Lung-kidney interaction in Critically ill Patients

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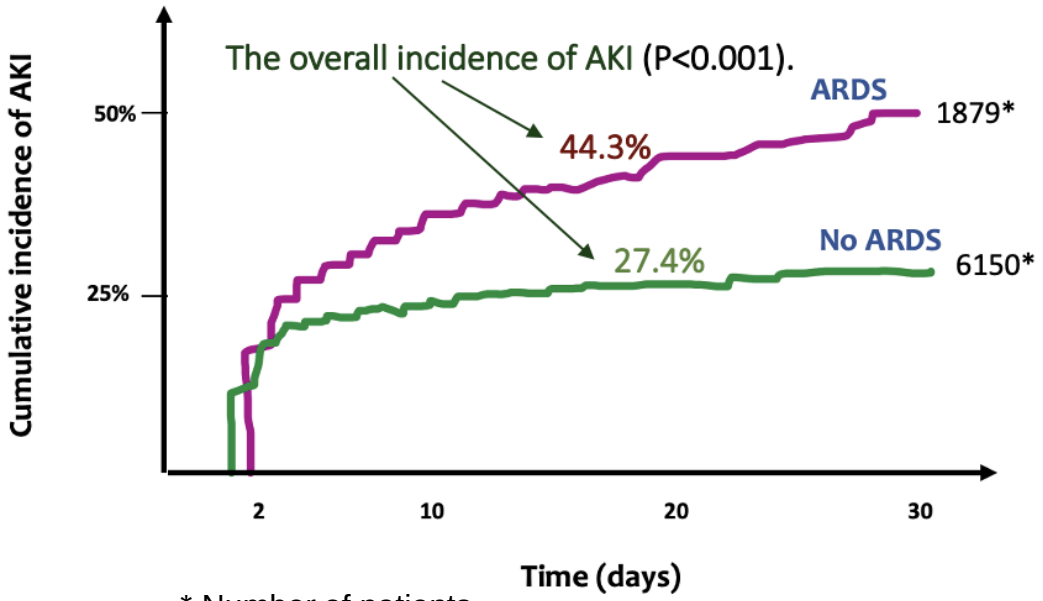
Epidemiology

- In critically ill patients with respiratory failure, the estimated incidence of AKI is 35%.
- The mortality rate among patients with both respiratory failure and AKI can reach as high as 80%.
- Typically, the cause of death in patients with respiratory failure is sepsis and multiorgan failure rather than hypoxia.
- In patients with AKI receiving RRT, the estimated incidence of respiratory failure is between 23 and 44%.

Acute Respiratory Distress Syndrome (ARDS) and Risk of AKI in Critically ill Patients

The results of an observational study on a prospective database of 18 intensive care units



* Number of patients

Factors independently associated with AKI after adjustment for cofounders

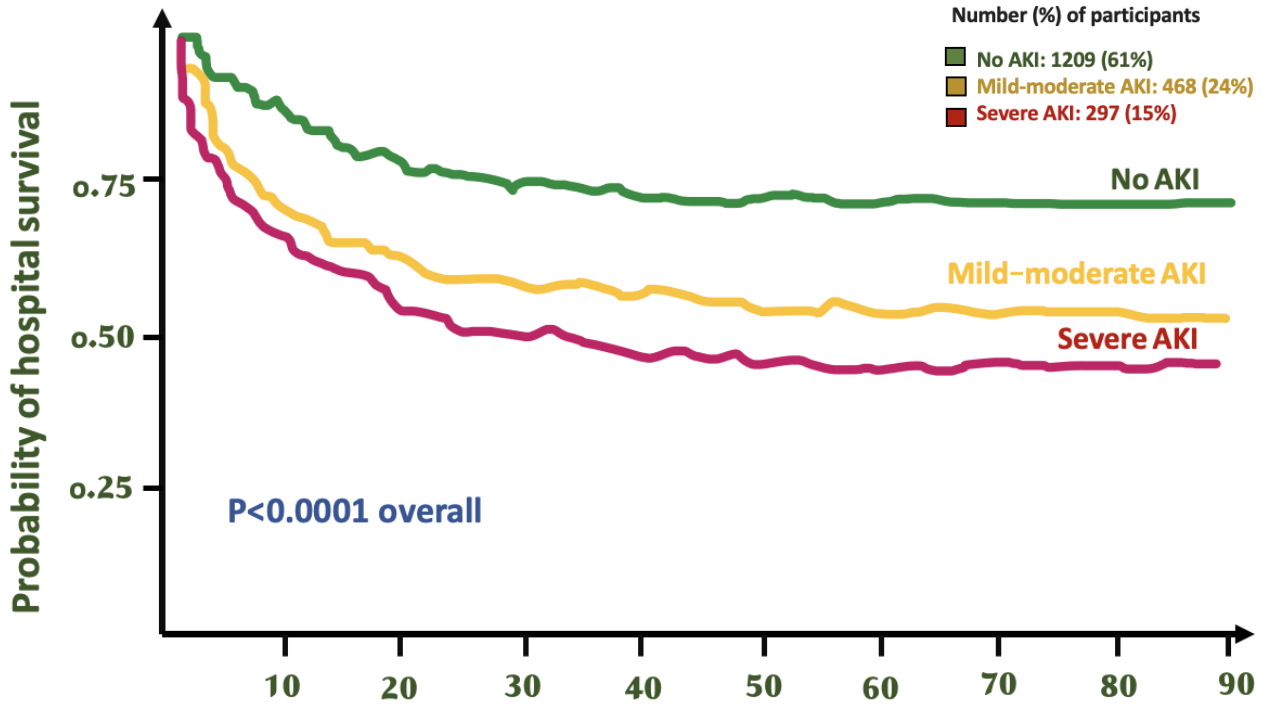
Variable	OR(95% CI)	*P* Value
Respiratory status		
No MV (reference)		
MV, no ARDS	4.34 (3.71 to 5.10)	<0.001
MV and ARDS	11.01 (6.83 to 17.73)	<0.001

MV: Mechanical ventilation

Darmon M, et al. Clin J Am Soc Nephrol 2014

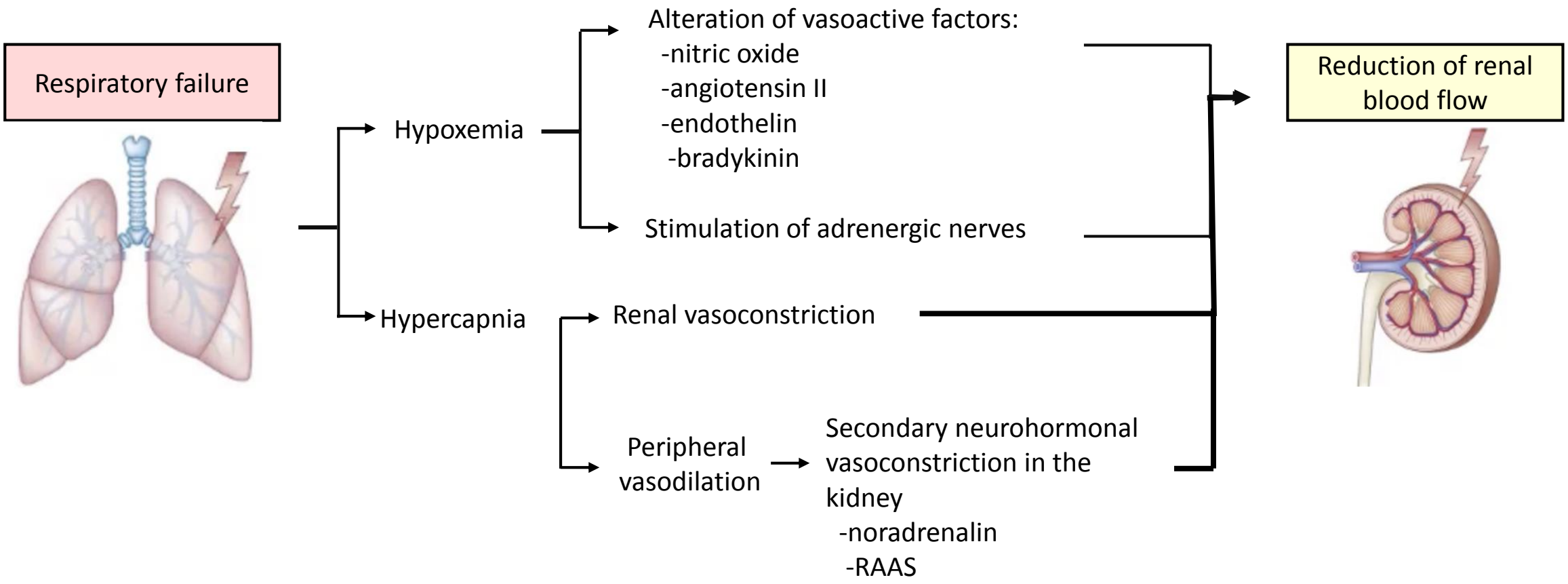
Impact of AKI on survival in Patients With ARDS

A secondary analysis of the results of a large multicenter observational study, evaluating patients with ARDS from 50 countries: the LUNG SAFE trial



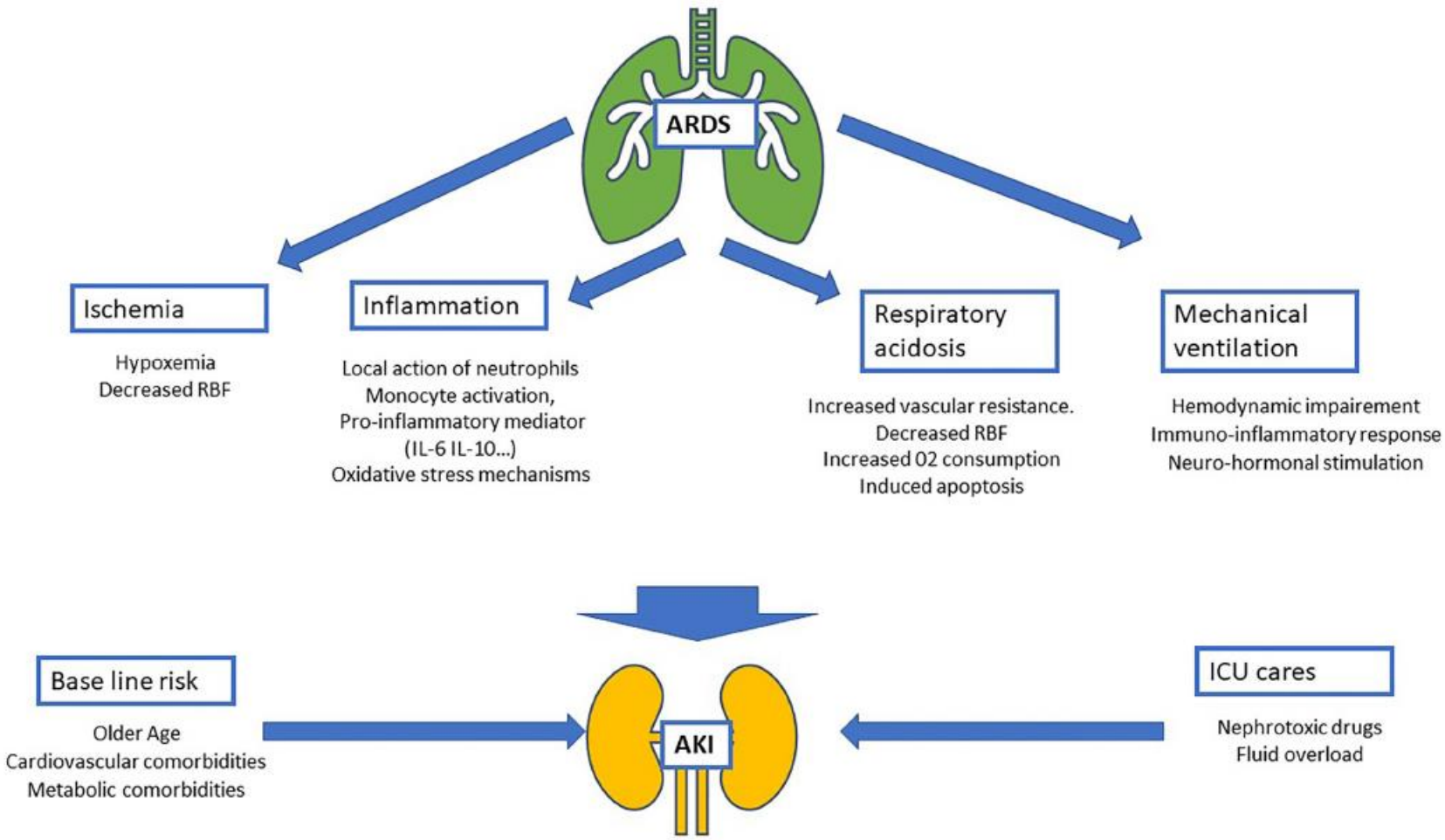
McNicholas BA, et al. Crit Care Med 2019

Suggested mechanisms to explain correlation between blood gas disturbances and renal blood flow



Sharkey RA,et al. Eur Respir J 1998 ; Sharkey RA, et al. Chest 1999; Hemlin M,et al. Clin Res J 2007

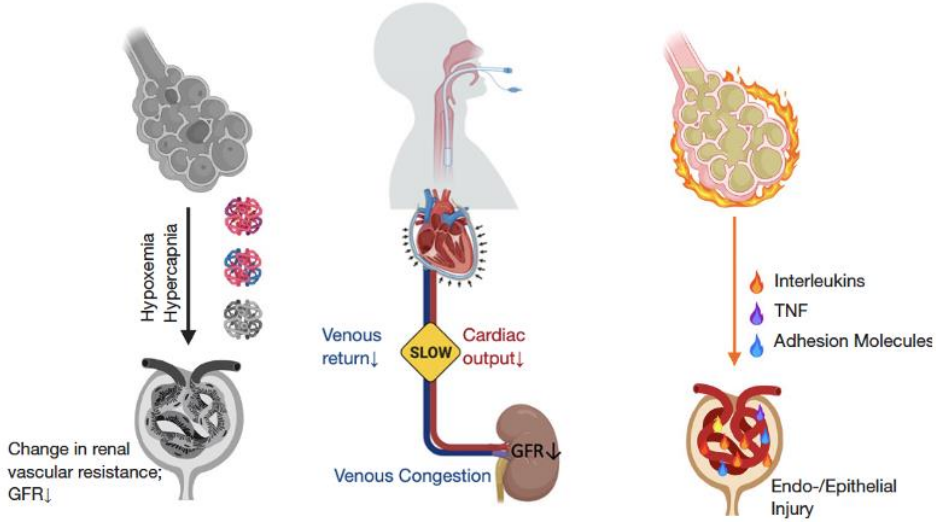
The reasons for the higher risk of AKI in Patients With ARDS



Marchiset A, and Jamme M. Frontiers in Nephrology 2022

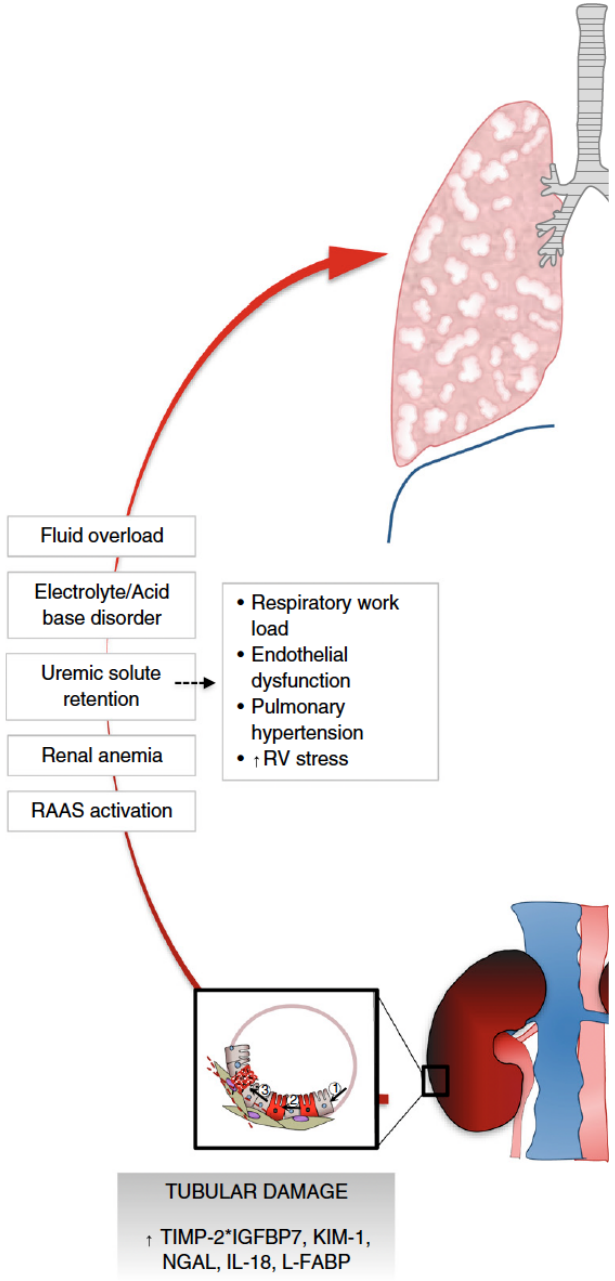
Ventilator induced kidney injury (VIKI)

- Gas exchange disturbances, can lower renal vascular resistance, leading to decrease in GFR.
- Unlike spontaneous breathing, mechanical ventilation reduces venous return due to positive intrathoracic pressure. This, along with an increased right ventricular afterload, can lower cardiac output.
- Increased sympathetic tone and elevated plasma renin activity during mechanical ventilation may also lead to reduction in renal blood flow.
- Inflammatory mediators released from the lung can trigger both endothelial and epithelial cell injury.
- Elevated levels of ADH may contribute to a positive fluid balance in patients undergoing mechanical ventilation; however, this correlation has not been definitely confirmed.



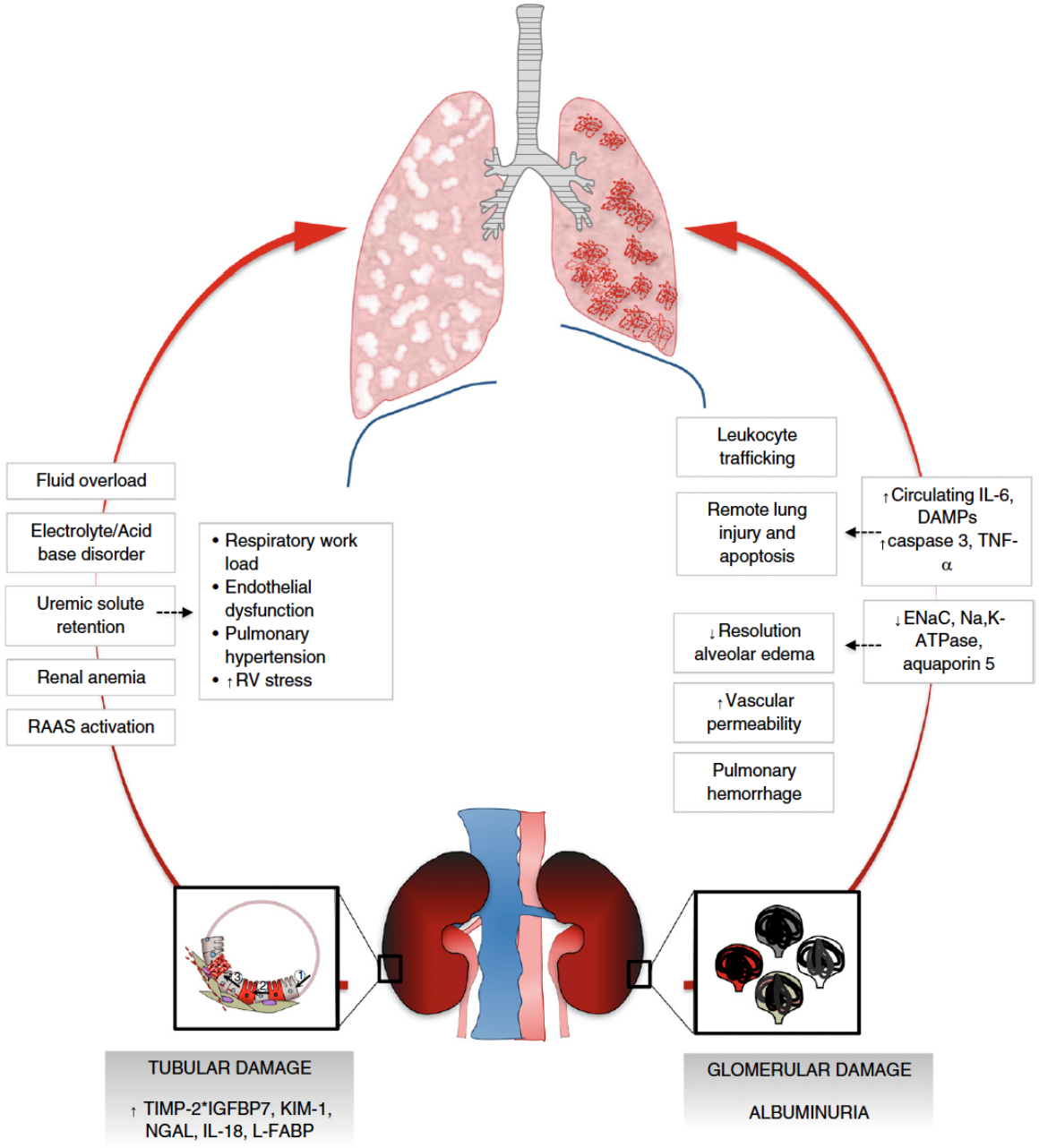
Yang H, et al. Ann Transl Med 2020

Kidney mediated lung injury



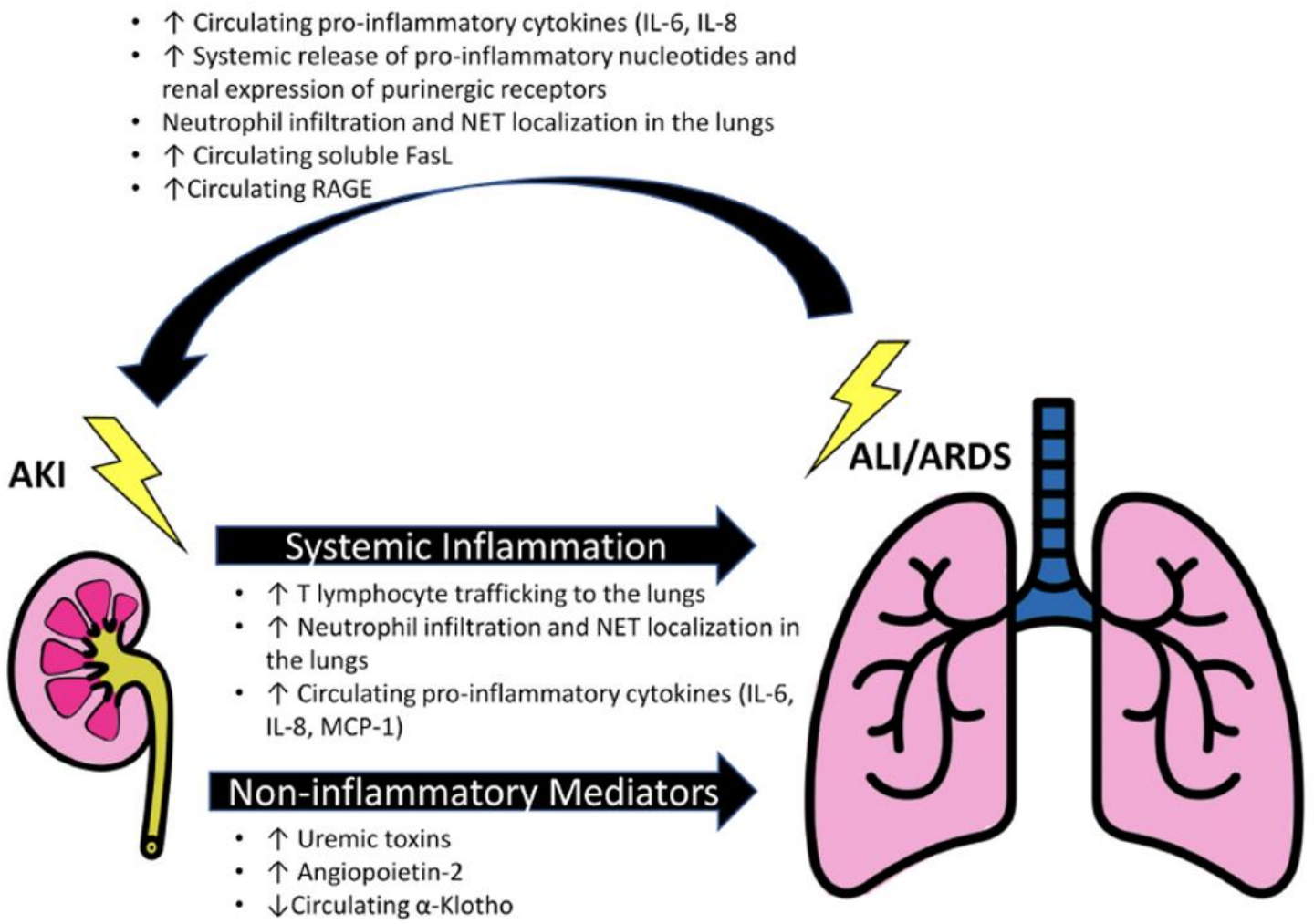
Husain-Syed et al. AJRCCM 2017

Kidney mediated lung injury

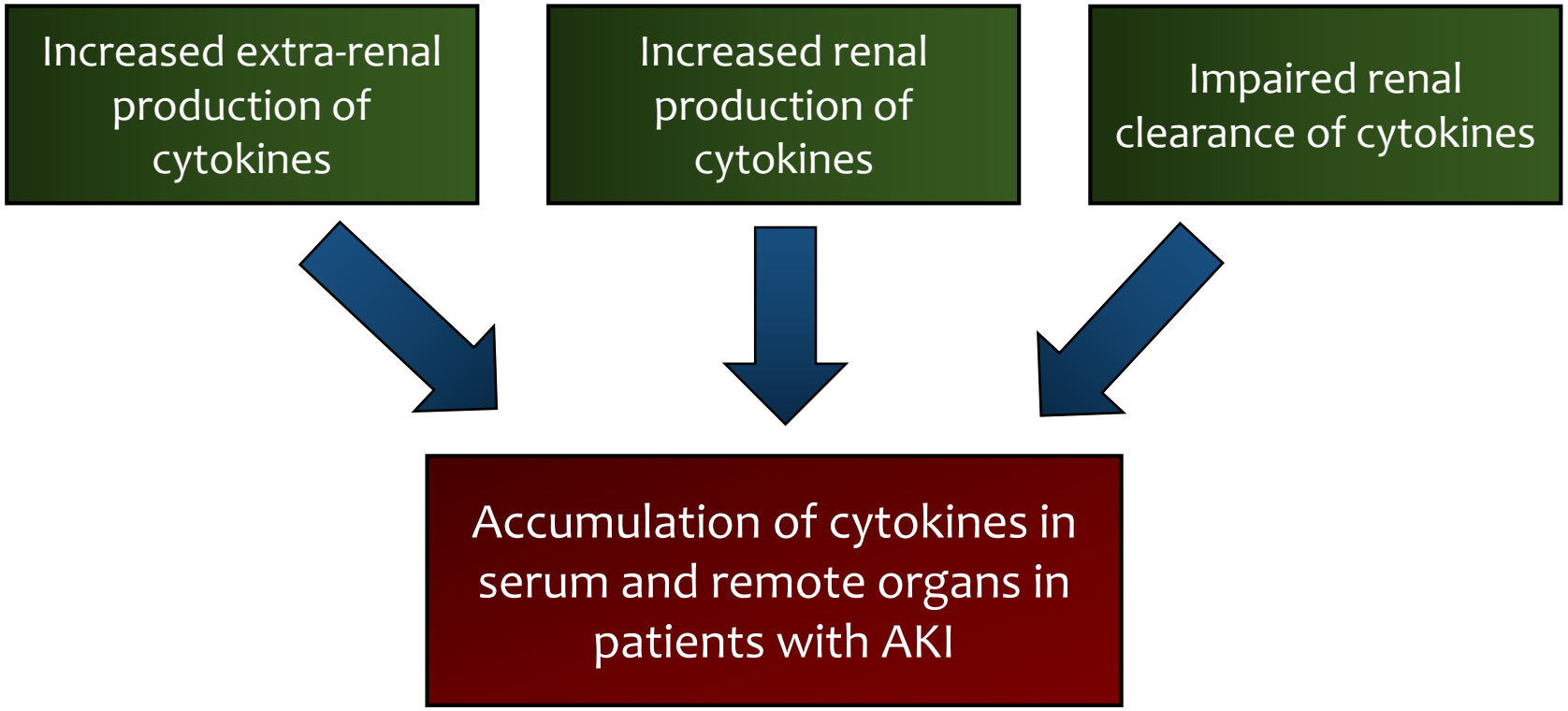


Husain-Syed et al. AJRCCM 2017

Molecular and cellular mediators of kidney-lung crosstalk

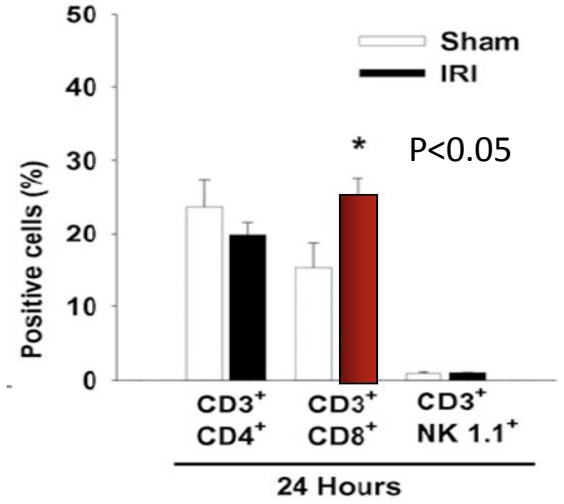


Alge et al. Frontiers in Pediatrics 2021

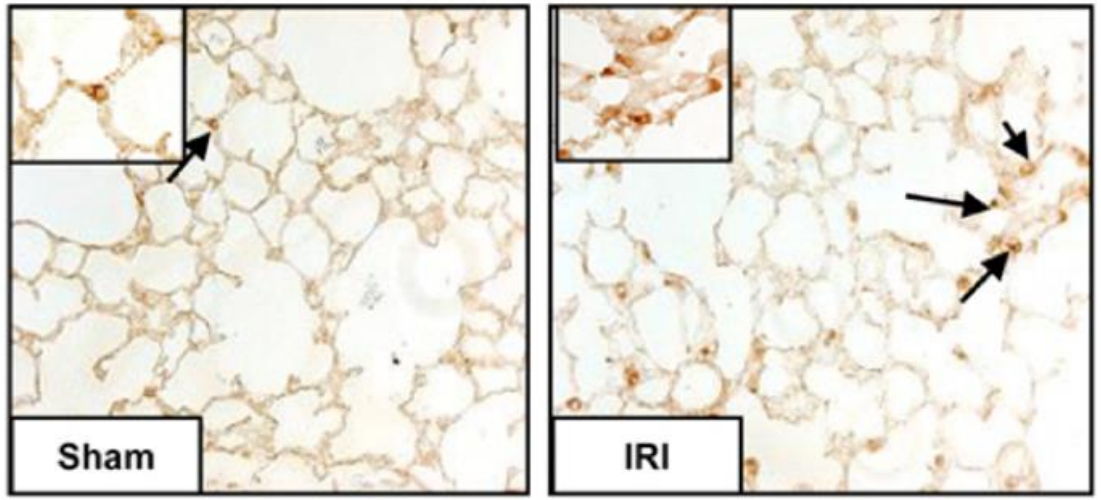

Increased extra-renal production of cytokines
Increased renal production of cytokines
Impaired renal clearance of cytokines
Accumulation of cytokines in serum and remote organs in patients with AKI

Lung T lymphocyte trafficking during ischemic AKI

Activated T lymphocytes in kidney ischemia-reperfusion injury would migrate to the lungs and induce pulmonary apoptosis, as indicated by a rise in caspase-3 activity in pulmonary tissue.



A predominant infllux of pulmonary CD3+CD8+ T lymphocytes at 24 hours in IRI treated mice

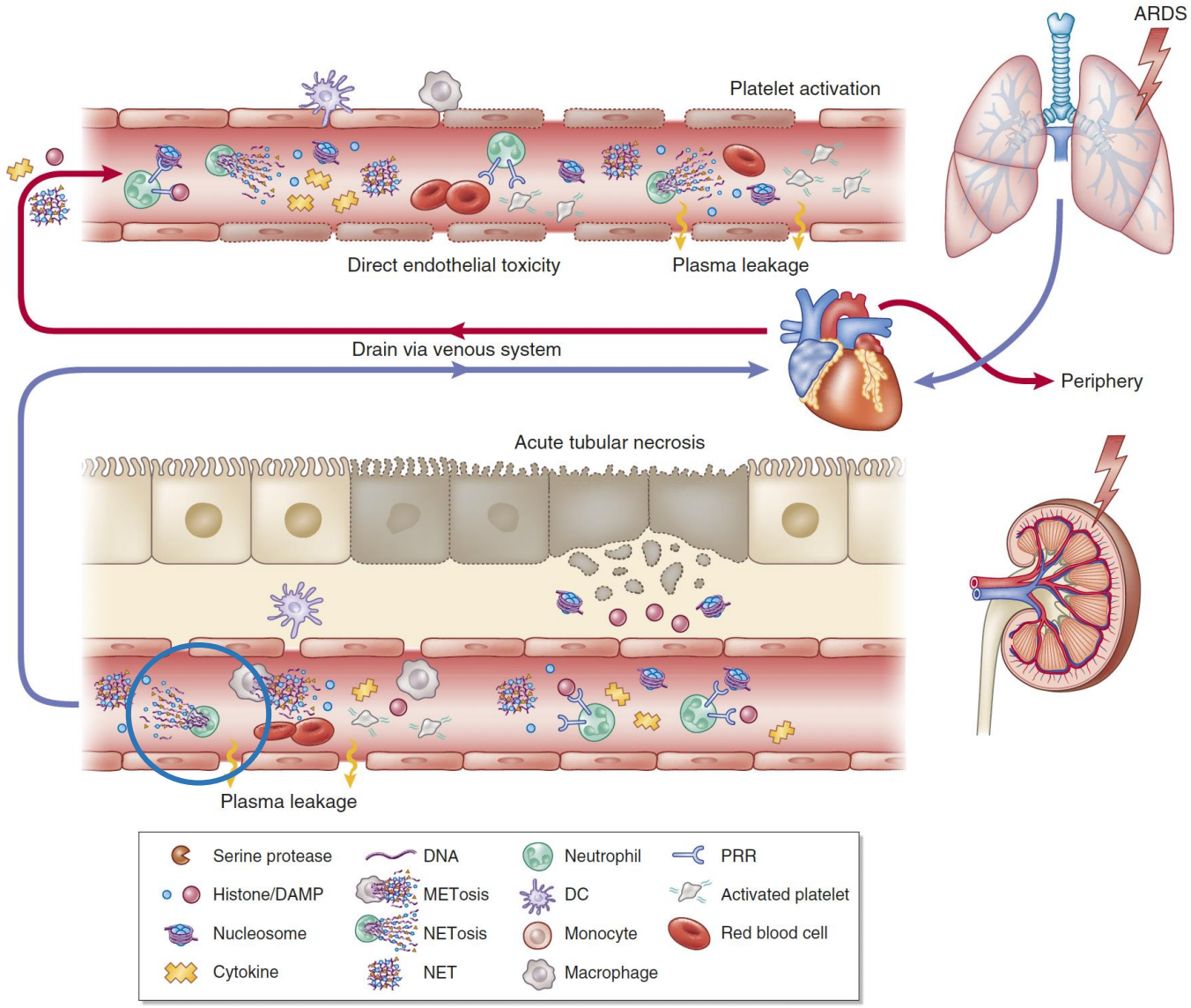


IHC staining of CD3+ T lymphocytes in the lung in a mouse model of IRI

IRI: Ischemia reperfusion injury

Lie M, et al., J Immunol 2012

Neutrophil extracellular traps (NETs) and histones in lung injuries related to intrarenal cell necrosis

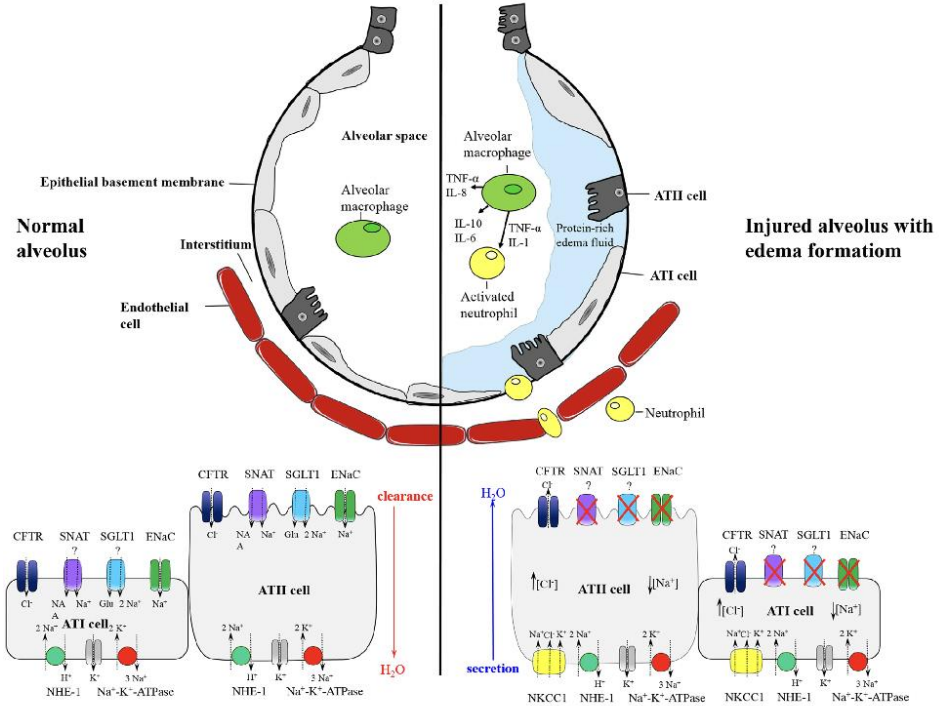


Nakazawa D, et al. Kidney Int 2019

Mechanisms suggested for accumulation of fluid in patients with AKI

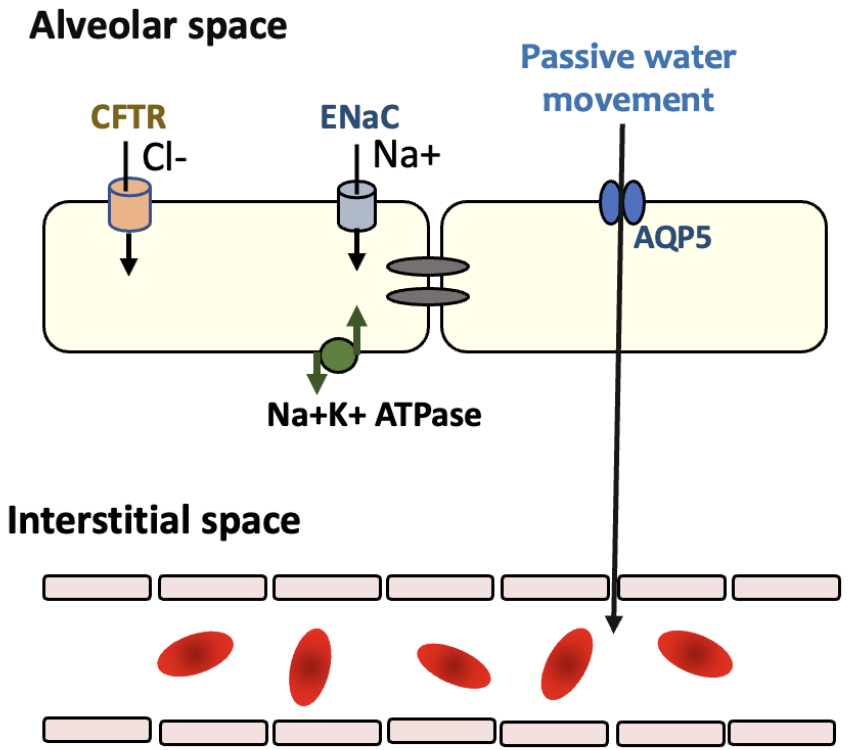
- The release of inflammatory mediators from the injured kidney results in diffuse pulmonary epithelial and endothelial cellular damage, leading to increased alveolar-capillary permeability and the development of protein rich pulmonary edema.

- AKI can cause dysregulated expression or impaired function of ion channels in alveolar epithelial cells, leading to the accumulation of alveolar fluid.



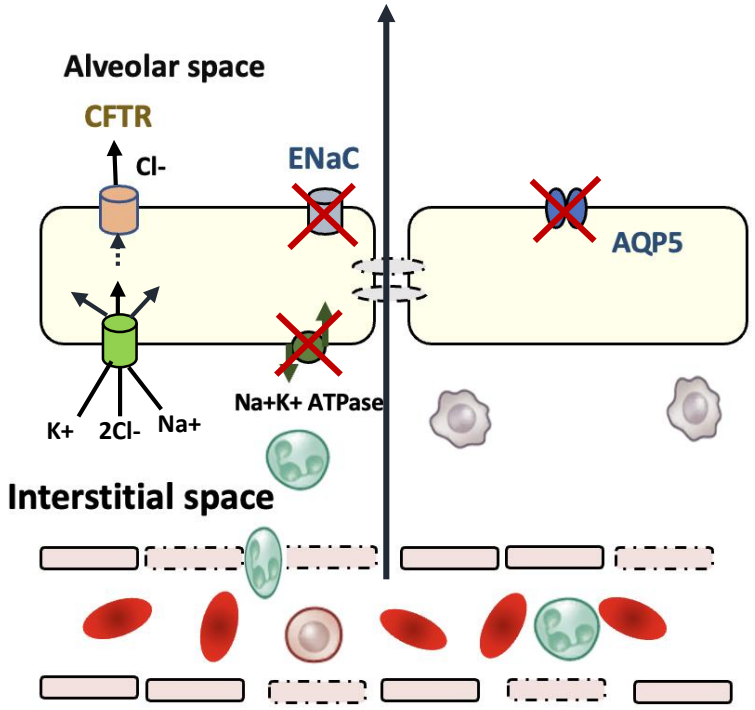
Weidenfeld S, and Wolfgang K. Frontier in immunology 2017

Alveolar-capillary barrier



The effect of pro-inflammatory cytokines and AKI on expression and activity of ion channels involved in alveolar fluid transport

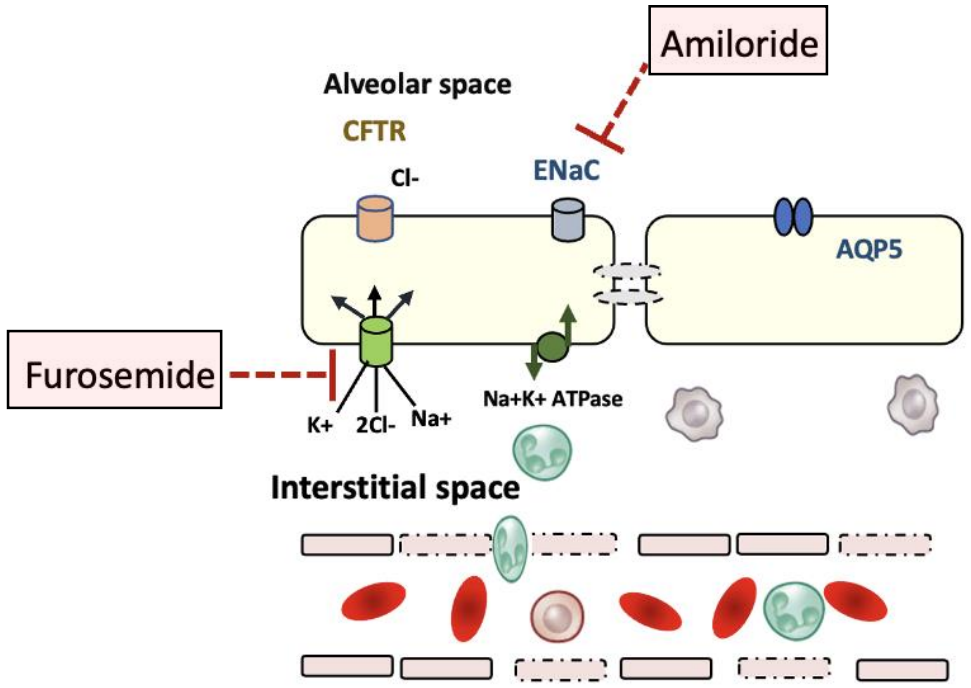
There is evidence that proinflammatory cytokines can down regulate the activity of pulmonary ENaC, Na/K/ATPase, and AQP5, and affect the expression of the Na+K+2Cl-1 (NKCC1) and chloride (CFTR) channel. This components are essential for the fluid clearance in the alveoli.



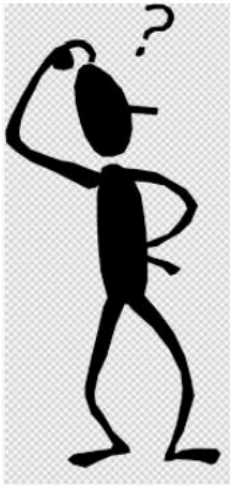
AKI is also associated with reduced expression of epithelial sodium channels, sodium potassium ATPase, and aquaporin5.

Diuretics and alveolar fluid secretion

Amiloride can reproduce alveolar fluid by inhibiting of epithelial sodium channels , while furosemide can prevent active alveolar fluid secretion by inhibiting Na+K+2CL cotransporter-1. This explain furosemide’s rapid, diuresis-independent action in pulmonary edema.

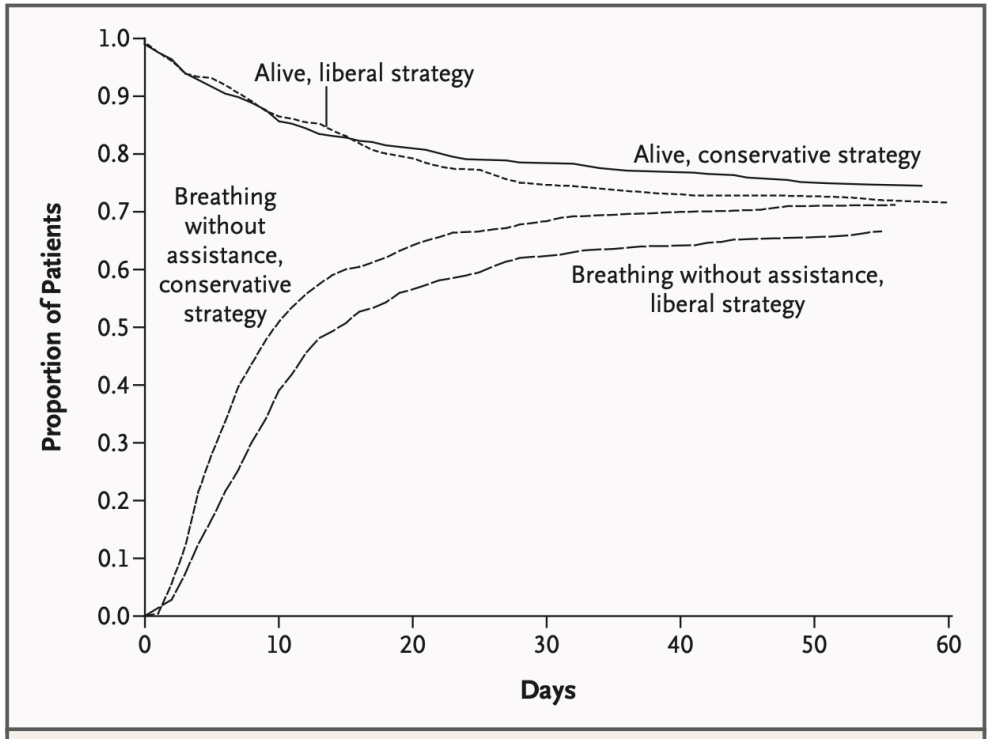


Therapeutic interventions to modify risk factors in critically ill patients to prevent lung-kidney interaction



Conservative vs. liberal fluid-management strategy in patients with ARDS

FACTT Trial (n=1000)



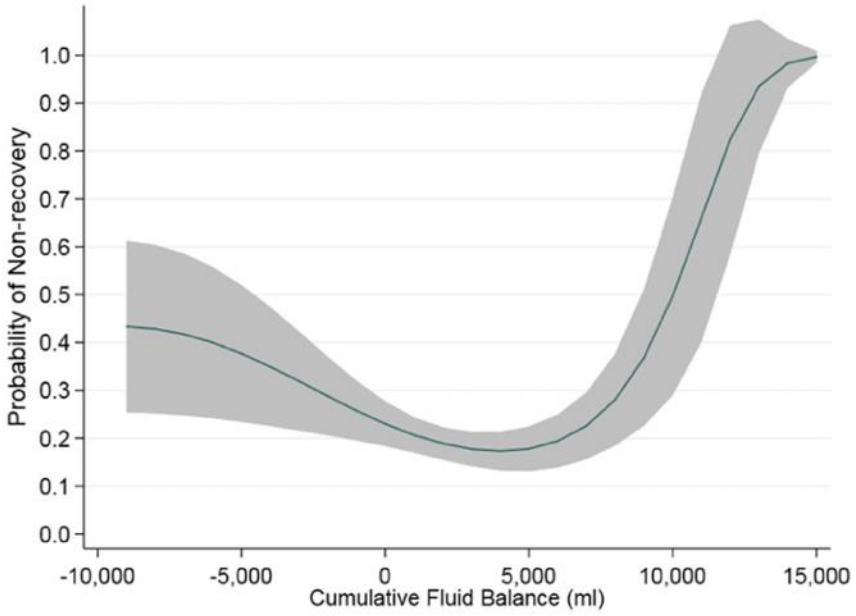
	Conservative strategy	Liberal strategy	P Value
Cumulative fluid balance	-136± 491	6992±502	<0.001
outcome			
Death at 60 days%	25.5	28.4	0.3
Ventilator free days (day 1 to 28)	14.6±0.5	12.1± 0.5	<0.001
Renal failure free day (day 1 to 28)*	21.5±0.5	21.5±0.5	0.59
Dialysis:			
Patients (%)	10	14	0.06
Days	11.0±1.7	10.9±1.4	096

*AKI was defined as cr>2 mg/dL

In patients with ARDS, excess fluid is associated with fewer ventilator free days.

NHLBI ARDS Network NEJM 2006

Association of cumulative fluid balance on the recovery of kidney function in critically ill patients



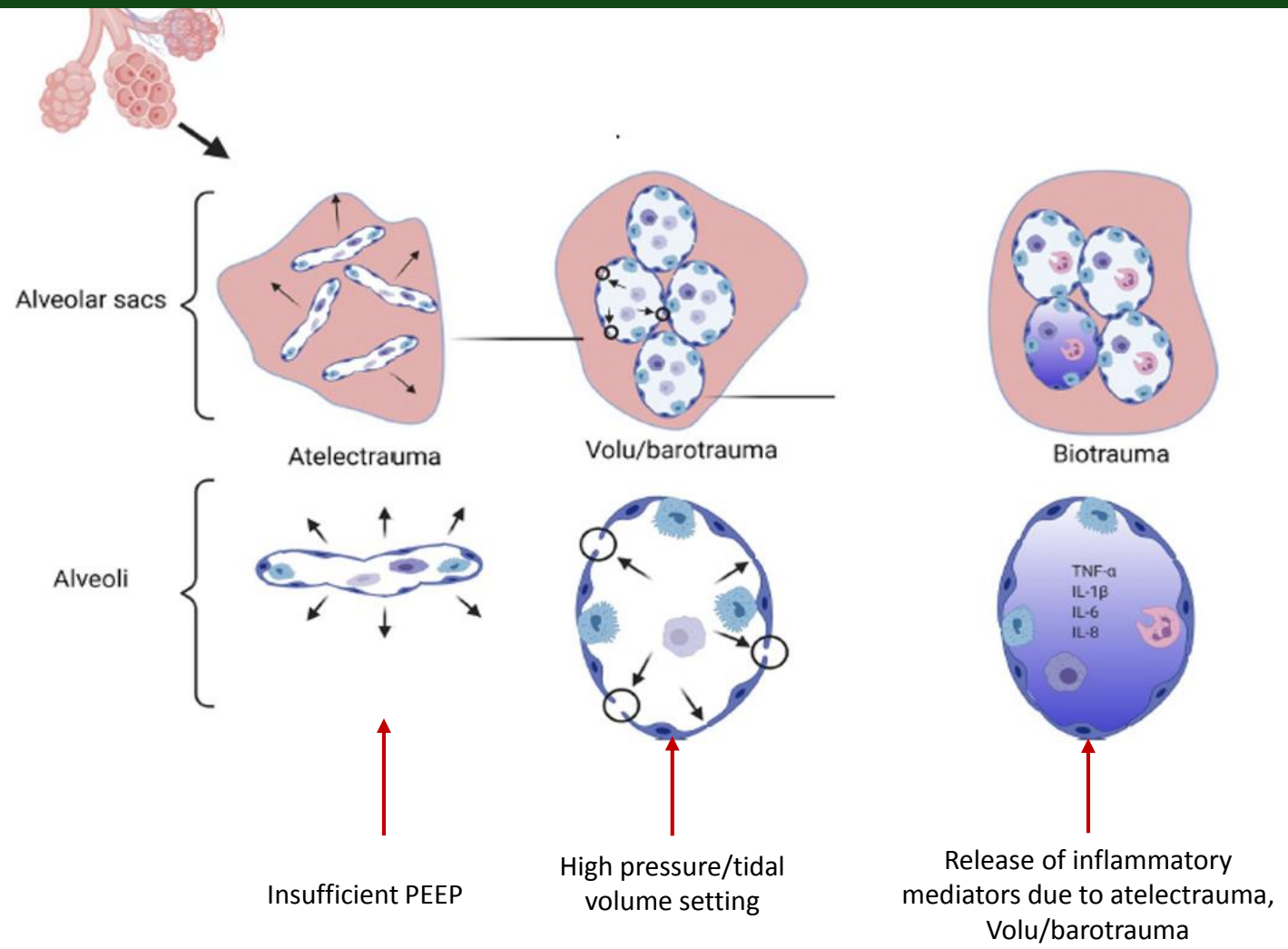
Multivariate analysis of risk factors for the development of new acute kidney injury

Variables	OR	95% CI for OR		*p* value
		Lower	Upper	
Age	1.00	1.00	1.01	0.24
BMI	1.06	1.04	1.07	<0.001
SOFA score on admission to the ICU	1.04	1.00	1.08	0.05
Lowest MAP	1.00	0.99	1.01	0.84
Sepsis	1.11	0.80	1.53	0.53
Chronic kidney disease	1.81	1.34	2.45	<0.001
Atherosclerotic cardiovascular disease	1.13	0.90	1.40	0.29
Congestive heart failure	1.12	0.81	1.56	0.50
Diabetes mellitus	1.06	0.85	1.33	0.60
Cancer	0.84	0.69	1.03	0.10
Mechanical ventilation	0.94	0.77	1.17	0.60
Norepinephrine use	1.20	0.94	1.54	0.15
NSAID use	0.48	0.22	1.05	0.07
Cumulative fluid balance on the day of AKI or day 3 in the ICU	1.11	1.08	1.14	<0.001

Total number of patients :2525
The incidence of early ICU-acquired AKI: 33.2%

Zhang J et al. Crit Care 2019

Ventilator induced lung injury (VILI)



To reduce the risk of VILI, lung protective strategies, including low tidal volume (6 ml/kg) to prevent volutrama and adequte PEEP to prevent atelectrauma, are recommended. The optimal PEEP level is currently a subject of debate.

Joelsson JP, et al. Anim Res 2021

The results of the ARDS Net trial, evaluating the effect of lung protective ventilation on clinical outcomes

The New England Journal of Medicine

VOLUME 342 MAY 4, 2000 NUMBER 18

VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

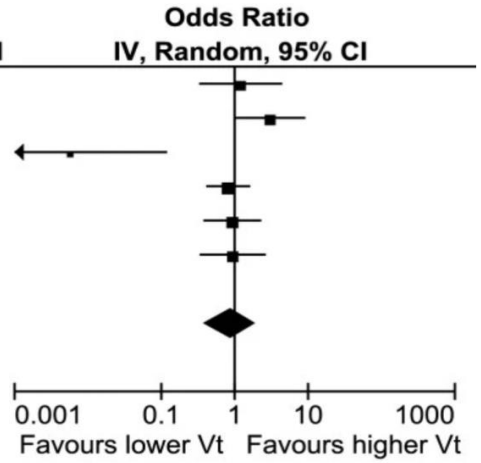
Number of patients: 861
Patients' population: ARDS
Trial type: RCT

	Group receiving lower tidal volume	Group receiving traditional tidal volume	P-value
Death before discharge home (%)	31.0	39.8%	**0.007**
Number of ventilator-free days, day 1 to 28	12±11	10±11	**0.007**
Number of days without failure of non-pulmonary organs, day 1 to 28	15±11	12±11	**0.006**
Number of days without renal insufficiency, day 1 to 28 (Cr<2mg/dL)	20±11	18±11	**0.005**

lung protective strategy the occurrence of AKI, the results of a meta-analysis

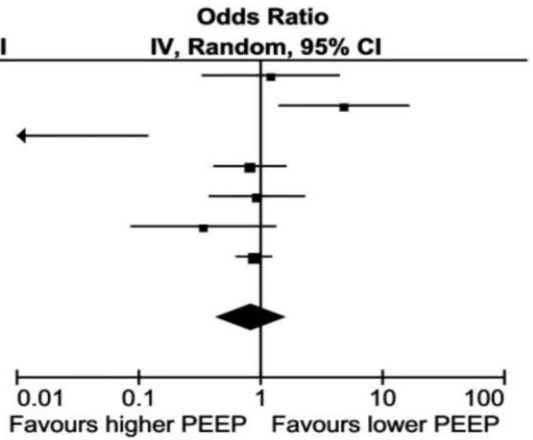
Study	Lower Vt Events	Lower Vt Total	Higher Vt Events	Higher Vt Total	Weight	Odds Ratio IV, Random, 95% CI
Amato 1998	7	29	5	24	15.7%	1.21 [0.33, 4.44]
Stewart 1998	13	60	5	60	17.8%	3.04 [1.01, 9.16]
Ranieri 2000	0	18	16	19	5.5%	0.01 [0.00, 0.12]
Parikh 2005	27	76	25	62	22.4%	0.82 [0.41, 1.63]
Villar 2006	14	43	14	41	20.0%	0.93 [0.38, 2.31]
Cortjens 2011	9	44	9	42	18.5%	0.94 [0.33, 2.67]
Total (95% CI)		**270**		**248**	**100.0%**	**0.88 [0.40, 1.96]**
Total events	70		74			

Heterogeneity: Tau² = 0.62; Chi² = 15.46, df = 5 (P = 0.009); I² = 68%
Test for overall effect: Z = 0.31 (P = 0.75)



Study	Higher PEEP Events	Higher PEEP Total	Lower PEEP Events	Lower PEEP Total	Weight	Odds Ratio IV, Random, 95% CI
Amato 1998	7	29	5	24	12.5%	1.21 [0.33, 4.44]
Vivino 1998	11	15	28	77	13.1%	4.81 [1.40, 16.55]
Ranieri 2000	0	18	16	19	3.9%	0.01 [0.00, 0.12]
Parikh 2005	27	76	25	62	19.2%	0.82 [0.41, 1.63]
Villar 2006	14	43	14	41	16.7%	0.93 [0.38, 2.31]
Manzano 2008	3	64	8	63	11.8%	0.34 [0.09, 1.34]
Meade 2008	71	428	85	459	22.8%	0.88 [0.62, 1.24]
Total (95% CI)		**673**		**745**	**100.0%**	**0.83 [0.43, 1.61]**
Total events	133		181			

Heterogeneity: Tau² = 0.46; Chi² = 19.97, df = 6 (P = 0.003); I² = 70%
Test for overall effect: Z = 0.54 (P = 0.59)

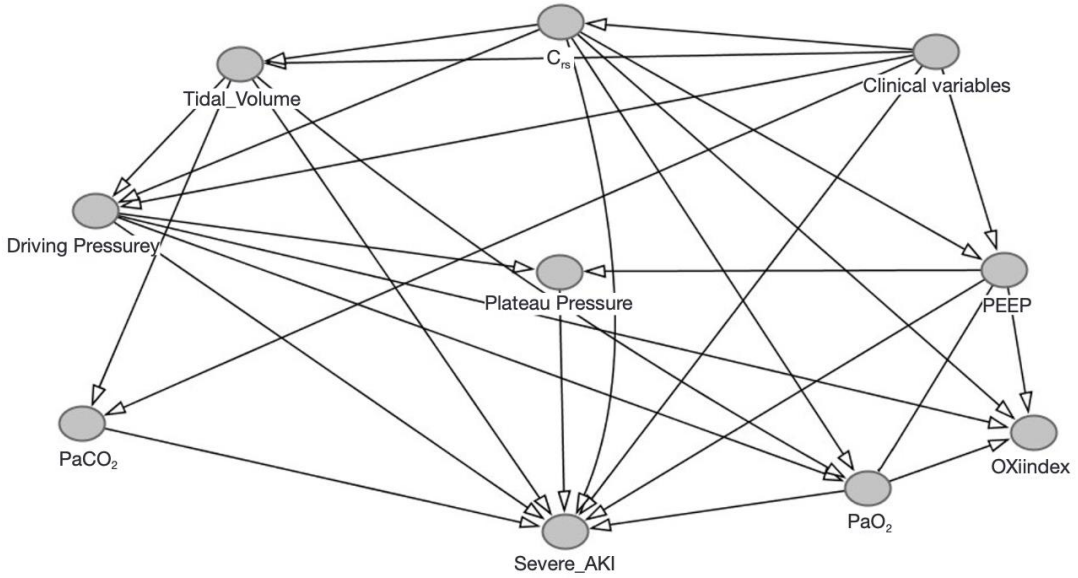


- The varied setting of tidal volume and PEEP had no effect on the occurrence of AKI.
- Large diversity in study designs and variation in AKI definitions may affect the results.

Van den Akker JPC, et al. Crit Care 2013

Original Article

Respiratory parameters and acute kidney injury in acute respiratory distress syndrome: a causal inference study

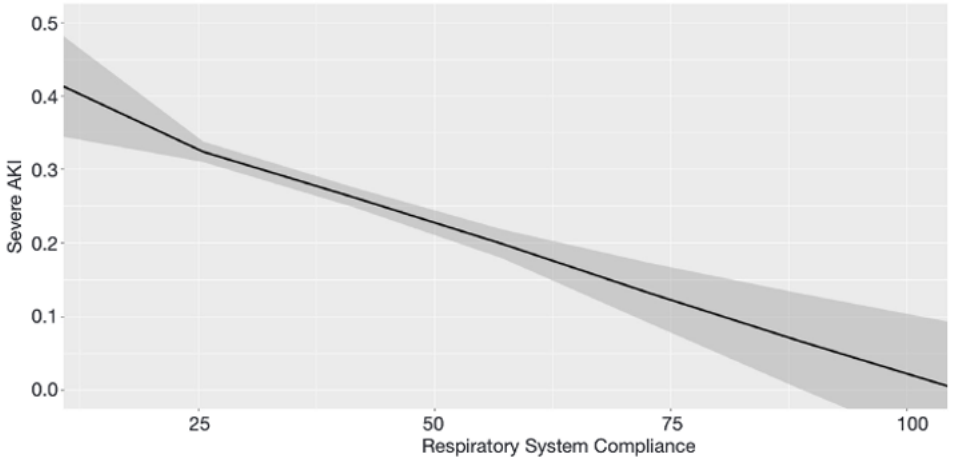


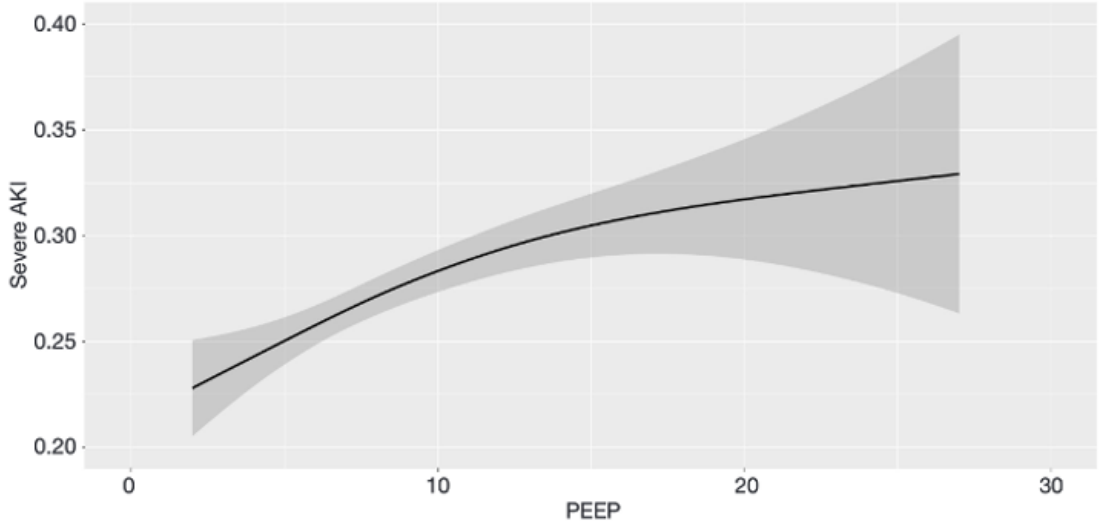
Using a causal directed acyclic graph (DAG), this figure illustrates the relationships among respiratory variables in ARDS patients and their causal links to severe AKI. A DAG is a visual map, simplifying the analysis of complex systems by highlighting directional and acyclic variable relationships.

Leite TT, et al. Ann Transl Med 2019

Original Article

Respiratory parameters and acute kidney injury in acute respiratory distress syndrome: a causal inference study



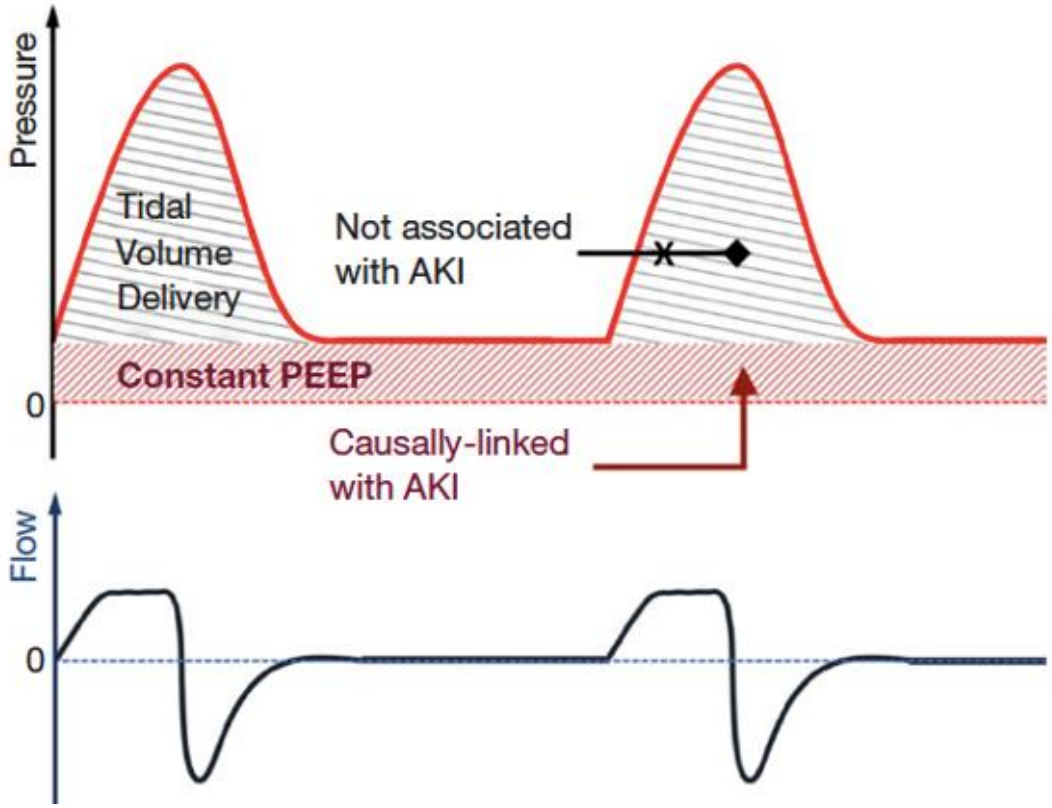


- Compliance of respiratory system (Crs) and PEEP were the only respiratory- related variables with a direct causal association with severe AKI.

- This study suggests that approaches reducing tidal volume or ΔP in ARDS can have limited effect on renal protection

Leite TT, et al. Ann Transl Med 2019

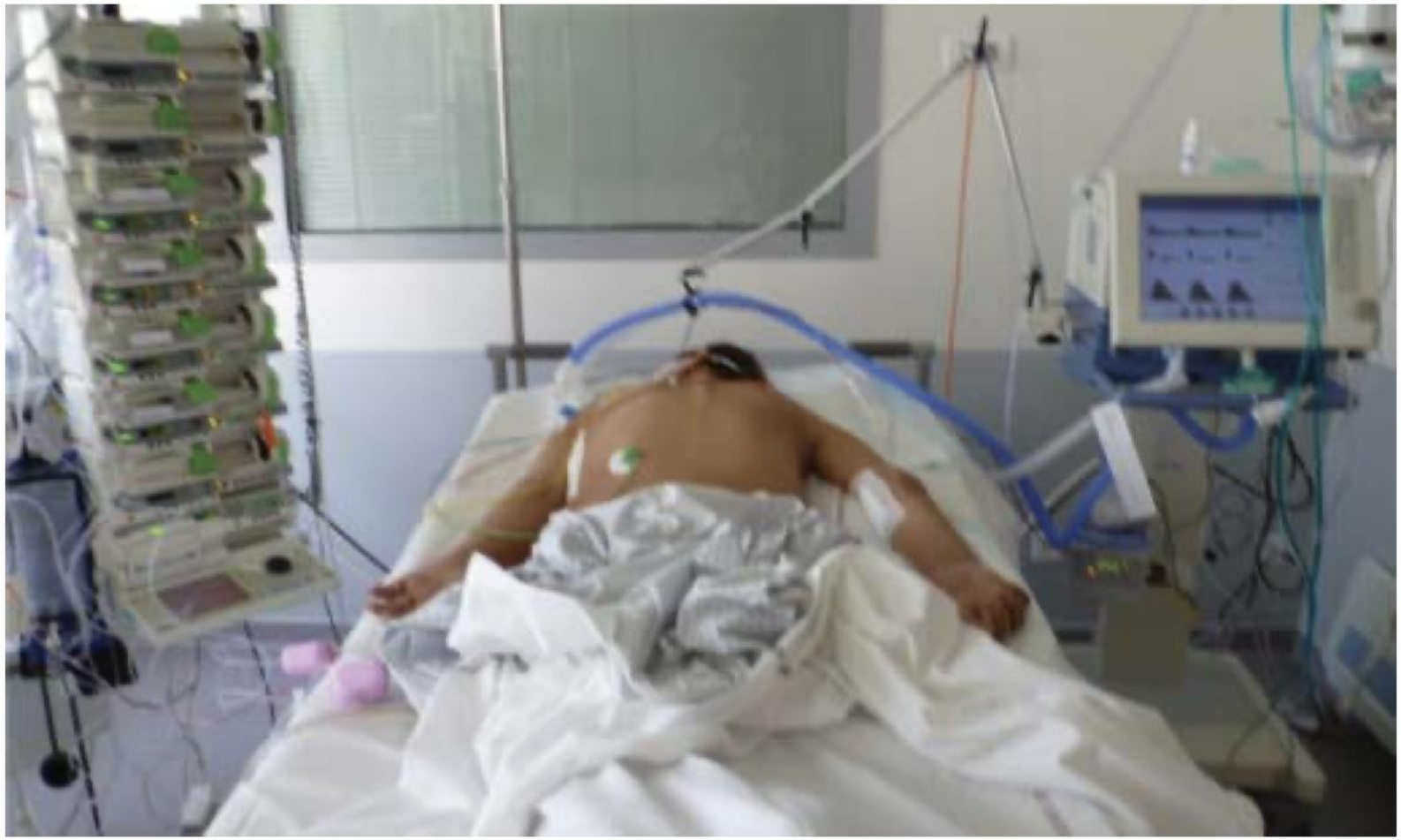
PEEP and VIKI



It seems that constantly applied PEEP was casually linked to AKI while the cyclic rises in pulmonary pressure from tidal volume delivery with each mechanical breath was not.

Yang H, et al. Ann Transl Med 2020

Prone position in mechanically ventilated patients



Many studies have indicated that maintaining a patient prone for 16 hours/day improves oxygenation and reduces VILI in patients on mechanical ventilation for ARDS.

Guerin C. Eur Respir Rev 2014

CRITICAL CARE AND TRAUMA
SECTION EDITOR
PETER M. SUTER

Anesth Analg 2001;92:1226–31

The Effects of Prone Positioning on Intraabdominal Pressure and Cardiovascular and Renal Function in Patients with Acute Lung Injury

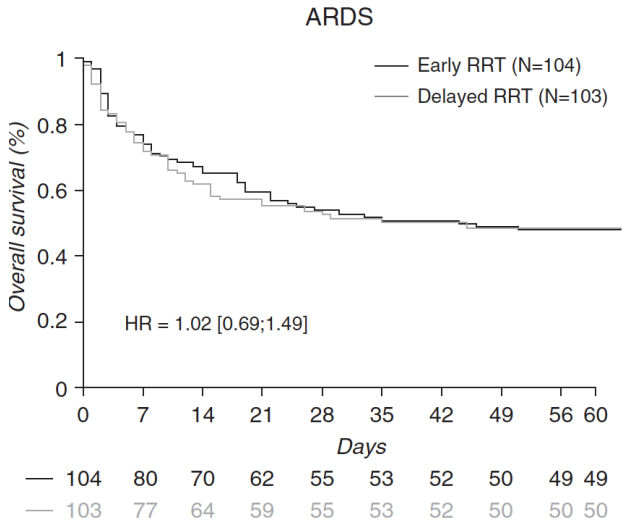
Rudolf Hering, MD*, Hermann Wrigge, MD*, Ralph Vorwerk, MD*, Karl A. Brensing, MD†, Stefan Schröder, MD*, Jörg Zinserling, MSc*, Andreas Hoeft, MD*, Tilman V. Spiegel, MD*, and Christian Putensen, MD*

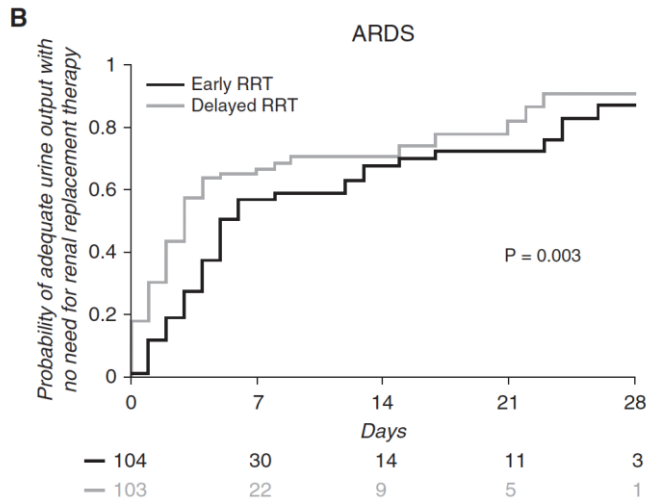
	Supine position	Prone position	P-value
Urine volume (mL/hour)	101 ± 42	101 ± 531	**NS**
Effective renal blood flow index (mL/min/m²)	710 ± 364	653 ± 353	**NS**
Renal fraction of cardiac output (%)	19.1 ± 12.5	15.5 ± 8.8	**<0.05**
GFR (mL/min/m²)	52 ± 26	52 ± 32	**NS**
Fraction excretion of Na (%)	1.48 ± 1.19	1.84 ± 1.95	**NS**
Free water clearance	-0.73± 0.38	-0.65 ± 0.3	**NS**

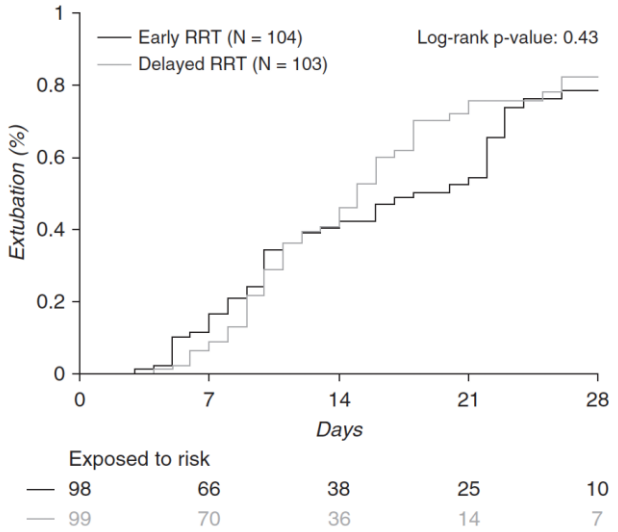
In hemodynamically stable patients with ARDS without abdominal hypertension, the prone position does not worsen renal function as long as cardiovascular function remains stable.

The optimal strategy for initiation of RRT in patients with septic shock and ARDS

Post hoc analysis of AKIKI (Artificial Kidney Initiation in Kidney Injury) trial







The early initiation of RRT did not show any benefit in terms of reducing 60-day mortality or time to successful extubation in patients experiencing severe AKI and ARDS. Renal function recovery occurred earlier with delayed RRT strategy.

Gaurdry S, et al. Am J Respir Crit Care Med 2018

CRRT + CO2 removal

- Lung protective ventilation by using a lower tidal volume can result in a permissive hypercapnia and acidemia.
- This elevated CO2 level may negatively impact the kidney by decreasing renal blood flow and increasing renal vascular resistance.
- RRT plays a role in compensating respiratory acidosis and can facilitate the removal of carbon dioxide through additional filters integrated into the CRRT circuit, also known as ECCO2R (extracorporeal co2 removal).

Conclusion

- AKI is a common complication in patients experiencing respiratory failure and is associated with poor outcome in these patients.
- The occurrence of AKI can adversely impact the lung, leading to ARDS through both immunologic and non-immunologic mechanisms.
- Multiple molecular and inflammatory pathways are involved in organ cross talk between the lung and kidney.
- Volume overload in critically ill patients is associated with fewer ventilator-free days and an increased rate of AKI.
- Mechanical ventilation is an independent risk factor for AKI development, and our current knowledge has not yet identified a therapeutic strategy or specific ventilator setting to prevent it.
- There is a significant knowledge gap regarding organ crosstalk between the lung and kidney in critically ill patients.
- With an in-depth understanding of lung-kidney interaction, goal directed therapeutic interventions can be applied to disrupt the early stages of the vicious cycle, thereby preventing the onset of multiorgan dysfunction.

Badab-e-surt, Mazandarn, Iran