney cell types.

Mechanical ventilation, systemic mediator release and the kidney

The importance of MV in morbidity and mortality of patients suffering from acute respiratory distress syndrome is stressed by the 2000 landmark study by the ARDS Network. In this multi-center trial, lung protective ventilation decreased morbidity and mortality rates compared to a conventional strategy [5]. Although the exact mechanisms remain unknown, the biological response of the lungs to the effects of MV was aptly named biotrauma to describe the ongoing changes in pulmonary inflammation and the systemic release of inflammatory mediators [6]. The biotrauma hypothesis is supported by evidence from experimental models ranging from mechanically stressed cell systems to isolated lungs, intact animals, and humans [7]. Various mechanisms are responsible for the ventilation-induced release of mediators. There are four principal mechanisms, all of which appear to be clinically relevant: stress failure of the plasma membrane (necrosis); stress failure of endothelial and epithelial barriers (decompartmentalization); overdistension without tissue destruction (mechanotransduction); and effects on vasculature, independent of stretch and rupture [8]. The possible effects of systemically released and circulating mediators during ventilator-induced lung injury on organs distant from the lungs has prompted research to focus on the potential effects of mediators on the kidney (Table 1). Thus far only one clinical study has compared a conventional MV strategy with a lung-protective strategy in patients with acute respiratory distress syndrome. This single-center study found increased kidney failure in the conventional strategy group. A correlation was found between plasma IL-6 levels and the number of failing organs in the same patients [9]. In these patients an association between plasma soluble Fas ligand (sFasL) levels and changes in creatinine was also found [10]. The authors conclude that mediator release during MV is correlated to the development of multi-organ failure and these findings may partially explain the decrease in morbidity and mortality in patients ventilated with a lung protective strategy. In animal experiments the role of MV on the kidney was further explored, focusing on the role of pro-inflammatory mediators [11-14], renal apoptosis [10], vasoactive mediators and renal blood flow [15], coagulation and fibrinolysis [16,17], and other mediators such as vascular endothelial growth factor (VEGF) (Table 1) [18]. Of specific importance is the previously mentioned study by Imai and colleagues [10]. In contrast to other animal studies that are observational by nature, this is the only study that used specific blocking of mediators, albeit *in vitro*. Imai and colleagues found increased renal apoptosis after injurious ventilation in rabbits. *In vitro* blocking of sFasL prevented induction of apoptosis of cultured kidney cells by plasma from rabbits ventilated with an injurious ventilatory strategy [10]. Although limited in number, studies linking MV with acute respiratory failure have discovered several new potential pathways in addition to pro-inflammatory pathways through which MV may cause acute respiratory failure. To date, however, no study has established a causal relationship between specific mediators and acute respiratory failure during MV *in vivo* through, for instance, intervention studies where the release of mediators is prevented or by blocking released mediators.

Table 2 shows the mediators whose increased release was attributable to MV. Several clinical studies identified a large number of plasma mediators [5,19-24]. These plasma mediators are not only pro-inflammatory by nature, but anti-inflammatory mediators have been identified as well [22-24]. Furthermore, identified mediators are also involved in coagulation, fibrinolysis, cell adhesion and surfactant homeostasis [5,19-26]. Most research has focused on pro- and anti-inflammatory mediators as well as chemokines, and only limited studies have outlined a role for mediators primarily involved in cell growth and differentiation or apoptosis (Table 2) [10,18]. A more in-depth analysis of the various mediators summarized in Table 2 may provide new therapeutic insights.

Potential effects of mediators on the kidney

Pro-inflammatory

Tumor necrosis factor-α

In 1986 Tracey and colleagues [27] administered TNF-α intravenously to rats and observed, among other things,

Table 1. Effects of mechanical ventilation on the kidney

Reference	Model/injury	Ventilation strategy	Plasma mediators	Renal endpoints
Ranieri *et al*. 2000 [9]	ARDS patients	11 ml/kg, PEEP 6 versus 8 ml/kg, PEEP 15	IL-6, TNF-α, IL-1β, IL-8	Renal failure according to Knaus [198]
Choi *et al*. 2003 [18]	Healthy rats	20 ml/kg versus 7 ml/kg	VEGF	Proteinuria, albuminuria, eNOS expression, microvascular leak
Gurkan *et al*. 2003 [200]	Acid aspiration in mice	17ml/kg, PEEP 3 versus 6 ml/kg, PEEP 3		IL-6, VEGFR-2 expression
Imai *et al*. 2003 [10]	Acid aspiration in rabbits	15 to 17 ml/kg, PEEP 0 to 3 versus 5 to 7 ml/kg, PEEP 9 to 12	MCP-1, IL-8, GRO, sFasL	Creatinine, apoptosis, histological changes with EM
Crimi *et al*. 2006 [11]	Hemorrhagic shock and resuscitation in rats	12 ml/kg, PEEP 0 versus 6 ml/kg, PEEP 5	IL-6, MIP-2	Creatinine, apoptosis
Dhanireddy *et al*. 2006 [12]	Bacterial aspiration (*S. aureus*) in mice	Spontaneous breathing versus 10 ml/kg	IL-6, KC, MIP-2	Creatinine
O'Mahony *et al*. 2006 [13]	LPS i.p. in mice	Spontaneous breathing versus 10 ml/kg	IL-6, KC, MIP-2, TNF-α	Creatinine
Kuiper *et al*. 2008 [15]	Healthy rats	20 cmH_2O, PEEP 2 versus 14 cmH_2O, PEEP 5		Decreased renal blood flow, increased renal ET-1
Vaschetto *et al*. 2008 [14]	LPS aspiration in rats	15 ml/kg, PEEP 0 versus 6 ml/kg, PEEP 5	IL-6, TNF-α	Kidney apoptosis. Decreased creatinine clearance
Hegeman *et al*. 2009 [201]	Healthy mice	20 cmH_2O, PEEP 0 for 1, 2, 4 hours versus spontaneous breathing		Increased E-selectin, VCAM-1, ICAM-1, PECAM-1, IL-1β, KC mRNA expression. Increased MPO activity
Kobr *et al*. 2009 [26]	Healthy piglets	10 ml/kg versus 6 ml/kg versus spontaneous breathing	VCAM-1, ICAM-1	Decreased creatinine clearance and free water clearance

ARDS, acute respiratory distress syndrome; EM, electron microscopy; eNOS, endothelial nitric oxide synthase; ET, endothelin; ICAM, intercellular adhesion molecule; i.p., intraperitoneal; LPS, lipopolysaccharide; GRO, growth-regulated oncogene; KC, keratinocyte-derived chemokine; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; MPO, myeloperoxidase; PECAM, platelet endothelial cell adhesion molecule; PEEP, positive end-expiratory pressure (in cmH_2O); sFasL, soluble Fas ligand; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2.

hypotension, metabolic acidosis, hemoconcentration, acute tubular necrosis and death. This pleiotropic character of TNF-α is reflected by its multitude of effects on the kidney [28]. TNF-α has been implicated in renal inflammation, inflammatory cell recruitment, adhesion and infiltration, apoptosis and necrosis, vasoconstriction and vasodilatation, alterations in cell morphology and proliferation, coagulation and fibrinolysis, downregulation of urea, glucose, sodium and chloride transporters and renal lipid metabolism and signaling (Table 3). TNF-α, through activation of NF-κB, induces its own expression by mesangial cells [29-31], podocytes [32-34], and tubular epithelial cells [35,36].

In a TNF-α receptor knock-out mouse model of cisplatin nephrotoxicity and renal tubular epithelial cells, TNF-α increased gene expression of a variety of inflammatory mediators, such as transforming growth factor-β, RANTES (regulated upon activation, normal T-cell expressed, and secreted), IL-1β, TNF-α, T-cell activation-3, IL-6 and IL-8 (see Table 3 for a complete list) [37-42]. TNF-α is also capable of increasing expression of major histocompatibility complex (MHC) I on mesangial cells [43], which indicates the stimulation of antigen-presenting properties by mesangial cells under inflammatory circumstances. *In vitro* exposure of mesangial cells and tubular epithelial cells to TNF-α increased expression of CC and CXC chemokines (Table 3), which are involved in neutrophil, monocyte and T-lymphocyte recruitment [44-46]. In both tubular epithelial cell monolayer and tubular epithelial and endothelial cell bilayer experiments, TNF-α increased leukocyte transmigration [41,42]. By increasing the expression of intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1 and L-selectin on mesangial cells and glomerular endothelial cells, TNF-α also facilitates leukocyte adhesion and infiltration into the kidney [47-49].

Both *in vitro* and *in vivo* studies have shown that TNF-α induces caspase 8-dependent apoptosis of renal tubular cells and renal endothelial cells by binding to either the TNF-receptor-1 or Fas-receptor [50-53]. In glomerular endothelial cells, cytochrome c influx in the cytosol was found after TNF-α stimulation, suggesting a role in the mitochondrial pathway as well [54]. Ceramide is an important signaling molecule in cellular responses, including apoptosis [55]. In both mesangial cells and glomerular endothelial cells TNF-α stimulated ceramide formation, but only in the latter did this lead to increased apoptosis [56,57]. TNF-α also suppresses expression of anti-apoptotic proteins, both *in vitro* and *in vivo* [53,54]. Hruby and colleagues [58] showed *in vitro* that TNF-α induced cytolysis in mesangial cells, but not in glomerular epithelial cells. This may be partially attributable to the TNF-α-induced production of reactive oxygen species by mesangial cells [59].

Table 2. Plasma mediator release during mechanical ventilation; patient and animal data

Reference	Model/injury	Ventilation strategy	Systemic mediators
Calfee *et al*. [19]	ICU patients	12 ml/kg versus 6 ml/kg	sICAM-1
Eisner *et al*. [20]	ICU patients	12 ml/kg versus 6 ml/kg	SP-D
Parsons *et al*. [21]	ICU patients	12 ml/kg versus 6 ml/kg	IL-6, IL-8
Parsons *et al*. [22]	ICU patients	12 ml/kg versus 6 ml/kg	sTNFR-1
Ranieri *et al*. [23]	ARDS patients	11 ml/kg, PEEP 6 versus 8 ml/kg, PEEP 15	TNF-α, IL-1β, IL-6, IL-8, IL-1RA, sTNFR-55/75
Stuber *et al*. [24]	ICU patients	12 ml/kg, PEEP 5 versus 5 ml/kg, PEEP 15	IL-6, TNF-α, IL-10, IL-1RA
ARDS Network [5]	ICU patients	12 ml/kg versus 6 ml/kg	IL-6
Ware *et al*. [25]	ICU patients	12 ml/kg versus 6 ml/kg	PAI-1, aPC
Chen *et al*. [17]	Healthy rats	Non-ventilated versus 40 ml/kg	Active PAI-1
Chiumello *et al*. [202]	Acid aspiration in rats	16 ml/kg versus 16 ml/kg, 5 PEEP versus 9 ml/kg versus 9 ml/kg, 5 PEEP versus same with recruitment maneuvers	TNF-α, MIP-2
Choi *et al*. [18]	Healthy rats	20 ml/kg versus 7 ml/kg	VEGF
Crimi *et al*. [11]	Hemorrhagic shock and resuscitation in rats	12 ml/kg, PEEP 0 versus 6 ml/kg, PEEP 5	IL-6, MIP-2
Dhanireddy *et al*. [12]	*S. aureus* aspiration in mice	SB versus 10 ml/kg	IL-6, KC, MIP-2
Guery *et al*. [203]	Healthy rats	30 ml/kg versus 10 ml/kg	TNF-α
Haitsma *et al*. [16]	Pneumonia in rats	12 ml/kg versus 6 ml/kg, PEEP 5, versus SB	TATc, active tPA
Haitsma *et al*. [204]	LPS aspiration and i.p. in rats	45 cmH_2O versus 45 cmH_2O, PEEP 10	TNF-α
Haitsma *et al*. [205]	LPS aspiration and i.p. in rats	45 cmH_2O versus 45 cmH_2O, PEEP 10	TNF-α
Haitsma *et al*. [206]	Healthy rats	32 cmH_2O versus 32 cmH_2O, PEEP 6 versus 13 cmH_2O, PEEP 3	IL-6, MIP-2
Herrera *et al*. [207]	Septic rats	20 ml/kg versus 6 ml/kg versus 20 ml/kg, PEEP AIP versus 6 ml/kg, PEEP AIP	TNF-α, IL-6
Imai *et al*. [10]	Acid aspiration in rabbits	15 to 17 ml/kg, PEEP 0 to 3 versus 5 to 7 ml/kg, PEEP 9 to 12	MCP-1, IL-8, GRO, sFasL
Kobr *et al*. [26]	Healthy piglets	SB versus 6 ml/kg versus 10 ml/kg	VCAM-1, ICAM-1
Murphy *et al*. [208]	LPS aspiration in rabbits	12 ml/kg versus 5 ml/kg, PEEP 10 to 12	TNF-α
Oliveira-Junior *et al*. [209]	Healthy rats	42 ml/kg versus 7 ml/kg	TNF-α, IL-1β
O'Mahony *et al*. [13]	LPS i.p. in mice	SB versus 10 ml/kg	IL-6, KC, MIP-2, TNF-α
Schortgen *et al*. [210]	*P. aeruginosa* aspiration in rats	27 ml/kg versus 6 ml/kg versus 6 ml/kg, PEEP 8 versus PLV versus SB	TNF-α
Vaschetto *et al*. [14]	LPS aspiration in rats	15 ml/kg, PEEP 0 versus 6 ml/kg, PEEP 5	IL-6, TNF-α
Vreugdenhil *et al*. [211]	Healthy rats	32 cmH_2O versus 32 cmH_2O, PEEP 6 versus 14 cmH_2O, PEEP 6	MIP-2
Wolthuis *et al*. [212]	Healthy mice	15 ml/kg versus 8 ml/kg	IL-6, KC

AIP, above inflection point; aPC, activated protein C; ARDS, acute respiratory distress syndrome; GRO, growth-regulated oncogene; ICAM, intercellular adhesion molecule; IL-1RA, interleukin-1 receptor antagonist; i.p., intraperitoneal; KC, keratinocyte-derived chemokine; LPS, lipopolysaccharide; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; PAI, plasminogen activator inhibitor; PEEP, positive end-expiratory pressure (in cmH_2O); PLV, partial liquid ventilation; SB, spontaneous breathing; sFasL, soluble Fas ligand; sICAM, soluble intercellular adhesion molecule; SP-D, surfactant protein D; sTNFR, soluble TNF-α receptor; TATc, thrombin-antithrombin complex; tPA, tissue-type plasminogen activator; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

TNF-α stimulates mesangial cells to produce a variety of vasoactive mediators *in vitro* (Table 3) [60-69]. Piepot and colleagues [70] showed impaired endothelium-dependent arterial relaxation after TNF-α exposure. By disturbing the balance between vasoconstriction and vasodilatation, TNF-α is thus potentially capable of reducing glomerular blood flow and glomerular filtration rate [71]. Additionally, TNF-α induced downregulation of angiotensin (Ang)-II type-1 receptor expression *in vivo*, which may explain the frequently observed vasodilation during sepsis [72].

Tubular epithelial cell shedding and tubular obstruction play a role in renal dysfunction. Glynne and colleagues [73] incubated proximal tubular epithelial cells with

Table 3. Potential effects on the kidney of mediators released during mechanical ventilation

Mediator	Effects on kidney	References
Pro-inflammatory		
TNF-α	Stimulated expression of TGF-β, RANTES, MIP-2, MCP-2, IL-1β, TNF-α, T-cell activation 3, IL-6, phospholipase-A2, LIF. MHC-I upregulation	[37-40,43]
	Leukocyte infiltration through MCSF, MCP-1, GRO-α, β, γ, ENA-78, GCP-2, IL-8, MIP-1β and 3α, RANTES, ICAM-1, VCAM-1, L-selectin	[44-49]
	Death receptor- and mitochondrial-mediated apoptosis and ceramide signaling. Necrosis through ROS. Downregulation of anti-apoptotic proteins.	[50-54,56-59]
	Production of vasoactive mediators: PAF, ET-1, PGs, adenosine, NO. Downregulation Ang-II-R	[60-69,72]
	NO tubular epithelial cell shedding. Decreased proliferation of tubular and mesangial cells	[73,74]
	Increased PAI-1 gene expression, increased TF production with fibrin deposition	[75,76]
	Decreased gene expression for urea, glucose, sodium and chloride transporters/channels	[77-80]
	Decreased gene expression of nuclear hormone receptor LXR, its target genes and coactivators	[81]
IL-1β	Stimulated expression of IL-6, IL-8, LIF, ceramide. MHC-I upregulation	[40,43,87-89]
	Increased expression of MCP-1, GMCSF, MSF, ENA-78, RANTES, MIP-1β, ICAM-1	[90-93]
	Downregulation of Ang-II-R. Expression of NO, PGE2	[39,72,94,95]
	Stimulated growth of glomerular epithelial cells	[96]
	Increased TF expression and activity, upregulation of tPA and PAI-1	[97,98]
	Decreased gene expression for urea, glucose, sodium and chloride transporters/channels	[77-80]
	Decreased gene expression of nuclear hormone receptor LXR, its target genes and coactivators	[81]
IL-6	TNF-α, IL-1β stimulation. Increased ICAM-1, P-selectin expression with neutrophil infiltration	[105-107]
	Increased survival, upregulation of pro- and anti-apoptotic genes	[108]
	Decreased expression of Ang-II-R	[72]
	Increased oxidative stress, but increased expression of HO-1, Ref-1	[105,106]
	Proliferation of rat mesangial and tubular cells, increased HGF and met-c receptor. Conflicting reports	[109-111]
	Decreased gene expression for urea, glucose and chloride transporters	[77-79]
	Abrogation of protective effect of hyperlipidemia	[115]
Anti-inflammatory		
IL-10	Decreased synthesis of TNF-α and IL-1β	[118,119]
	Contradictory effects on ICAM-1 expression and leukocyte infiltration	[118,120]
	Prevention of apoptosis and necrosis. Decreased cell cycle activity	[118]
	Reduction of VEGF, iNOS and nitrite formation	[118,121]
	Proliferation of mesangial cells	[122-124]
sTNFR	Decreased expression of TNF-α, MCP-1	[71]
	Inhibition of apoptosis, decreased cell proliferation and fibrosis	[128-130]
IL-1RA	Decreased gelatinase B, stromelysin, MCP-1 and IL-8	[132,133]
	Decreased ICAM-1 expression and leukocyte infiltration	[134-138]
Chemotactic		
IL-8	Increased COX1 and PGE2 expression	[145]
	Alterations in glomerular basement membrane sulfate metabolism	[146]
MIP-2	Increased MCP-1, RANTES, MIP-2	[151]
	Decreased neutrophil influx	[152,153]
	Decreased fibrin deposition	[152]
KC = GRO-α	Increased MCP-1, RANTES, MIP-2, KC	[151]
	Neutrophil infiltration	[153]
	Stimulated proliferation of medullary collecting duct cells	[154]
	Increased COX1 and PGE2 synthesis	[145]
MCP-1	Increased IL-6	[155]
	Increased ICAM-1 expression, chemotaxis and haptotaxis, monocyte/macrophage infiltration	[155-165]
	Increased apoptosis	[164]
	Increased fibrosis, TGF-β, collagen deposits	[165-167]
	Decreased nephrin	[168]

Continued overleaf

Table 3. Continued

Mediator	Effects on kidney	References
Coagulation/fibrinolysis		
Active PAI-1	Increased leukocyte infiltration	[169]
	Fibrin, collagen deposits, increased fibronectin, TGF-β, decreased urokinase and fibrosis	[169-172]
tPA	Conflicting reports on leukocyte infiltration	[175,178]
	Conflicting reports on fibrosis	[175-178]
aPC	Decreased TNF-α, IL-6, IL-8, IL-18	[180-182]
	Decreased KC, MIP-2, MCP-1, suppression of leukocyte rolling, adhesion and infiltration	[180-184]
	Decreased apoptosis, necrosis	[180-185]
	Decreased nitrosative stress	[185]
	Decreased adrenomedullin, iNOS, angiotensin (II), ACE. Increased renal and peritubular blood flow, decreased permeability	[180,181,184]
	Decreased extracellular matrix depositions	[180,185]
Miscellaneous		
VEGF	Decreased MCP-1, ICAM-1, leukocyte infiltration	[188]
	Decreased apoptosis and necrosis	[189-192]
	Stimulated eNOS and NO expression	[193,194]
	Increased permeability	[195,196]
	Increased proliferation of glomerular cells, podocytes, mesangial cells, fibroblasts and capillaries	[192,194,213-220]
	Conflicting reports of fibrosis and sclerosis	[194,217,219-221]
	Sustained nephrin expression	[221]
sFasL	Increased apoptosis	[10]

ACE, angiotensin converting enzyme; Ang-II-R, angiotensin-II receptor; aPC, activated protein C; COX, cyclooxygenase; ENA, epithelial neutrophil activating protein; eNOS, endothelial nitric oxide synthase; ET, endothelin; GCP, granulocyte chemotactic peptide; GMCSF, granulocyte macrophage colony-stimulating factor; GRO, growth related oncogene; HGF, hepatocyte growth factor; HO, heme-oxygenase; ICAM, intercellular adhesion molecule; IL-1RA, interleukin-1 receptor antagonist; iNOS, inducible nitric oxide; KC, keratinocyte-derived chemokine; LIF, leukemia inhibitory factor; LXR, liver X receptor/retinoid X receptor; MCP, monocyte chemoattractant protein; MCSF, macrophage colony stimulating factor; MHC, major histocompatibility complex; MIP, macrophage inflammatory protein; MSF, migration stimulating factor; NO, nitric oxide; PAF, platelet activating factor; PAI, plasminogen activator inhibitor; PG, prostaglandin; RANTES, regulated upon activation, normal T-cell expressed, and secreted; Ref, restriction factor; ROS, reactive oxygen species; sFasL, soluble Fas ligand; sTNFR, soluble TNF-α receptor; TF, tissue factor; TGF, transforming growth factor; tPA, tissue type plasminogen activator; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

TNF-α and observed disruption of the actin cytoskeleton and elongation of cells and shedding of viable, apoptotic and necrotic cells dependent on nitric oxide (NO). Cell shedding was accompanied by dispersal of β1-integrins and E-cadherin. The same authors also found decreased proximal tubule epithelial cell proliferation, an effect that was also observed in mesangial cells [73,74].

TNF-α-induced histologic kidney damage is frequently characterized by glomerular fibrin deposition. By stimulating renal plasminogen activator inhibitor (PAI)-1 gene expression and increasing the production of tissue factor by mesangial and endothelial cells, TNF-α can contribute to fibrin deposition [75,76].

In a series of animal experiments, Schmidt and colleagues [77-80] hypothesized a role for urea, glucose, sodium and chloride transporters in sepsis-associated tubular dysfunction. Within hours after lipopolysaccharide injection in mice they showed decreased renal blood flow and glomerular filtration and impaired tubular sodium handling associated with decreased levels of the aforementioned transporters. In TNF-α-challenged mice they found significant downregulation of genes coding for urea, glucose, sodium and chloride transporters as well as for chloride channels and Na^+/K^+-ATPase-α_1 compared to wild-type mice.

In proximal tubule cells *in vitro*, TNF-α caused a downregulation of gene expression of the nuclear hormone receptor liver X receptor/retinoid X receptor (LXR) and several of its target genes and coactivators [81]. During the acute phase TNF-α interferes with lipid metabolism in the kidney, with potential subsequent effects on the anti-infective and anti-inflammatory properties of lipids [82].

Interleukin-1β

Cells of the innate immune system recognize microbial products and products released from dying and damaged cells, leading to the formation of complex proteins, termed inflammasomes [83,84]. Activation of caspase 1 by the inflammasome leads to cleavage and subsequent activation of IL-1β [85]. Glomerular endothelial cells, cortical tubular epithelial cells, podocytes and mesangial cells are capable of IL-1β production [86]. Despite its central role in the response to cell damage and microbes, surprisingly little *in vivo* research has focused on the role of IL-1β in acute kidney disease. IL-1β has been

implicated in inflammation and cell recruitment, vasoactivity, coagulation and fibrinolysis, and regulation of chloride, urea, sodium and glucose transporters (Table 3).

Through NF-κB signaling IL-1β stimulates human renal proximal tubular epithelial cells to produce IL-6 [87]. In mesangial cells, others showed IL-1β-driven expression of ceramide, IL-6, IL-8 and leukemia inhibitory factor [40,55,88,89]. Like TNF-α, IL-1β is also capable of up-regulating MHC class I expression in mesangial cells [43].

In mesangial and epithelial cell cultures, IL-1β induced upregulation of a multitude of chemoattractants, including CC and CXC chemokines [45,90-92]. Following chemoattraction, IL-1β also stimulates expression of ICAM-1 on mesangial cells, thereby facilitating leukocyte adhesion [93].

IL-1β is also involved in hemodynamic instability during septic shock. By downregulating Ang-II type-I receptors, IL-1β may be partially responsible for the decreased reactivity to vasoconstrictors [72]. Additionally, in mesangial cells, IL-1β, through inducible nitric oxide synthase (iNOS), caused increased production of NO, known for its vasodilatatory effects, and prostaglandin $(PG)E_2$, which has potential vasodilatory properties [39,94,95].

Data on the effects of IL-1β cell proliferation are limited. Tateyama and colleagues [96] showed that IL-1β could function as an autocrine growth factor for rat glomerular epithelial cells *in vitro*.

IL-1β can affect both coagulation and fibrinolysis *in vitro*. In mesangial cells, IL-1β upregulated tissue factor expression by a protein kinase C-dependent pathway, with an effect on tissue factor activity only when cells were rendered apoptotic [97]. Also in these cells, IL-1β was capable of inducing the fibrinolytic enzyme tissue type plasminogen activator (tPA), but also its inhibitor PAI-1 [98]. The effects of IL-1β on coagulation and fibrinolysis in the kidney *in vivo* remain unknown.

In the aforementioned series of animal experiments, Schmidt and colleagues [77-80] also found that IL-1β-challenged mice significantly downregulated genes coding for urea, glucose, sodium and chloride transporters as well as for chloride channels and Na^+/K^+-ATPase-α_1 compared to wild-type mice. This implicates IL-1β in sepsis-associated tubular dysfunction with decreased glomerular filtration rate, failure of urine concentration, decreased urine osmolality, increased fractional sodium excretion and glucosuria.

In human proximal tubule cells *in vitro*, IL-1β, like TNF-α, caused downregulation of gene expression of the nuclear hormone receptor LXR and several of its target genes and also of its coactivators [81]. The authors suggest a role for IL-1β in lipid metabolism in the kidney during the acute phase.

Interleukin-6

The exact nature of IL-6 remains the subject of debate - it has been extensively described as both pro- and anti-inflammatory [99,100]. IL-6 levels increase during hypoxia, tissue damage and organ failure [101-103] and predict mortality in patients with acute renal failure [104]. In the kidney, IL-6 is involved in inflammation, leukocyte adhesion and infiltration, apoptosis and survival, vasoactivity, prevention of oxidative stress, cell proliferation and lipid homeostasis during the acute phase (Table 3).

Ischemia/reperfusion (I/R) studies with IL-6 knock-out mice showed decreased levels of renal TNF-α and IL-1β compared to wild type [105]; this was accompanied by downregulated expression of ICAM-1 and P-selectin and decreased neutrophil infiltration [105-107].

The role of IL-6 in apoptosis and survival is complex. In cisplatin-induced renal failure, mice lacking IL-6 had better survival rates despite decreased renal function. This was associated with upregulation of both pro- and anti-apoptotic genes [108]. The authors explain these phenomena by the fact that the upregulation of pro-apoptotic genes disappears after 24 hours, while anti-apoptotic genes remain upregulated for 72 hours [108]. Others also found a positive effect on survival in IL-6 knock-out mice with improved renal function [105,106].

In mice exposed to intravenous IL-6, Schmidt and colleagues [72] found decreased expression of Ang-II type-I receptors, which are involved in vasoconstriction, potentially explaining vasodilatation during shock. In an I/R model and a mercury chloride-induced model of acute renal failure, IL-6 knock-out mice and mice treated with anti-IL-6 antibodies had lower levels of oxidative stress and NO-dependent oxidative stress. In addition, IL-6 bound to soluble IL-6 receptor, likely shedded from neutrophils during AKI, increased gene expression of heme oxygenase-1 and restriction factor-1, both known to protect against oxidative stress [105,106].

Conflicting reports delineate a role for IL-6 in proliferation of various kidney cells, associated with tissue repair and regeneration (Table 3) [109-114].

Similar to TNF-α and IL-1β, Schmidt and colleagues [77-79] hypothesized a role for urea, glucose and chloride transporters in sepsis-associated tubular dysfunction with failure of urine concentration, decreased urine osmolality and glucosuria. In IL-6-challenged mice they found significant downregulation of genes coding for urea, glucose and chloride transporters as well as for chloride channels and Na^+/K^+-ATPase-α_1 expression compared to wild-type mice, though to a lesser extent than TNF-α and IL-1β.

Poloxamer 407 induces hyperlipidemia that protects against renal I/R dysfunction. This was associated with decreased plasma levels of IL-6, but recombinant IL-6

infusion abrogated these effects. These results were confirmed in apolipoprotein-E- and angiopoietin-like 3-deficient mice, which suffer from hypercholesterolemia and hypolipidemia, respectively [115].

Anti-inflammatory

Interleukin-10

IL-10 exerts its anti-inflammatory effect through inhibition of MHC class II-associated antigen presentation and by decreasing circulating levels of CC and CXC chemokines [116]. However, in a dose-dependent manner, IL-10 can also promote inflammation through effects on B cells and natural killer cells and by stimulating cytokine production [116]. Increased levels of IL-10 predicted mortality in patients with acute renal failure and, interestingly, patients with specific IL-10 gene polymorphisms required less renal support during sepsis from pneumonia [104,117]. The effects of IL-10 on the kidney involve effects on inflammation, inflammatory cell recruitment and infiltration, apoptosis, necrosis and cell cycle activity, vasoactivity and cell proliferation (Table 3).

In vivo studies in different models of AKI, intravenous IL-10 administration decreased TNF-α production and prevented creatinine increase in mice [118]. Mesangial cells *in vitro* showed less production of TNF-α and IL-1β after stimulation with lipopolysaccharide in the presence of IL-10 [119]. Deng and colleagues [118] reported decreased ICAM-1 expression in mice during kidney injury and IL-10 injection; histological analysis also revealed decreased cast formation and leukocyte infiltration. Contradictory to these findings was an observation made by Chadban and colleagues [120] showing increased ICAM-1 expression on rat mesangial cells after stimulation with IL-10. In mice, administration of IL-10 prevented both apoptosis and necrosis, mainly in the outer stripe of the kidney, after cisplatin and I/R-induced kidney injury. IL-10 also decreased cell cycle activity [118].

IL-10 addition to glomerular epithelial cells *in vitro* reduced VEGF, a potent modulator of capillary permeability [121]. *In vivo*, IL-10 decreased iNOS, and in *in vitro* culture of cortical tubule cells, IL-10 exposure decreased nitrite formation [118].

In vitro experiments showed proliferation-stimulating effects of IL-10 on mesangial cells through platelet derived growth factor receptor α and β, but also upregulation of IL-10 mRNA, suggesting a possible autocrine mechanism [122-124]. These *in vitro* results were confirmed *in vivo* [124].

Soluble tumor necrosis factor-α receptor

Cleavage of the extracellular domain of the TNF-α receptor (TNF-αR) leads to soluble TNF-αR (sTNF-αR) capable of binding and thereby inactivating TNF-α. Blood sTNF-αR levels predicted acute renal failure in patients with septic shock and acute lung injury [125,126]. In rats subjected to ischemia reperfusion injury, sTNF-αR prevented loss of renal function, and prevented expression of TNF-α and monocyte chemotactic protein (MCP)-1 [127]. Without changes in hypotension, apoptosis, leukocyte infiltration or morphology, sTNF-αR preserved glomerular filtration rate, suggesting a role for vasoactive mediators [71]. Apoptosis of mesangial cells co-cultured with interferon-γ-stimulated macrophages was inhibited by sTNF-αR *in vitro* [128]. In *in vivo* studies in rats with unilateral ureteral obstruction, administration of sTNF-αR decreased tubular and interstitial cell proliferation and apoptosis and prevented renal fibrosis (Table 3) [129,130].

Interleukin-1 receptor antagonist

IL-1 receptor antagonist (IL-1RA) is a physiological inhibitor of IL-1β activity through competitive binding to the IL-1β receptor. Recombinant IL-1RA administration during sepsis showed a mortality benefit of almost 5% [131]. In mesangial cells addition of IL-1RA decreased gelatinase B, stromelysin, MCP-1 and IL-8 RNA and protein levels after stimulation with IL-1α and IL-1β [132,133]. In *in vivo* models of anti-glomerular basement membrane antibody glomerulonephritis and renal I/R treatment with IL-1RA resulted in improved kidney function, decreased expression of ICAM-1 and reduced renal histological damage, including decreased infiltration of lymphocytes, neutrophils and macrophages and less apoptosis (Table 3) [134-138].

Chemotactic

Interleukin-8

The chemokine IL-8 is produced mainly by macrophages, but also by renal tubular epithelial cells, mesangial cells and podocytes [139-142]. IL-8 levels predict the development of AKI, duration of MV and mortality in patients with AKI [104,143,144]. Exposure of mesangial cells to IL-8 *in vitro* leads to selective expression of cyclooxygenase (COX)1, but not COX2, and subsequent synthesis of PGE_2 [145]. *In vivo* infusion of IL-8 in rats causes increased albuminuria, mediated through alterations of sulfate metabolism by the glomerular basement membrane (Table 3) [146].

Macrophage inflammatory protein-2

Macrophage inflammatory protein (MIP)-2, a member of the superfamily of chemokines, is a potent chemotactic factor for neutrophils and stimulates the production of other inflammatory mediators such as IL-1β and TNF-α [147]. In kidneys, mesangial cells and glomerular epithelial cells stimulated by NO or IL-1β are capable of

synthesizing MIP-2 [148-150]. Exposure of mesangial cells to MIP-2 *in vitro* stimulates the release of MCP-1, RANTES and also MIP-2 [151]. Specific blocking of MIP-2 in *in vivo* models of shiga toxin-induced renal inflammation and anti-glomerular basement membrane antibody glomerulonephritis prevented renal neutrophil influx and fibrin deposition and decreased proteinuria (Table 3) [152,153].

Keratinocyte chemoattractant

Keratinocyte chemoattractant (KC), also known as growth related oncogene or CXCL1, in mesangial cells increased production of pro-inflammatory mediators such as MCP-1, RANTES, MIP-2 and KC [151]. KC exhibited neutrophil-attracting properties as shown in a mouse model of shiga toxin-induced renal injury [153]. *In vitro* KC stimulated proliferation of inner medullary collecting duct cells [154]. KC also stimulates mesangial cells to produce COX1 and enhances PGE_2 synthesis (Table 3) [145].

Monocyte chemotactic protein-1

MCP-1, or chemokine ligand 2, stimulates IL-6 synthesis *in vitro* through NF-κB and activator protein-1 activation [155]. *In vitro* and in several animal models of chronic kidney injury, MCP-1 has been shown to increase ICAM-1 expression leading to increased chemotaxis, haptotaxis, directional cell motility up a gradient of cellular adhesion sites, and leukocyte infiltration; macrophages and monocytes were mainly involved [155-165]. In rats transfected with a MCP-1 antagonist and protein overload proteinuria, decreased numbers of apoptotic cells were observed compared to wild type [164]. In models of crescentic nephritis and glomerulonephritis, blocking MCP-1 was shown to decrease collagen type I and IV deposition and decrease transforming growth factor-β levels [165,166]. Additionally, MCP-1 increased fibronectin production in mesangial cells, whereas finbronectin levels decreased in diabetic MCP-1 knock-out mice [167]. *In vitro* studies of podocytes showed decreased levels of nephrin, which is necessary for the proper functioning of the renal filtration barrier, after exposure to MCP-1 (Table 3) [168].

Coagulation and fibrinolysis

Plasminogen activator inhibitor-1

In patients with acute lung injury, PAI-1 is a prognostic factor for the development of acute renal failure [126]. In PAI-1 knock-out models or models overexpressing PAI-1 with anti-glomerular basement membrane glomerulonephritis, PAI-1 increases leukocyte infiltration, crescent formation, fibrin deposits, fibronectin synthesis and collagen accumulation [169-171]. Similar results were found in rodents with unilateral ureteral obstruction with increased transforming growth factor-β1 levels and decreased levels of urokinase [172]. Functionally, PAI-1 knock-out mice showed decreased albuminuria in a diabetes model (Table 3) [173].

Tissue type plasminogen activator

Similar to PAI-1, tPA is mainly involved in fibrosis through matrix metalloproteinase (MMP)-9 stimulation, myofibroblast activation and prevention of apoptosis of myofibroblasts and fibroblasts [174]. In tPA knock-out studies in I/R or unilateral ureteral obstruction models, tPA was shown to increase neutrophil influx, but other effects mainly concerned tissue remodeling, although conflicting reports exist [175-178] (Table 3).

Activated protein C

In patients with severe sepsis, baseline activated protein C (aPC) levels were inversely associated with worsening renal function and/or subsequent dialysis and treatment, whereas treatment with aPC was associated with improved renal function [179]. The anti-inflammatory effects of aPC are shown in the downregulation of the expression of TNF-α, IL-6, IL-8 and IL-18 [180-182]. By decreasing KC and MIP-2 protein and MCP-1 mRNA, aPC potentially prevents inflammatory cell recruitment [181-183]. Additionally, aPC suppresses leukocyte rolling and adhesion [184]. Histologically this leads to decreased leukocyte influx and also decreased renal myeloperoxidase levels [180,181]. In the same histological specimens, aPC prevented renal necrosis and apoptosis of glomerular and endothelial cells and podocytes [180-185]. In a model of diabetes, Isermann and colleagues [185] found aPC to have an antioxidant effect, decreasing nitrosative stress by decreasing kidney nitrotyrosine levels. Positive hemodynamic effects have been observed in various models, whereby aPC increased renal blood flow and peritubular flow, potentially by the observed decrease in adrenomedullin, iNOS, angiotensinogen mRNA, Ang converting enzyme and Ang-II [184]. Vascular permeability is also decreased by aPC [180,181]. The anticoagulant properties of aPC are highlighted by a decrease in circulating fibrin degradation products and decreased extracellular matrix depositions [180,185]. Combined, these effects of aPC preserve renal function as measured by creatinine, blood urea nitrogen levels and proteinuria (Table 3) [181-184].

Miscellaneous

Vascular endothelial growth factor

In a rodent model of ventilator-induced lung injury, Choi and colleagues [18] indicated a role for VEGF in endothelial NOS-mediated vasopermeability in lungs and kidneys. VEGF is a potent endothelial cell mitogen, promotes endothelial cell differentiation and survival,

stimulates angiogenesis and enhances vascular permeability. While deleterious in some forms of renal disease, VEGF may contribute to recovery in others [186,187].

In rodent models of glomeruolonephritis, intravenous VEGF decreased MCP-1 and ICAM-1 levels with a subsequent decrease in infiltrating leukocytes [188]. VEGF prevented glomerular and tubulointerstitial cell apoptosis and necrosis in models of hemolytic uremic syndrome and mesangio-proliferative nephritis, which was confirmed *in vitro* [189-192]. *In vivo* VEGF stimulated endothelial nitric oxide synthase expression in rats in a remnant kidney model, and in glomerular endothelial cells this increased NO expression [193,194]. One of the characteristics of VEGF is enhancement of vascular permeability; this was confirmed *in vitro* [195,196]. The proliferative effects of VEGF have been well described, both *in vivo* and *in vitro*, but these properties are likely of limited interest for the development of AKI (Table 3).

Soluble Fas ligand

sFasL is up to 1,000-fold less active than membrane-bound FasL in inducing apoptosis and has even been suggested to have antagonistic properties [197,198]. However, Imai and colleagues [10] showed apoptotic activity of serum of mechanically ventilated rabbits on renal tubular cells *in vitro*, which could be blocked by an anti-sFasL Fas:Ig fusion protein (Table 3).

Mediators - theory or causal relationship?

Central in the biotrauma hypothesis is the increase in intra-pulmonary mediator levels and the spill-over of these mediators from the lung into the systemic circulation. Several mediators are systemically increased during MV (Tables 1 and 2), although the exact cellular origins of the systemically measured mediators remains unknown [7]. Most of the mediators increased during MV have potential and well described effects on the kidney.

Most studies have focused on pro-inflammatory and chemotactic mediators, especially TNF-α, IL-6 and MIP-2. The effects of these pro-inflammatory mediators on the kidney have been studied to varying degrees. *In vivo* evidence indicates that TNF-α can cause and contributes to AKI, in contrast to IL-1β and MIP-2, for which sufficient *in vivo* data are lacking. IL-6 has been shown to be involved in AKI, but conflicting reports exist and no definite conclusion can be drawn. Much is known about the effects of anti-inflammatory and chemotactic mediators on the kidney. Strong evidence indicates a protective role for anti-inflammatory mediators, especially IL-10, in the development of AKI, but insufficient evidence exists to indicate a direct role in AKI for chemotactic mediators. Little is known about the potential effects on the kidney of some frequently studied mediators released during MV, such as soluble ICAM, soluble VCAM and sFasL. The potential of these mediators will remain unknown in the absence of studies on their possible effects on the kidney. Other mediators, for example, aPC and VEGF, have several well known effects on the kidney but have received little attention in studies on mediator release during MV. Studies of aPC and VEGF during MV have great potential to further delineate the effects of these mediators on the kidney.

IL-10, IL-8 and aPAI-1 all have predictive value for the development of AKI or AKI-associated mortality. Despite this, few studies have focused on the role of MV and, even though their increase may be an epiphenomenon, little is known about their potential role in the pathophysiology of AKI. Interestingly, we did not identify studies using specific blocking of mediators *in vivo* or specific knock-out models that could establish a causal relationship between MV-induced mediator release and AKI. However, we describe a multitude of potential effects on the kidney of several mediators that can be blocked rather specifically now in both animal models and humans. For example, anakinra, a synthetic IL-1RA, and infliximab, a monoclonal antibody against TNF-α, have found their way into clinical practice.

Before targeting mediators to prevent AKI in patients, care must be taken to learn from past experiences. Attempting to alter the course of sepsis, numerous studies have targeted a variety of mediators in critically ill patients, mainly suffering from sepsis. The rather disappointing results of these studies have led to insights into the possible mechanisms of failure in these studies. Several issues should be taken into account. The agent's biological activity, shown *in vitro* or in simple animal models, may not be replicable in humans. Dosage, timing and duration of the novel therapy are usually unknown. In most trials in critical care medicine the target population is heterogeneous, also including genetic polymorphisms. The complexity of mediator interdependency may also require the targeting of multiple mediators simultaneously or combined targeting of pro- and anti-inflammatory mediators.

Conclusion

From a theoretical point of view, the systemic release of several mediators induced by MV may play an important role in the pathophysiology of AKI. However, evidence supporting this hypothesis or showing causal relationships is lacking for the studied mediators. Future studies should therefore not only focus on the release of mediators during MV and a possible relationship with AKI, but should also study in-depth the pathophysiology by which these mediators may contribute to AKI.

Abbreviations

AKI, acute kidney injury; Ang, angiotensin; aPC, activated protein C; COX, cyclooxygenase; ICAM, intercellular adhesion molecule; IL, interleukin; IL-1RA,

interleukin-1 receptor antagonist; iNOS, inducible nitric oxide synthase; I/R, ischemia/reperfusion; KC, keratinocyte chemoattractant; LXR, liver X-receptor/retinoid X-receptor; MCP, monocyte chemoattractant protein; MHC, major histocompatibility complex; MIP, macrophage inflammatory protein; MV, mechanical ventilation; NF, nuclear factor; NO, nitric oxide; PAI, plasminogen activator inhibitor; PG, prostaglandin; sFasL, soluble Fas ligand; sTNF-αR, soluble TNF-α receptor; TNF, tumor necrosis factor; TNF-αR, TNF-α receptor; tPA, tissue type plasminogen activator; VCAM, vascular cellular adhesion molecule; VEGF, vascular endothelial growth factor.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
JWK performed the literature search and drafted the manuscript. RV performed the literature search and critically reviewed the manuscript. FDC critically reviewed the manuscript. FBP helped to draft the manuscript. ABJG conceived of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

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