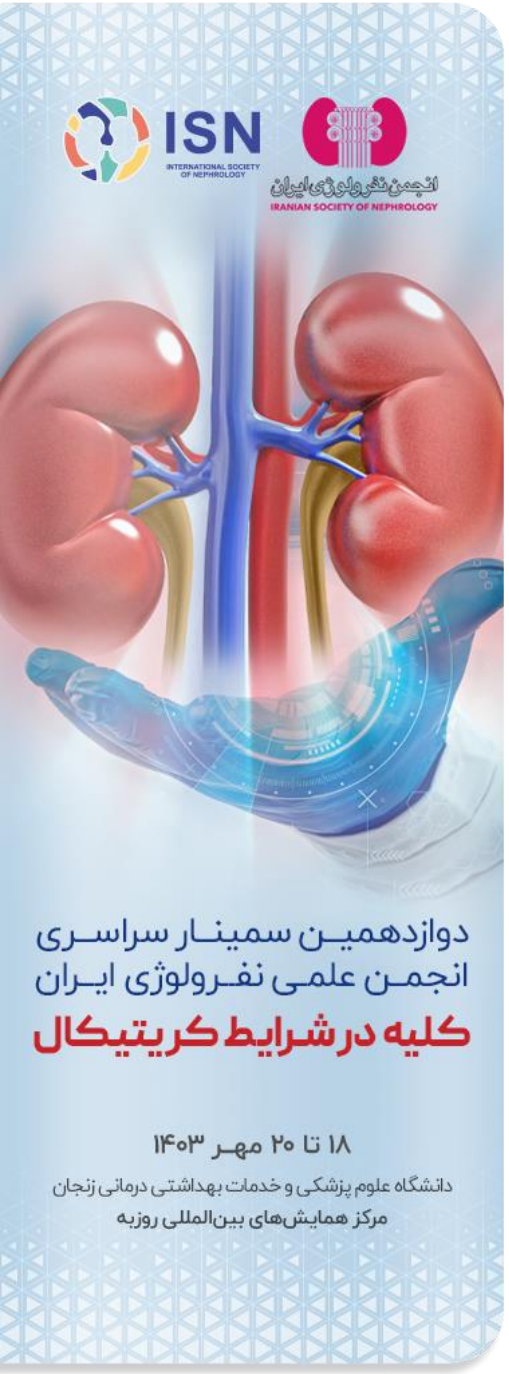
به نام خدا که رحمتش بسیار و مهربانی‌اش همیشگی است.

DR MOHAMMADI.S.R MD ZANJAN UNIVERCITY OF MEDICAL SCIENCE INTERNAL MEDICINE WARD NEPHROLOGY DEPARTMENT



Ventilator induced kidney injury

VIKI

it is likely that mecheanical ventilation greatly affects the kidney

(Drury et al[1])

VIKI

- Drury et al[1] reported the first observation of changes in renal function related to positive-pressure ventilation in 1947.

- They observed an instantaneous decline in renal blood flow (RBF), glomerular filtration rate (GFR), and urine output using standard methods of evaluation (para-aminohippuric acid and inulin clearances) after administering CPAP to healthy, spontaneously breathing, human study subjects.

VIKI

- Mechanical ventilation increased odds ratio of AKI 3 times(van den akker et al)
- Invasive versus non invasive mechanical ventilation
- Causal relationship
- Univariant analysis v/s multivariant analysis
- Data befor RIFLE criteria and after
- [[[{High Vt v/s low Vt
- Idial PEEP in ventilator and respiratory system compliance in volume dependent ventilators (one size fits all)}}]]

Abdulkader 2010 [21]	19	31	6	16	3.1%	2.64 [0.76, 9.15]
Jung 2011 [27]	37	116	13	105	4.8%	3.31 [1.65, 6.67]
Martin-Loeches 2011 [29]	103	408	15	253	5.2%	5.36 [3.04, 9.45]
Pettila 2011 [32]	97	334	17	190	5.3%	4.16 [2.40, 7.23]
Subtotal (95% CI)		**889**		**564**	**18.4%**	**4.17 [3.00, 5.82]**
Total events	256		51			

Heterogeneity: Tau² = 0.00; Chi² = 1.68, df = 3 (P = 0.64); I² = 0%
Test for overall effect: Z = 8.44 (P < 0.001)

Sepsis

Schortgen 2001 [12]	36	92	6	37	3.9%	3.32 [1.26, 8.75]
Hoste 2003 [14]	24	137	6	48	3.9%	1.49 [0.57, 3.89]
Yegenaga 2004 [15]	25	209	4	48	3.5%	1.49 [0.49, 4.52]
Lopes 2009 [20]	64	147	35	168	5.5%	2.93 [1.79, 4.81]
Subtotal (95% CI)		**585**		**301**	**16.7%**	**2.49 [1.71, 3.63]**
Total events	149		51			

Heterogeneity: Tau² = 0.00; Chi² = 2.68, df = 3 (P = 0.44); I² = 0%
Test for overall effect: Z = 4.74 (P < 0.001)

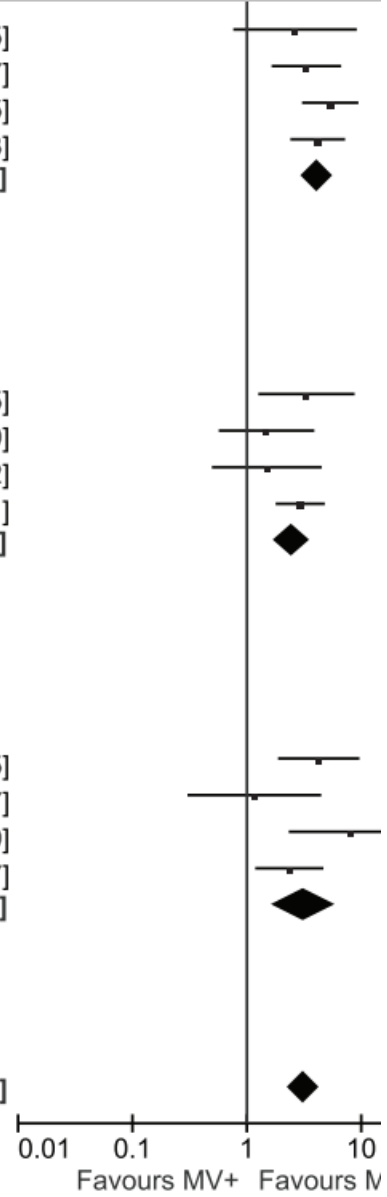
Miscellaneous

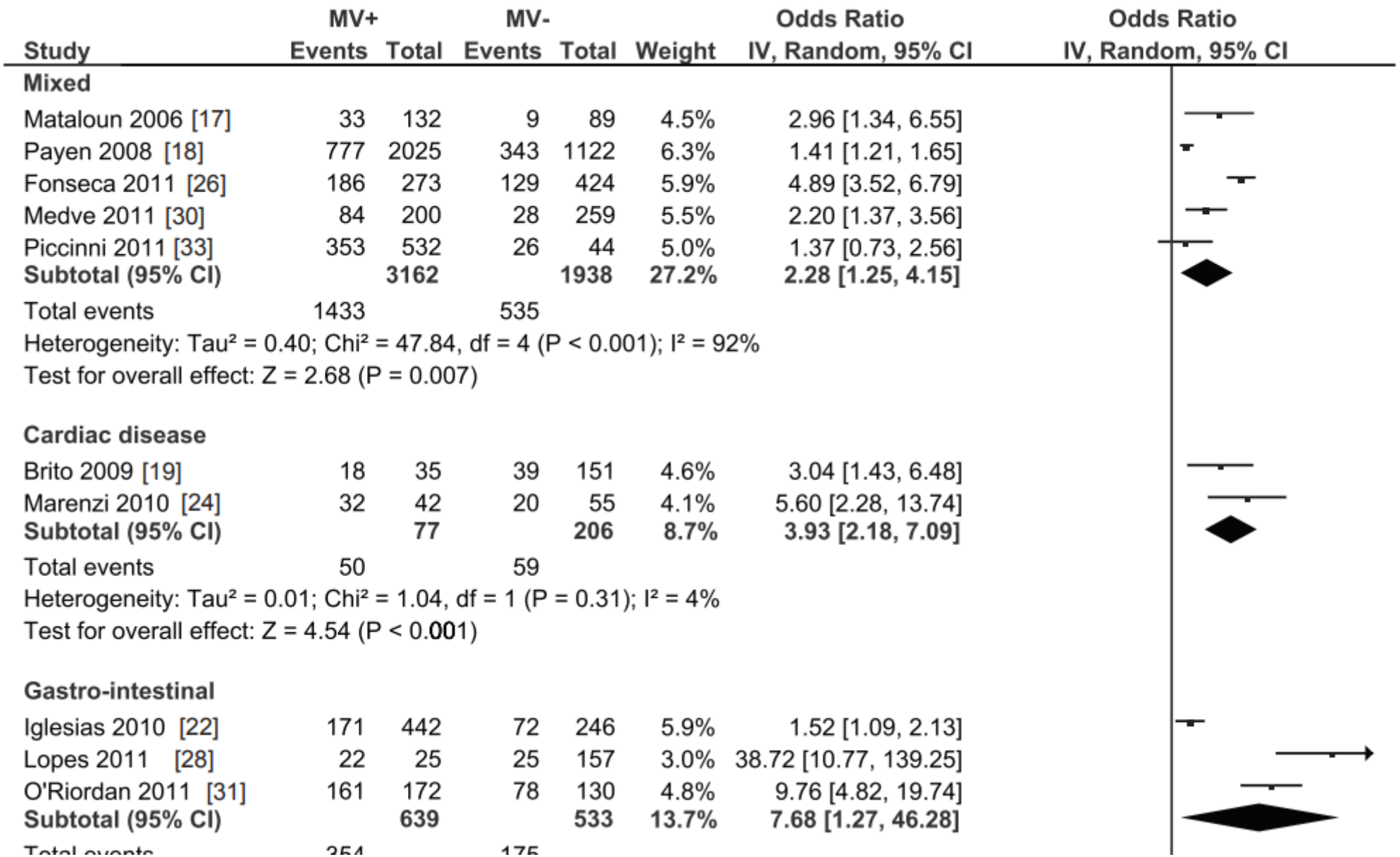
Vivino 1998 [11]	39	92	9	61	4.4%	4.25 [1.87, 9.65]
Letourneau 2002 [13]	32	43	10	14	2.9%	1.16 [0.30, 4.47]
Rocha 2005 [16][a]					3.1%	8.01 [2.33, 27.59]
Murugan 2010 [25]	116	129	129	163	4.8%	2.35 [1.18, 4.67]
Subtotal (95% CI)		**264**		**238**	**15.2%**	**3.14 [1.63, 6.04]**
Total events	187		148			

Heterogeneity: Tau² = 0.20; Chi² = 5.49, df = 3 (P = 0.14); I² = 45%
Test for overall effect: Z = 3.43 (P < 0.001)

Total (95% CI)		**5616**		**3780**	**100.0%**	**3.16 [2.32, 4.28]**
Total events	2429		1019			

Heterogeneity: Tau² = 0.38; Chi² = 129.18, df = 21 (P < 0.001); I² = 84%
Test for overall effect: Z = 7.37 (P < 0.001)
Test for subgroup differences: Chi² = 6.75, df = 5 (P = 0.24), I² = 25.9%

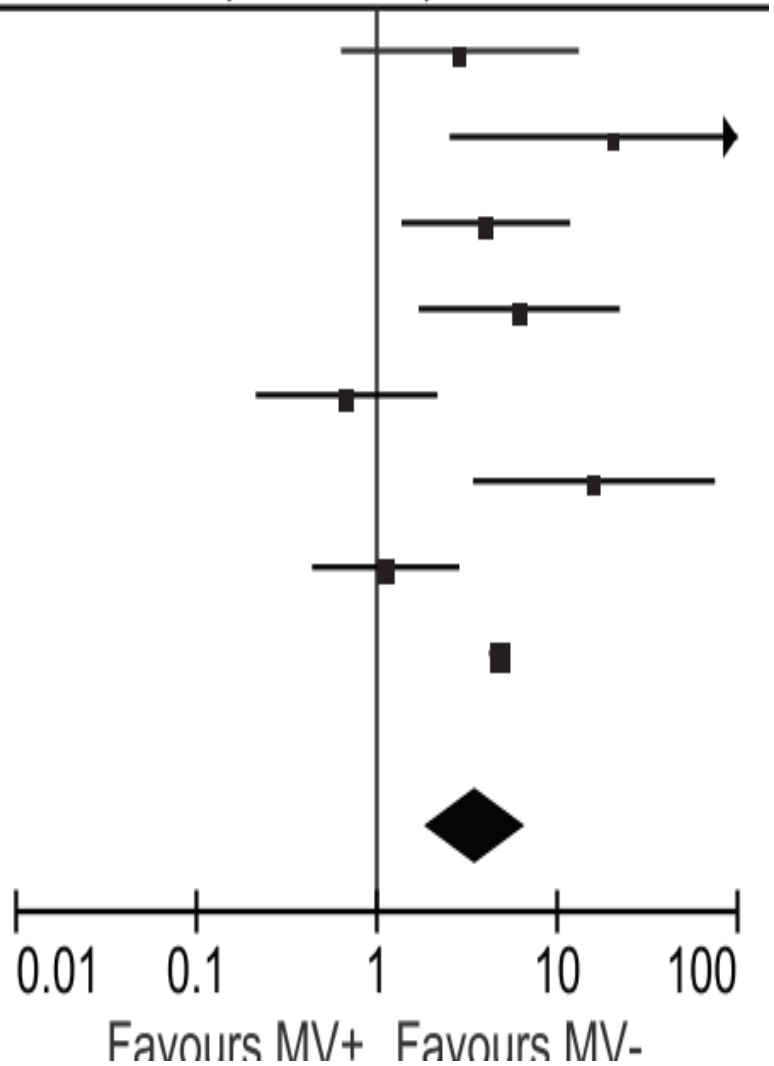



MV+
MV-
Odds Ratio
Odds Ratio
Study
Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Mixed
Mataloun 2006 [17] 33 132 9 89 4.5% 2.96 [1.34, 6.55]
Payen 2008 [18] 777 2025 343 1122 6.3% 1.41 [1.21, 1.65]
Fonseca 2011 [26] 186 273 129 424 5.9% 4.89 [3.52, 6.79]
Medve 2011 [30] 84 200 28 259 5.5% 2.20 [1.37, 3.56]
Piccinni 2011 [33] 353 532 26 44 5.0% 1.37 [0.73, 2.56]
Subtotal (95% CI) 3162 1938 27.2% 2.28 [1.25, 4.15]
Total events 1433 535
Heterogeneity: Tau² = 0.40; Chi² = 47.84, df = 4 (P < 0.001); I² = 92%
Test for overall effect: Z = 2.68 (P = 0.007)
Cardiac disease
Brito 2009 [19] 18 35 39 151 4.6% 3.04 [1.43, 6.48]
Marenzi 2010 [24] 32 42 20 55 4.1% 5.60 [2.28, 13.74]
Subtotal (95% CI) 77 206 8.7% 3.93 [2.18, 7.09]
Total events 50 59
Heterogeneity: Tau² = 0.01; Chi² = 1.04, df = 1 (P = 0.31); I² = 4%
Test for overall effect: Z = 4.54 (P < 0.001)
Gastro-intestinal
Iglesias 2010 [22] 171 442 72 246 5.9% 1.52 [1.09, 2.13]
Lopes 2011 [28] 22 25 25 157 3.0% 38.72 [10.77, 139.25]
O'Riordan 2011 [31] 161 172 78 130 4.8% 9.76 [4.82, 19.74]
Subtotal (95% CI) 639 533 13.7% 7.68 [1.27, 46.28]

Study	Weight	Odds Ratio IV, Random, 95% CI
Vivino 1998 (PEEP < 6) [11]	9.9%	2.89 [0.63, 13.20]
Vivino 1998 (PEEP > 6) [11]	6.7%	20.70 [2.53, 169.35]
Schortgen 2001 [12]	13.5%	4.02 [1.37, 11.80]
Rocha 2005 [16]	11.7%	6.16 [1.71, 22.24]
Brito 2009 [19]	12.7%	0.68 [0.21, 2.17]
Lahoti 2010 [23]	9.8%	16.00 [3.41, 75.00]
Jung 2011 [27]	14.7%	1.12 [0.44, 2.87]
O'Riordan 2011 [31]	20.9%	4.78 [4.19, 5.45]
Total (95% CI)	**100.0%**	**3.58 [1.85, 6.92]**

Heterogeneity: $Tau^2 = 0.54$; $Chi^2 = 24.50$, df = 7 ($P < 0.001$); $I^2 = 71\%$

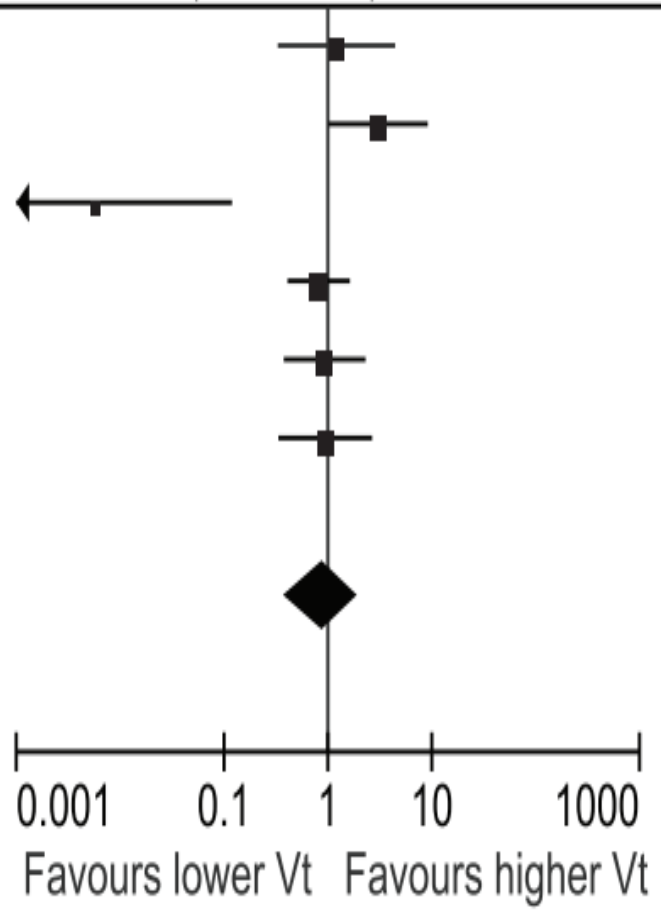
Test for overall effect: $Z = 3.79$ ($P < 0.001$)



Study	Lower Vt Events	Lower Vt Total	Higher Vt Events	Higher Vt Total	Weight	Odds Ratio IV, Random, 95% CI
Amato 1998 [34]	7	29	5	24	15.7%	1.21 [0.33, 4.44]
Stewart 1998 [35]	13	60	5	60	17.8%	3.04 [1.01, 9.16]
Ranieri 2000 [36][ab]	0	18	16	19	5.5%	0.01 [0.00, 0.12]
Parikh 2005 [37]	27	76	25	62	22.4%	0.82 [0.41, 1.63]
Villar 2006 [38][a]	14	43	14	41	20.0%	0.93 [0.38, 2.31]
Cortjens 2011 [41][a]	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: $Tau^2 = 0.62$; $Chi^2 = 15.46$, df = 5 (P = 0.009); $I^2 = 68\%$

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 [34]	7	29	5	24	12.5%	1.21 [0.33, 4.44]
Vivino 1998 [11]	11	15	28	77	13.1%	4.81 [1.40, 16.55]
Ranieri 2000 [36][ab]	0	18	16	19	3.9%	0.01 [0.00, 0.12]
Parikh 2005 [37]	27	76	25	62	19.2%	0.82 [0.41, 1.63]
Villar 2006 [38][a]	14	43	14	41	16.7%	0.93 [0.38, 2.31]
Manzano 2008 [39]	3	64	8	63	11.8%	0.34 [0.09, 1.34]
Meade 2008 [40][c]	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: $Tau^2 = 0.46$; $Chi^2 = 19.97$, df = 6 (P = 0.003); $I^2 = 70\%$

Test for overall effect: Z = 0.54 (P = 0.59)

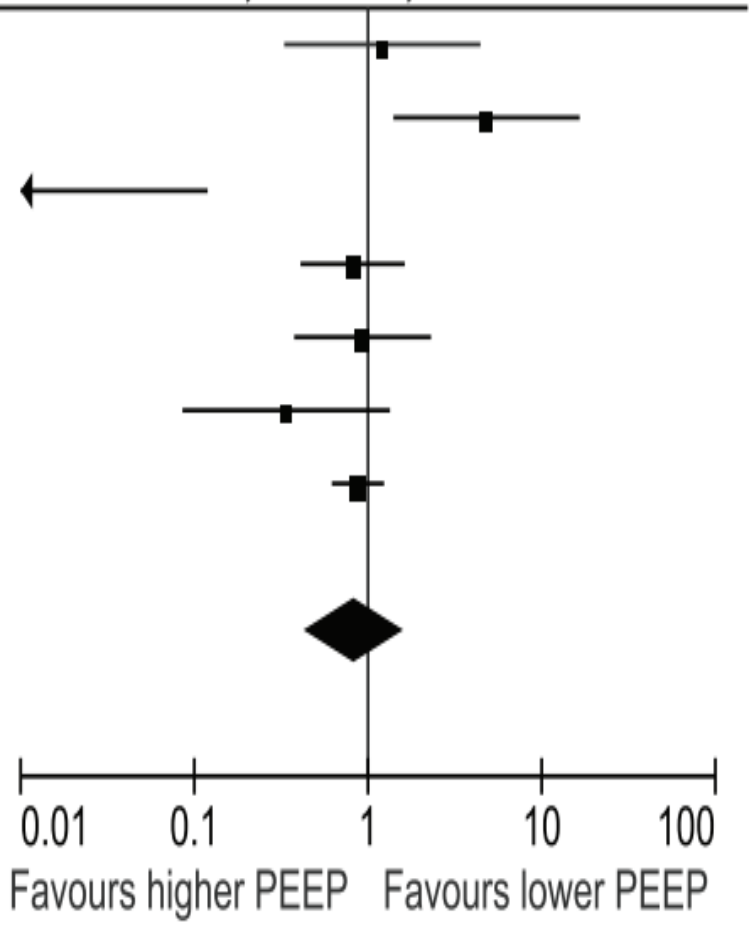
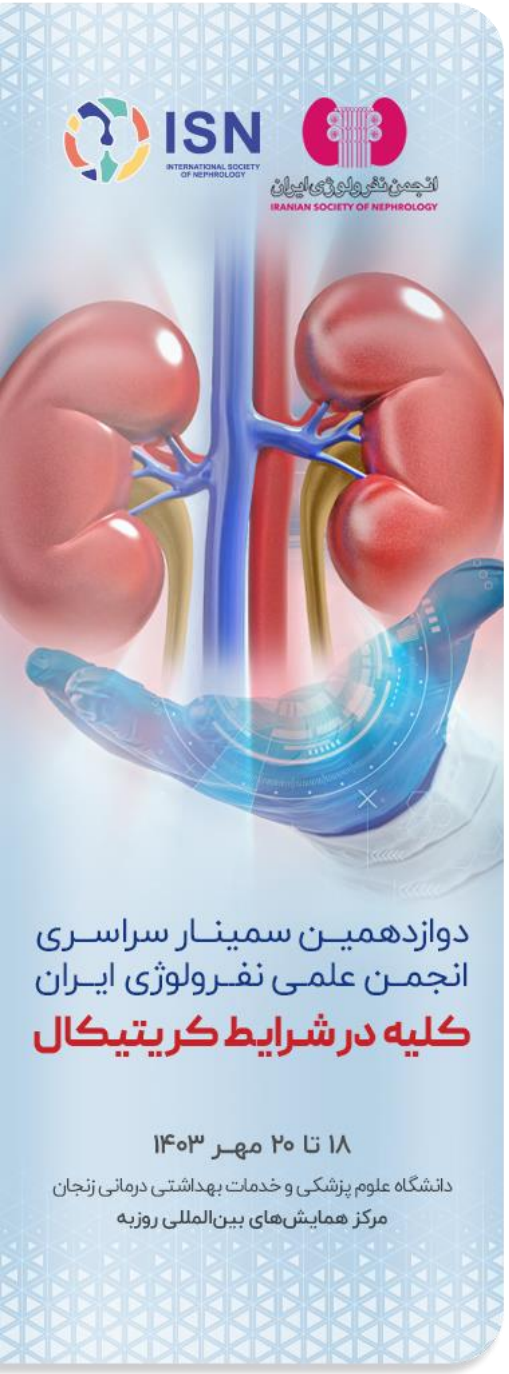


Figure 5 Forest plot of the studies comparing higher with lower positive end-expiratory pressure on the occurrence of acute kidney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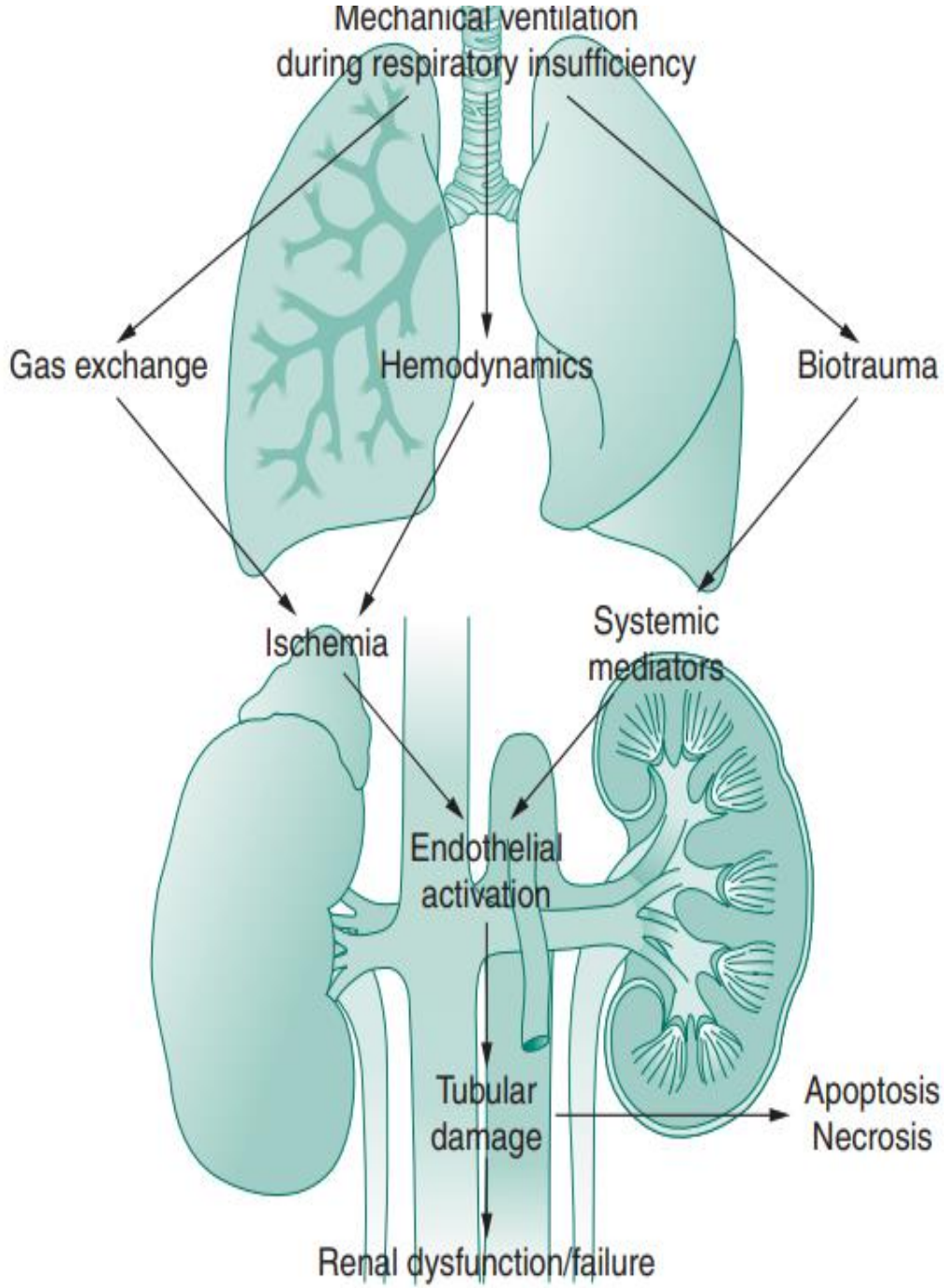
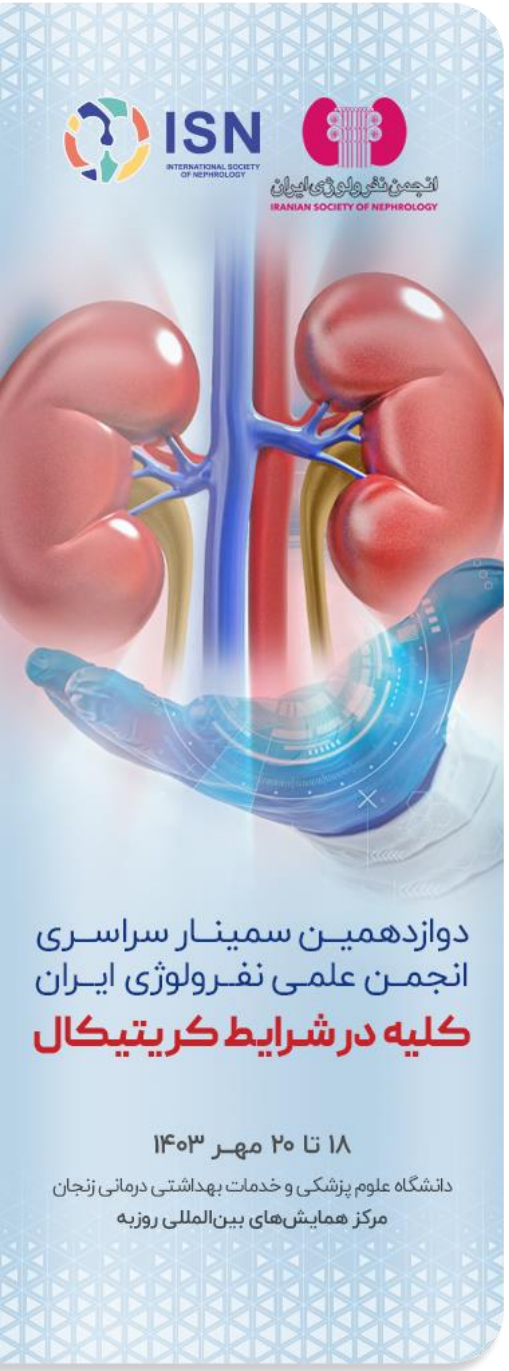
انجمن نفرولوژی ایران
IRANIAN SOCIETY OF NEPHROLOGY
دوازدهمین سمینار سراسری
انجمن علمی نفرولوژی ایران
کلیه در شرایط کریتیکال
۱۸ تا ۲۰ مهر ۱۴۰۳
دانشگاه علوم پزشکی و خدمات بهداشتی درمانی زنجان
مرکز همایش‌های بین‌المللی روزبه


Mechanical ventilation
during respiratory insufficiency
Gas exchange
Hemodynamics
Biotrauma
Ischemia
Systemic
mediators
Endothelial
activation
Tubular
damage
Apoptosis
Necrosis
Renal dysfunction/failure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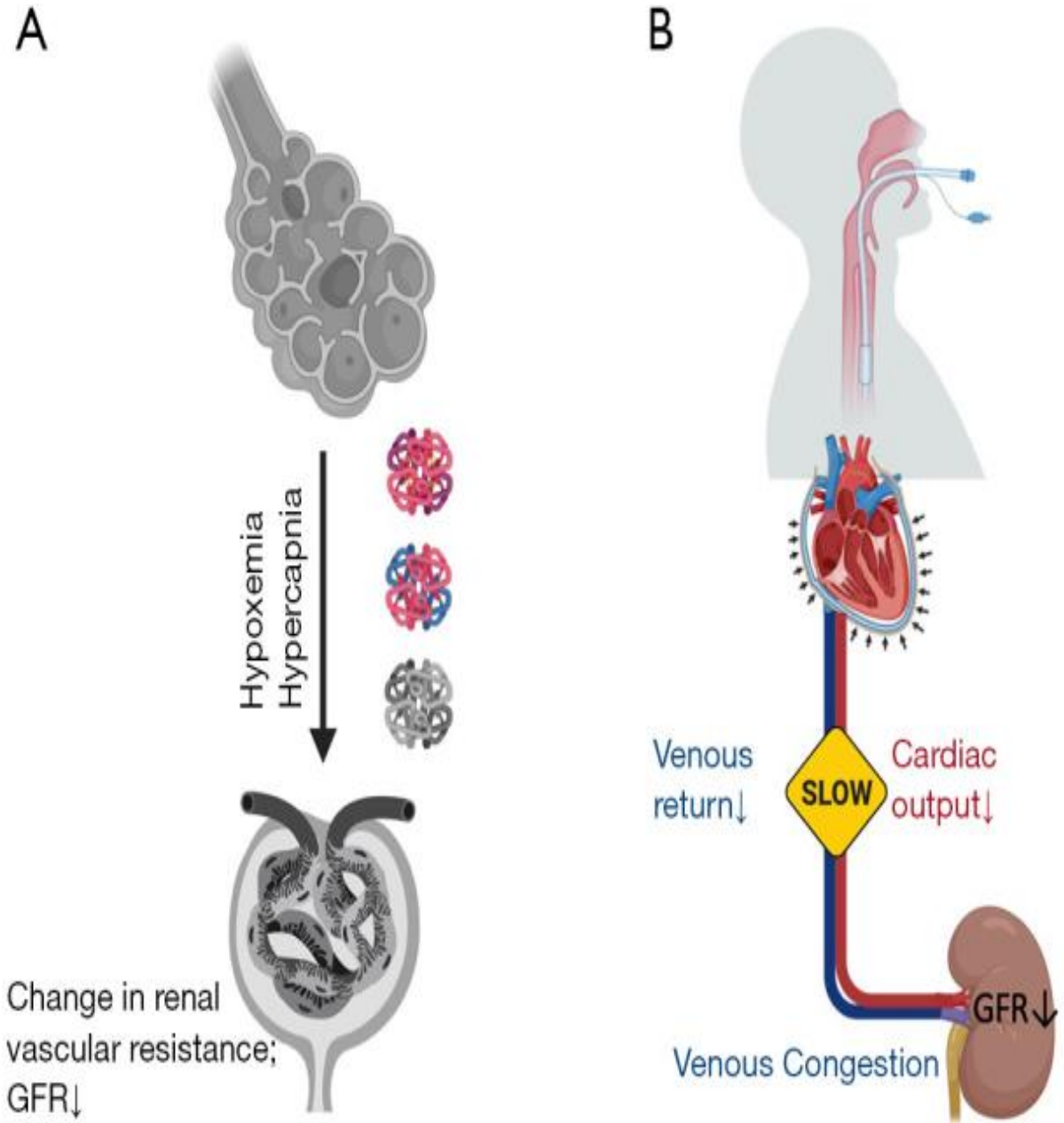
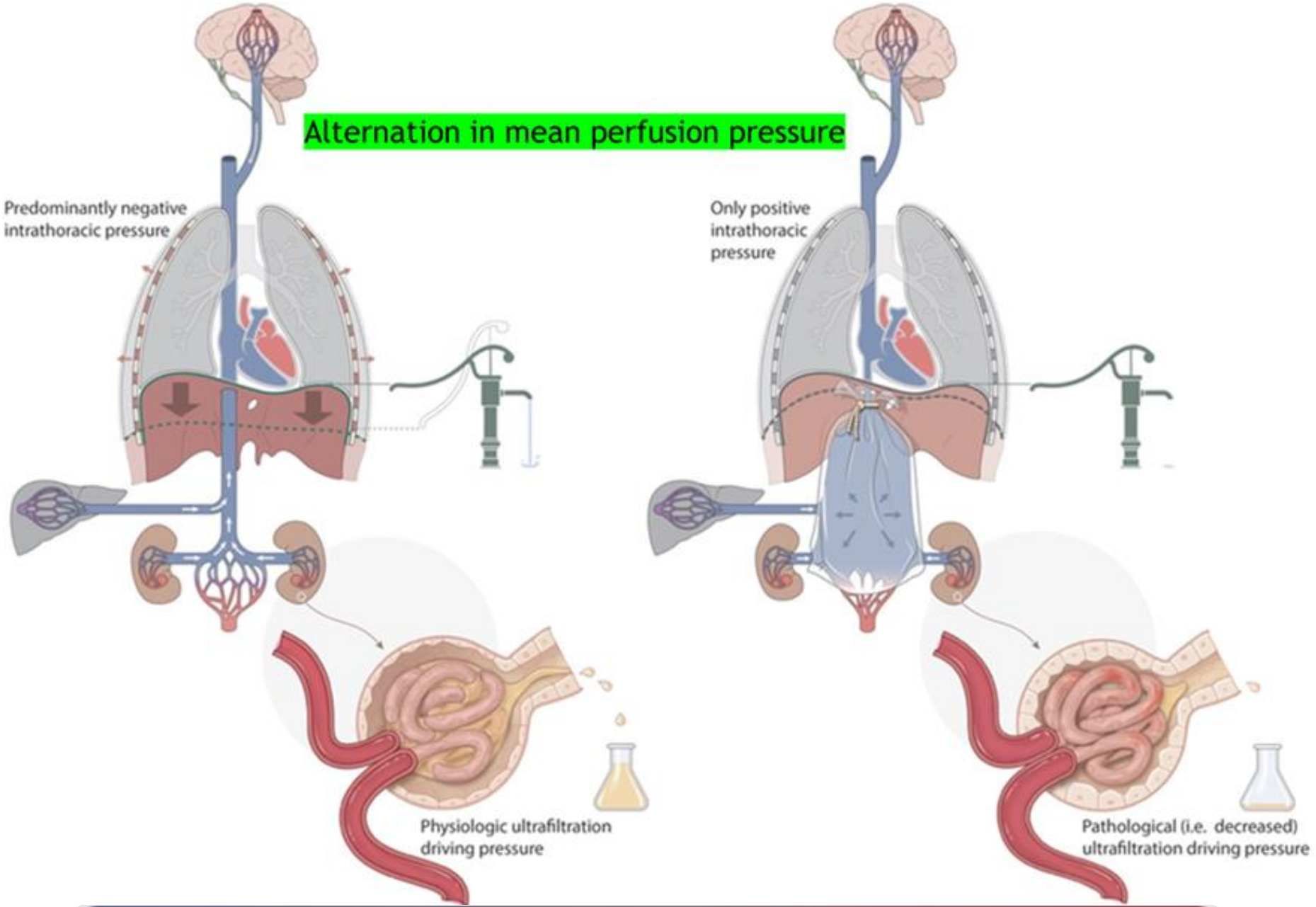

A
Hypoxemia
Hypercapnia
Change in renal vascular resistance; GFR↓
B
Venous return↓
SLOW
Cardiac output↓
GFR↓
Venous Congestion
C
Interleukins
TNF
Adhesion Molecules
Endo-/Epithelial Injury

mechanical ventilation may affect

- systemic hemodynamics can alter renal blood flow
- , changes in PaCO2 and PaO2 can affect renal hemodynamics
- suppression of peripheral immune response
- translocation of bacteria and endotoxin from lung and intestine to the systemic circulation
- biotrauma hypothesis have been distinguished: (1) Ventilation may cause release of mediators, and (2) these mediators have biologic activity
- spillover of mediators in the circulation, also may initiate and propagate a systemic inflammatory response

ventilation alters renal perfusion

- a reduction in cardiac output
- stimulation of hormonal and sympathetic pathways
- Alternation in mean perfusion pressure


Alternation in mean perfusion pressure
Predominantly negative intrathoracic pressure
Only positive intrathoracic pressure
Physiologic ultrafiltration driving pressure
Pathological (i.e. decreased) ultrafiltration driving pressure

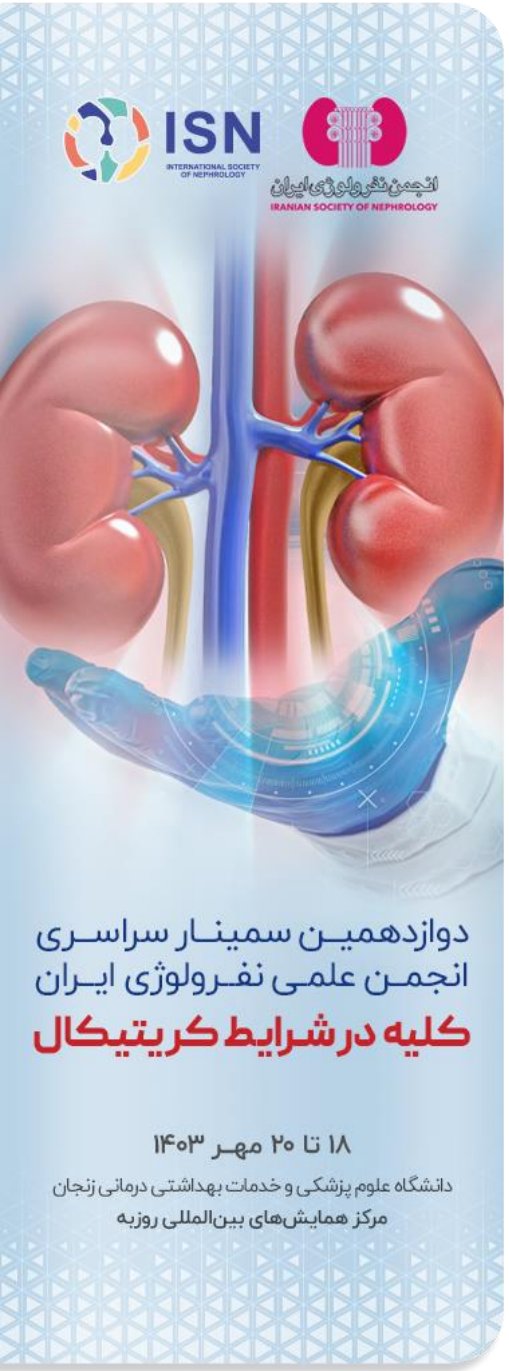
reduction in cardiac output

- decreased renal perfusion and is associated with reduced renal function as reflected in sodium handling, glomerular filtration rate (GFR), urinary output, and urea and creatinine clearance
- stimulation of water- and sodium-retaining hormonal systems
- exacerbated by PEEP
- differences in hydration status, patient acuity, possible underlying pulmonary dysfunction, and anesthetics used
- decrease oxygen delivery and increase oxygen consumption(imbalance in oxygen delivery-utilization)

hormonal and sympathetic pathways

Inflammatory, Vasoactive, and Proapoptotic Mediators That Potentially Mediate the Effects of Mechanical Ventilation on the Kidney

INFLAMMATORY MEDIATORS	VASOACTIVE MEDIATORS	PROAPOPTOTIC MEDIATORS	COAGULATION
IL-1β	Nitric oxide	Soluble Fas ligand	(a)PAI-1
IL-6	Vasopressin (ADH)	MCP-1	TATc
IL-8	Catecholamines		Active tPA
IL-10	RAAS		
TNF-α	Prostaglandins		
Soluble IL-1RA	ANF		
Soluble TNF receptors	Endothelin		
sICAM-1			
aPC			
MIP-2			
GRO / KC			
VCAM-1			



Inflammatory, Vasoactive, and Proapoptotic Mediators That Potentially Mediate the Effects of Mechanical Ventilation on the Kidney

INFLAMMATORY MEDIATORS	VASOACTIVE MEDIATORS	PROAPOPTOTIC MEDIATORS	COAGULATION
IL-1β	Nitric oxide	Soluble Fas ligand	(a)PAI-1
IL-6	Vasopressin (ADH)	MCP-1	TATc
IL-8	Catecholamines		Active tPA
IL-10	RAAS		
TNF-α	Prostaglandins		
Soluble IL-1RA	ANF		
Soluble TNF receptors	Endothelin		
sICAM-1			
aPC			
MIP-2			
GRO / KC			
VCAM-1			

ADH, Antidiuretic hormone; *ANF,* atrial natriuretic factor; *(a)PAI,* (activated) plasminogen activator inhibitor; *aPC,* activated protein C; *GRO,* growth-related oncogene; *IL,* interleukin; *KC,* keratinocyte chemoattractant; *MCP-1,* monocyte chemotactic protein-1; *MIP,* macrophage inflammatory protein; *RA,* receptor antagonist; *RAAS,* renin-angiotensin-aldosterone system; *sICAM,* soluble intercellular adhesion molecule; *TATc,* thrombin antithrombin complex; *TNF,* tumor necrosis factor; *tPA,* tissue-type plasminogen activator.

the Kidney and Hypercapnia

- directly causes
  - renal vasoconstriction
  - stimulates norepinephrine release, acting on the sympathetic nervous system
  - rapid and marked decrease in renal blood flow in response to hypercapnia also occurs in the presence of normal or increased PaO2
- Indirectly
  - systemic vasodilation that decreases systemic vascular resistance
  - , “inactivating” the baroreceptors with a subsequent release of norepinephrine and stimulation of the renin-angiotensin-aldosterone system

The Kidney and Hypoxemia(Pa2, PaO2)

mild hypoxemia without concomitant hypercapnia exerts no significant effect on renal hemodynamics

acute normocapnic hypoxemia increases renal vascular resistance

- (in)activation of vasoactive factors such as nitric oxide (NO), angiotensin II, endothelin, and bradykinin and a chemoreceptor-mediated sympathetic reflex
- decrease oxygen delivery and increase oxygen consumption

BIOTRAUMA AND THE KIDNEY

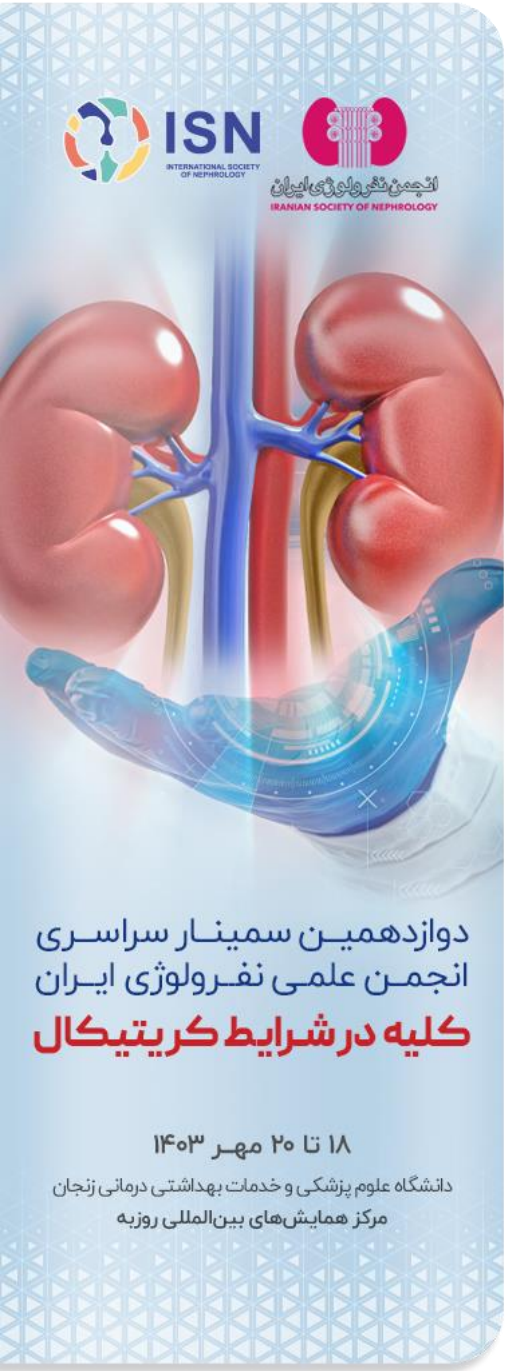
- a direct effect on renal blood flow through the release of several vasoactive mediators
- induction of a local renal inflammatory response by proinflammatory mediators from pulmonary origin,
- direct induction of apoptosis by proapoptotic factors.
- Soluble Fas ligand is known to induce apoptosis of glomerular cells, and interleukin (IL)-1ß, IL-6, and tumor necrosis factor-alpha (TNF-α) may facilitate this process by activating platelet-activating factor and inducing an inflammatory reaction

??????causal effect v/s associated effect?????

- lung-protective strategy may significantly lower concentrations of a number of cytokines (TNF-α, IL-1β, IL-6, IL-8, soluble TNF receptors, IL-1 receptor antagonist) in plasma and bronchoalveolar lavage fluid at 36 hours

- TNF-α and IL-6 has been shown to be involved in AKI

- IL-10 appears to have a protective role



Conclusions:

The development of acute renal failure during mechanical ventilation likely represents a multifactorial process that may become more important in the presence of comorbidities. Development of optimal interventional strategies requires an understanding of physiologic principles and greater insight into the precise molecular and cellular mechanisms that may also play a role.

LUNG AND KIDNEY CROSS TALK

- inflammation/oxidant-mediated injury to the alveolar-capillary barrier and downregulation of the epithelial active ion transport system

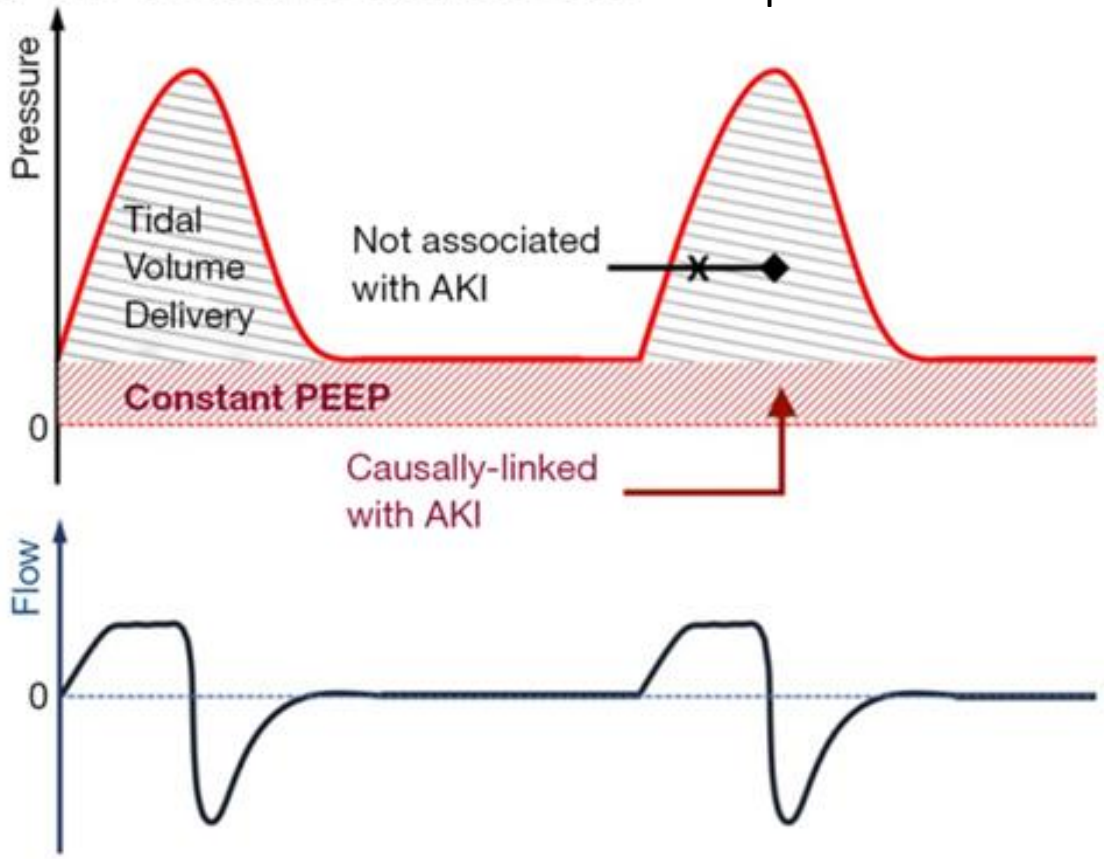
- blood gas disturbances that compromise renal blood flow and renal compensatory mechanisms; pulmonary hypertension, which may aggravate renal impairment by causing renal congestion and tissue edema; and mechanical ventilation–induced alterations, including systemic release of mediators, all which promote end-organ cell injury.

LUNG AND KIDNEY CROSS TALK

- perpetuate lung injury resulting from fluid overload and the systemic release of mediators that promote increased pulmonary vascular permeability, lung inflammation, and apoptosis, and breakdown of the transepithelial electrolyte and water transport, ultimately leading to respiratory failure.

Pressure support v/s volume support ventilation

- Elasticity and resistance and [redacted] Compliance



Well known risk factor for viki

- Low blood pressure
- Sepsis
- IV contrast injection
- Antibiotics
- Poor sedations

VIKI novel biomarker

Cell cycle arrest biomarkers in AKI(Urinary IGBP-7 muliplied TIMP-2)in critical care 2013

Mitochondrial dysfunction in AKI(Urinery ATP synthase sub unit and mitochondrial DNA(mtDNA) and ATP Synthase Subunit-β (ATPβ) base on Whitaker and colleagues (Toxicology 2015)

Mitochondreal dysfunction in AKI(Urinary mitochondrial DNA) KI 2015

DILEMA

- PARIKH et al
- Reports no difference exist between low tidal volume and high tidal volume if we diagnosed AKI with doubeling of creatinine or increased more than 50%

DILEMA

- Raniery et al
- Report high PEEP and low tidal volume decreased AKI in ICU patients

DILEMA

- Express study
- Showed if criteria of AKI is creatinine above 3.5 mg/dl there is no difference between low or high tidal volume

DILEMA

- ARDS network trial
- Low tidal volume have a higher chance of free days of AKI than high tidal volume groups

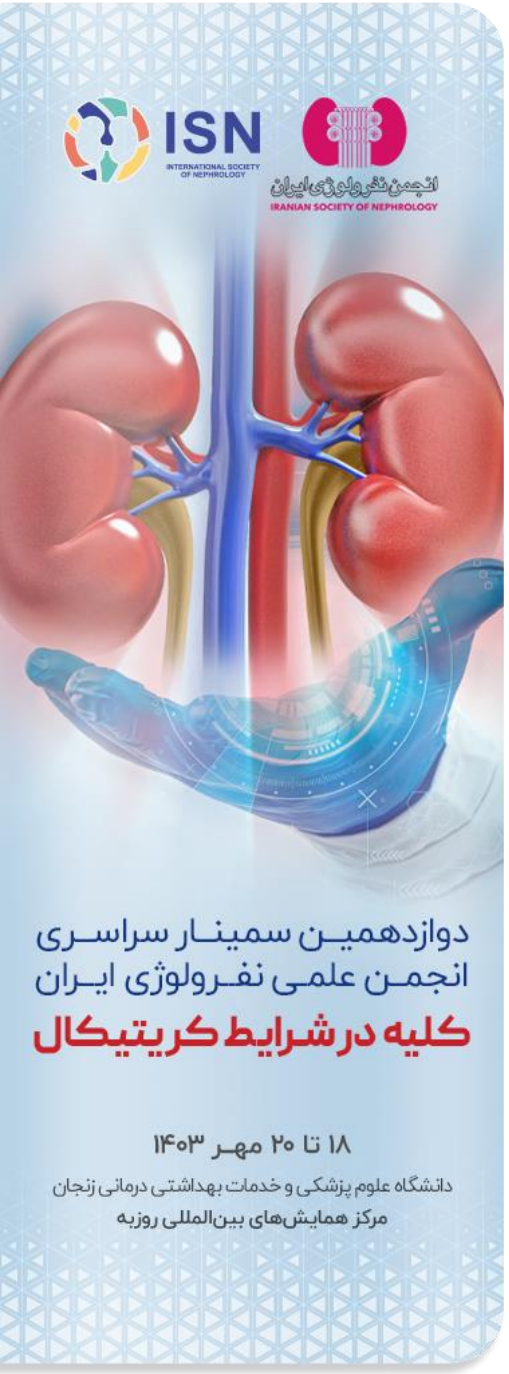
lung-protective mechanical ventilation does not protect against acute kidney injury

- **Design, Setting, and Patients**
- Secondary analysis of a randomized controlled trial (N = 150), comparing conventional tidal volume (V_T, 10 mL/kg) with low tidal volume (V_T, 6 mL/kg) mechanical ventilation in critically ill patients without ALI at randomization. During the first 5 days of mechanical ventilation, the RIFLE class was determined daily, whereas neutrophil gelatinase–associated lipocalin and cystatin C levels were measured in plasma collected on days 0, 2, and 4.
- **Results**
- Eighty-six patients had no AKI at inclusion, and 18 patients (21%) subsequently developed AKI, but without significant difference between ventilation strategies. (Cumulative hazard, 0.26 vs 0.23; P = .88.) The courses of neutrophil gelatinase–associated lipocalin and cystatin C plasma levels did not differ significantly between randomization groups.
- **Conclusion**
- In the present study in critically patients without ALI at onset of mechanical ventilation, lower tidal volume ventilation did not reduce the development or worsening of AKI compared with conventional tidal volume ventilation.

HOW TO PREVENT VIKI

- PREVENT VOLUME DEPLITION AND VOLUME OVERLOAD
- GOOD SEDATION AND CHOOSE BEST SEDATION(EARLY NEUROMUSCULAR BLOCKAGE)
- LOW TIDAL VOLUME AND HIGH PEEP (0PEN LUNG PROTECTIVE VENTILATION)
- HEAD RISING BELOW 20 DEGREE
- CHEAK MEAN PERFUSION PRESSURE(MAP-CVP)
- PREVENT O2 TOXICITY AND OVERCORRECTION OF HYPERCAPNEA
- PRONE POSITION V/S SUPINE POSITION
- USE NEW BIOMARKER FOR EARLEAR DIAGNOSIS TO PREDICT AKI AND FAILURE OF MANAGEMENT
- EARLY EXTRA CORPORAL MEMBRAINE OXYGENATION (ECMO)

HOW TO PREVENT VIKI



THANKS FOR YOUR ATTENTIONS