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Dialisi polmonare

Dr. Andrea Costamagna

Torino

Outline

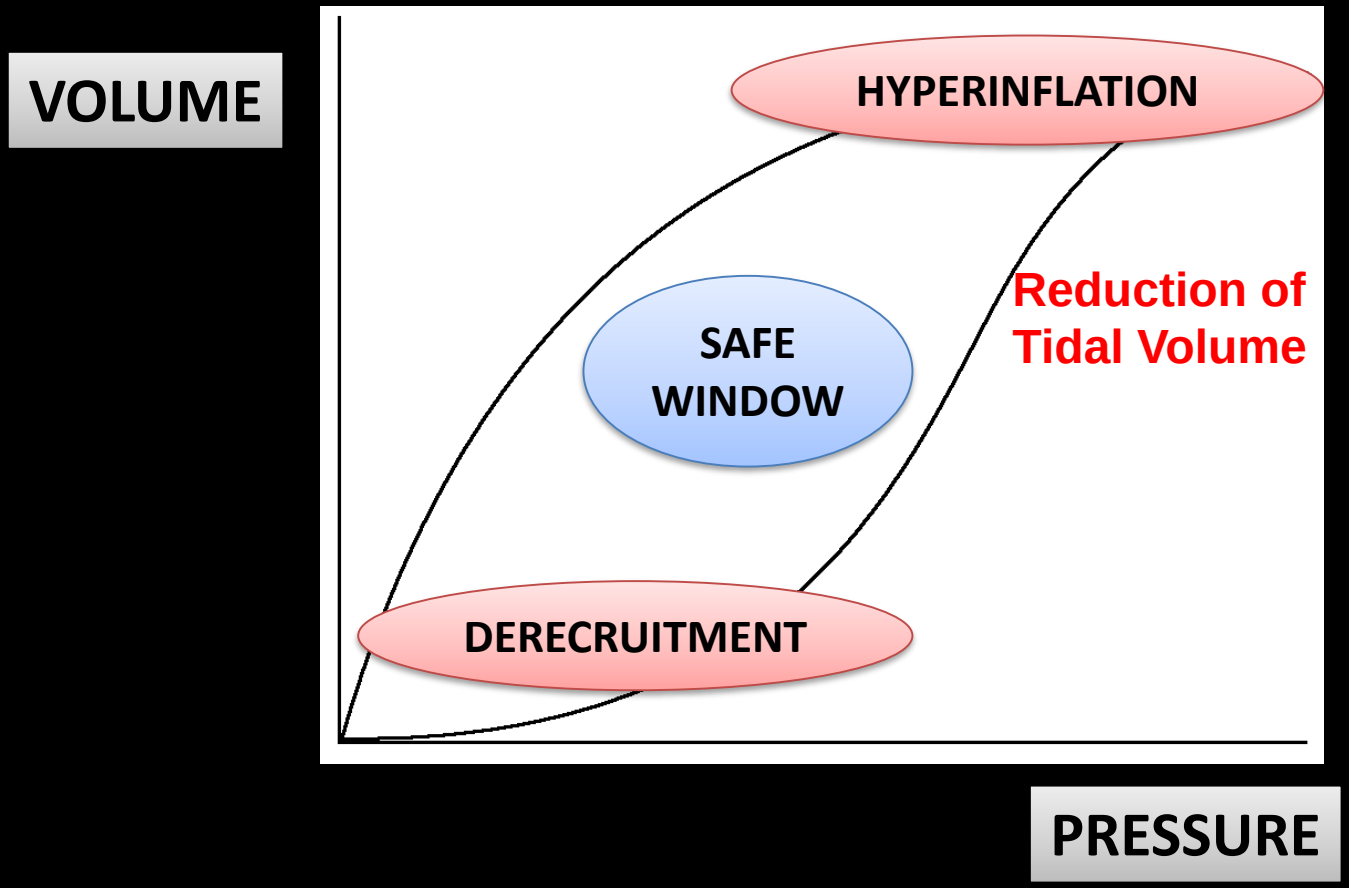
- Rationale of combining Pulmonary and Renal support
- How Lungs negatively affect Kidney and viceversa
  - Pathophisiology
  - Clinical evidence

Why combine Pulmonary and Renal Extracorporeal Support?

Historically, Lung Injury negatively affects Kidney homeostasis through VILI

What does VILI mean ?

Ventilator Induced Lung Injury



Froese AB 1997 Crit Care Med

“Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure (PEEP)”

- Rats ventilated with high peak inspiratory pressures and without PEEP had alveolar and perivascular edema, hypoxemia and decreased compliance
- Rats ventilated with low peak inspiratory pressures had no pathologic changes
- Rats ventilated with high peak inspiratory pressures and PEEP had no edema

HH Webb & DF Tierney ARRD 1974; 110:556-65

Systemic Consequences of VILI

"Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial"

- ARDS patients were randomized to a control group and a lung "protective strategy" group, to minimize stress on lungs
- CONTROL GROUP: increase in Broncho alveolar lavage (BAL) concentrations of IL 1β, IL-6, and IL-1Ra and in both BAL and plasma concentrations of TNFα, IL-6, and TNF-α receptors
- LUNG PROTECTIVE STRATEGY GROUP: reduction in BAL concentrations of PMN cells, TNF-α, IL-1β, soluble TNF-αR55, and IL-8, and in plasma and BAL concentrations of IL-6, soluble TNF-αR75, and IL-1Ra
- MECHANICAL VENTILATION can trigger a cytokine response and a lung protection strategy can attenuate this response

Ranieri VM et al JAMA 1999 282: 54-61

“Injurious Mechanical Ventilation and End-Organ Epithelial Cell Apoptosis and Organ Dysfunction in an Experimental Model of Acute Respiratory Distress Syndrome”

- Acid-aspiration lung injury was induced in rabbits
- Animals were randomly assigned to receive a non-injurious or injurious ventilation strategy
- EPITELIAL CELLS APOPTOSIS IN DISTAL ORGANS:

  Apoptosis of tubular epithelial cells in the **kidney** was higher in the injurious ventilation strategy group

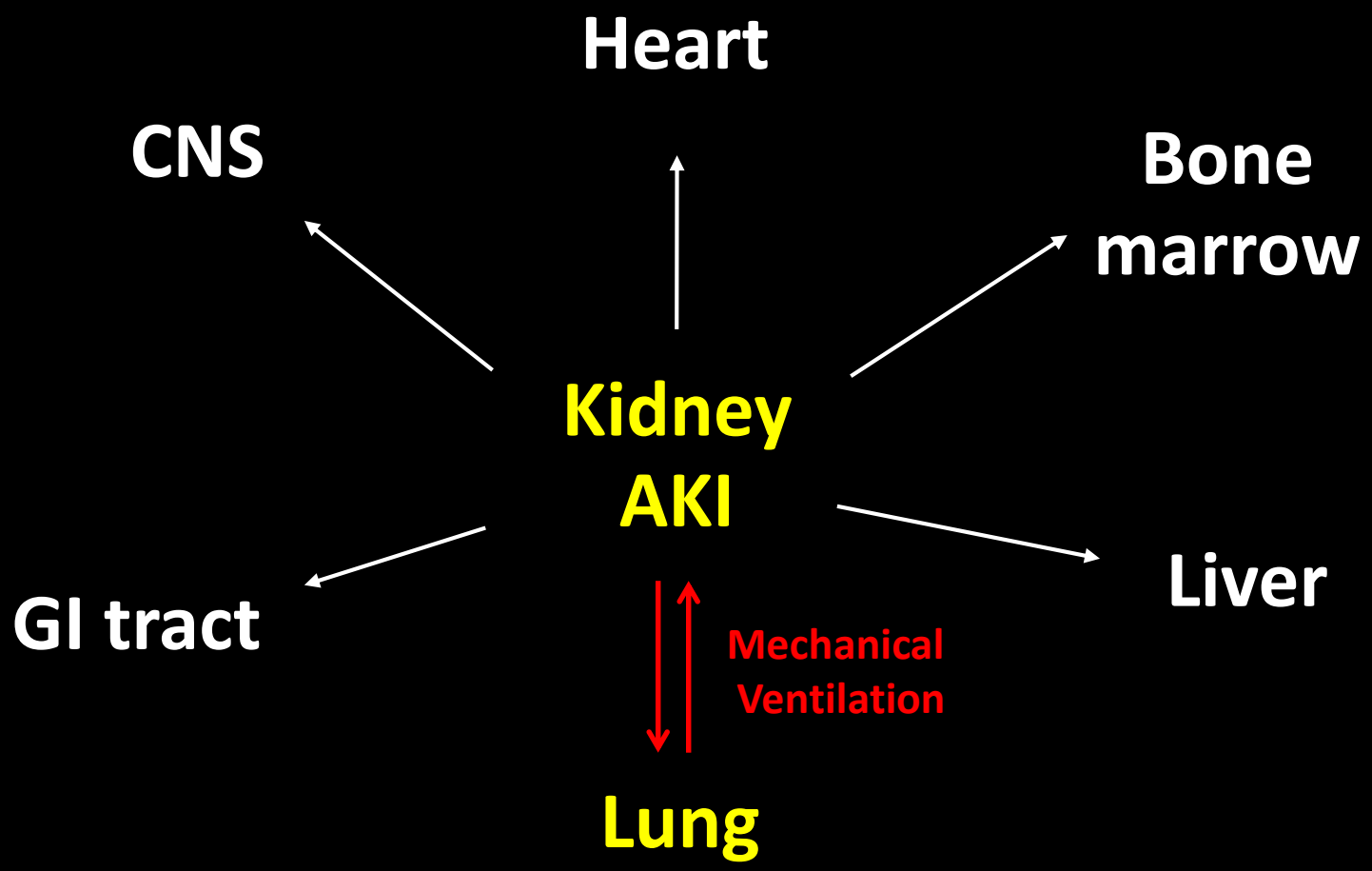
  Apoptosis of epithelial cells in **small intestinal villi** was higher in the injurious ventilation strategy group

Imai Y et al JAMA 2003 289(16):2104-12

Flipping down the problem

What about the role of kidney as driving force of lung damage?

Distant Organ Effect of AKI



Grams ME Kidney Internat 2012

"Acute Renal Failure after Bilateral Nephrectomy Is Associated with Cytokine-Mediated Pulmonary Injury"

- Mice were subjected to sham operation, unilateral ischemia, ischemic acute renal failure or bilateral nephrectomy
- All experimental groups lost weight at 24h from the procedure
- An increase in several **serum pro-inflammatory cytokines**, including IL-6 and IL-1β, was detected in the ischemic ARF and bilateral nephrectomy groups (see text for details)
- **Lung histology** showed septal edema, hemorrhage, inflammation and neutrophils infiltration in the ischemic ARF and bilateral nephrectomy groups
- **Lung histology** improved when the anti-inflammatory cytokine IL-10 was administered to a separate set of bilateral nephrectomized mice

Hoke, T.S. et al. J Am Soc Nephrol 18: 155–164, 2007.

“Acute renal failure leads to dysregulation of lung salt and water channels”

- Rats were subjected to bilateral I/R injury, sham surgery, unilateral I/R injury or bilateral nephrectomy
- Lung ENaC and Na,K-ATPase were downregulated after bilateral I/R injury and bilateral nephrectomy
- Lung Aquaporin-5 was downregulated after bilateral I/R injury and bilateral nephrectomy
- These findings could suggest negative effects on **lung fluid homeostasis**, in particular when lung injury occurs

Rabb, H. et al. Kidney Int. 63 (2003), 600–606.

What about humans?

Epidemiology of AKI

- In the intensive care unit (ICU), acute kidney injury develops in about 6% to more than 50%, depending on inclusion criteria and classifications
- Approximately 4% of patients requires renal-replacement therapy during the ICU stay
- Mortality among ICU patients with acute kidney injury and multiorgan failure has been reported to be more than 50%, depending on classifications and AKI stage

Uchino, et al. (2005). Jama 294, 813–818.
Hoste et al. (2015). Intensive Care Medicine 41, 1411–1423.

“Plasma inflammatory and apoptosis markers are associated with dialysis dependence and death among critically ill patients receiving renal replacement therapy”

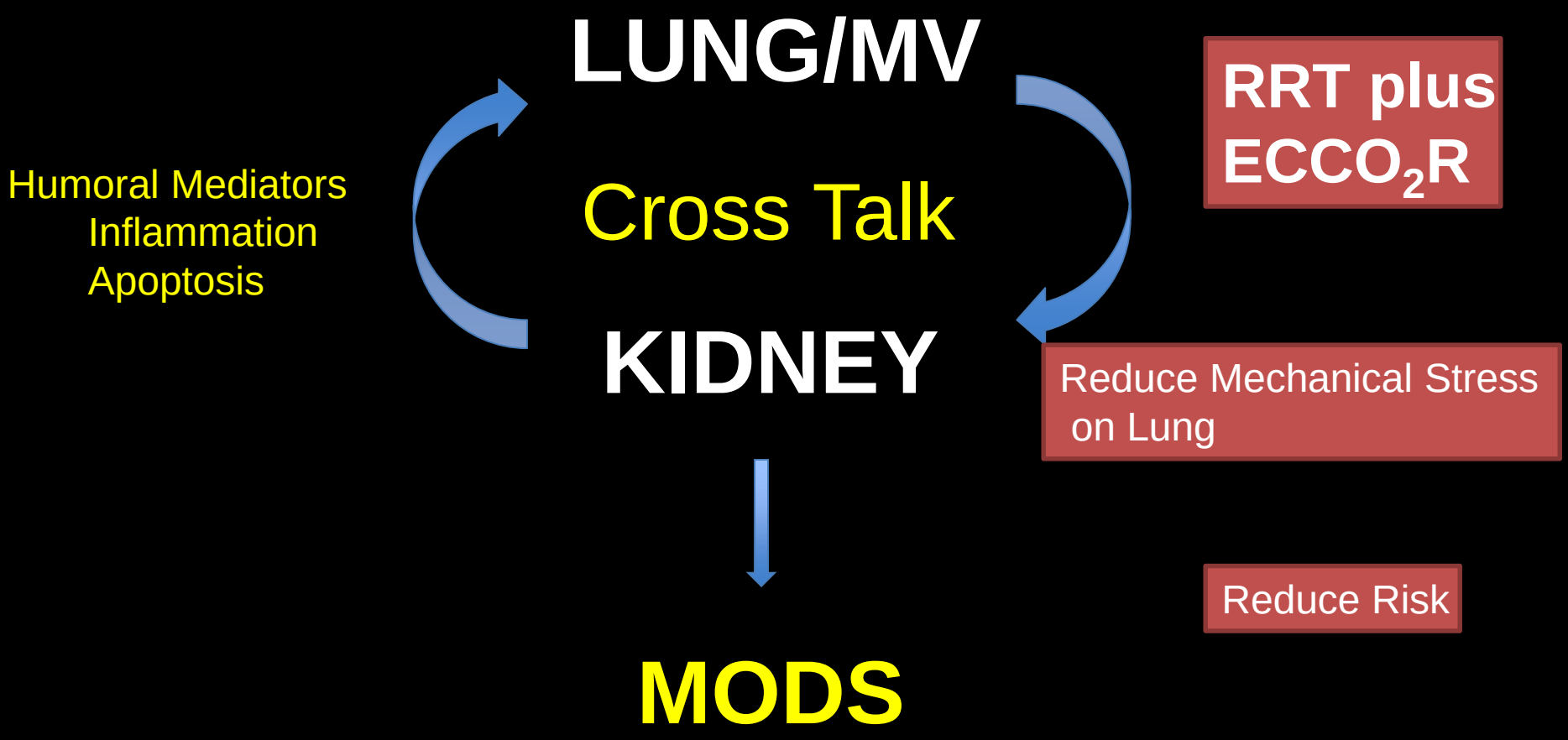
- Ancillary study of VA/NIH ATN clinical trial
- Multicenter prospective cohort study of 817 critically ill pts receiving RRT
- The authors demonstrated an association between plasma inflammatory and apoptotic mediators at day 1 and mortality at 60 day

Murugan R et al, Nephrol Dial Transplant 2014, 29: 1854–1864

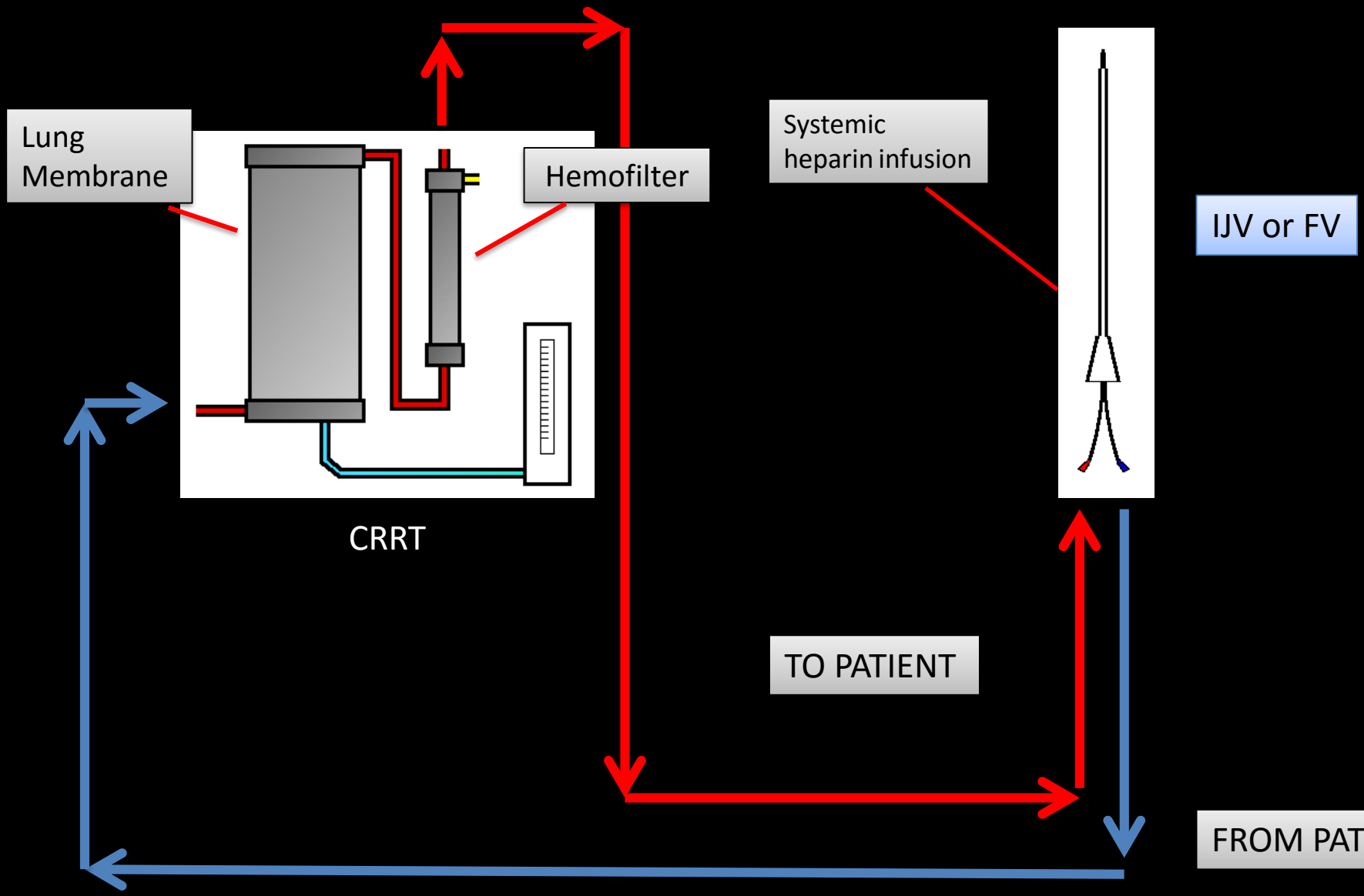
“Acute renal failure in critically ill patients: a multinational, multicenter study”

- Multinational, multicenter, prospective, epidemiological survey of ARF in intensive care unit (ICU) patients
- 29 269 ICU patients were screened; 4,2% of them were treated for ARF with RRT
- The multivariate regression analysis for hospital mortality in ICU patients with ARF showed an OR of 2.11 (1.58-2.82 - 95% CI) for mechanical ventilation as independent variable

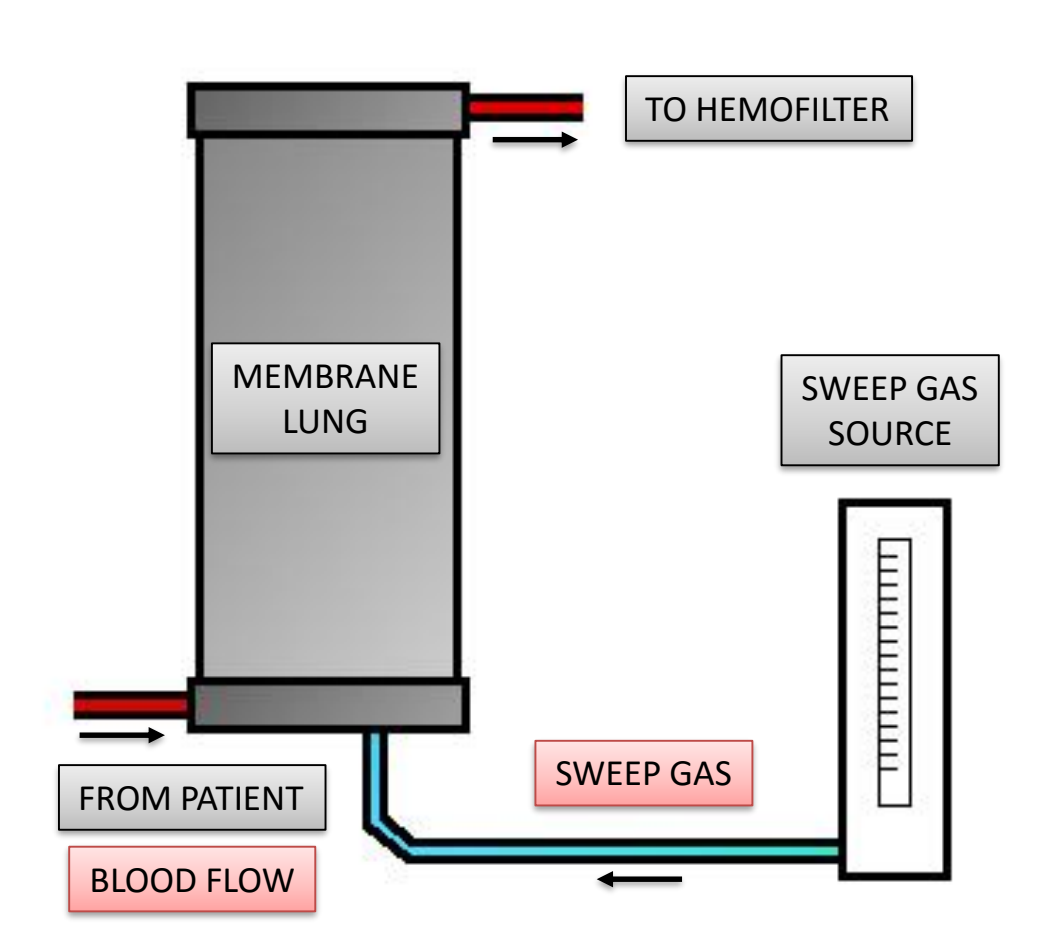
Uchino, S. et al. Jama 2005 294, 813–818.


LUNG/MV
Cross Talk
KIDNEY
MODS
Humoral Mediators
Inflammation
Apoptosis
RRT plus ECCO2R
Reduce Mechanical Stress on Lung
Reduce Risk

RRT and $ECCO_2R$ (heparin)

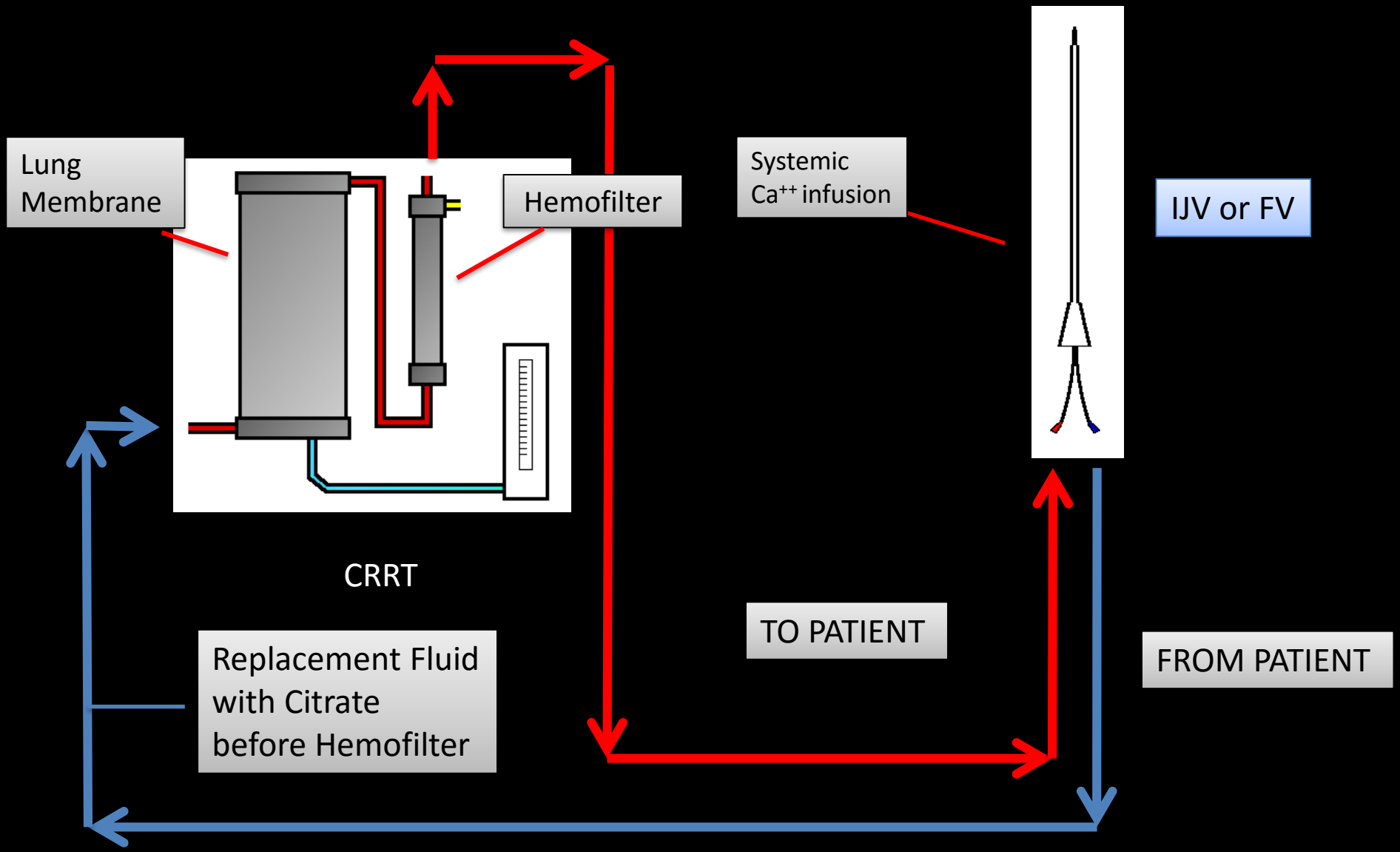


CO_2 removal by artificial membrane lung



Blood flow And Sweep gas Are the determinants of CO_2 clearance

RRT and $ECCO_2R$ (citrate)



Research proposals

- A Matched Cohort Study with Historical Control
  - Feasibility and Safety
- Multicentre Prospective Interventional Clinical Trial
  - Efficacy

RRT and $ECCO_2R$ clinical trial

- Combined Strategy of Renal Replacement Therapy Plus Extracorporeal Carbon Dioxide Removal in Patients With Acute Kidney Injury
- Principal investigator: Vito Fanelli MD, PhD, University of Turin, Italy (A.O. Città della salute e della scienza)
- ClinicalTrials.gov Identifier: NCT02595619

RRT and $ECCO_2R$ clinical trial

Inclusion Criteria:

- Patients with acute kidney injury (AKI) requiring renal-replacement therapy and mechanical ventilation of duration ≥ 48 hours

Exclusion Criteria:

- little chance of survival at 24 h (according to clinical judgment), pregnancy, mechanical ventilation with expected duration lower than 48h, age under 18 and over 90

RRT and $ECCO_2R$ clinical trial

Primary Outcome Measures:

- Achievement of tidal volume reduction to 4 mL/kg while maintaining pH and $PaCO_2$ to ± 20% of baseline values

Secondary Outcome Measures:

- Evaluation of inflammatory mediators release in plasma samples of patients
- Assessment of the changes in pH, $PaCO_2$, PaO_2

Conclusions

- Lung and Kidney injury cross talk negatively affects whole organism homeostasis
- Combining pulmonary and renal extracorporeal support may interrupt this vicious cycle
- Large studies with clinical relevant end points are needed