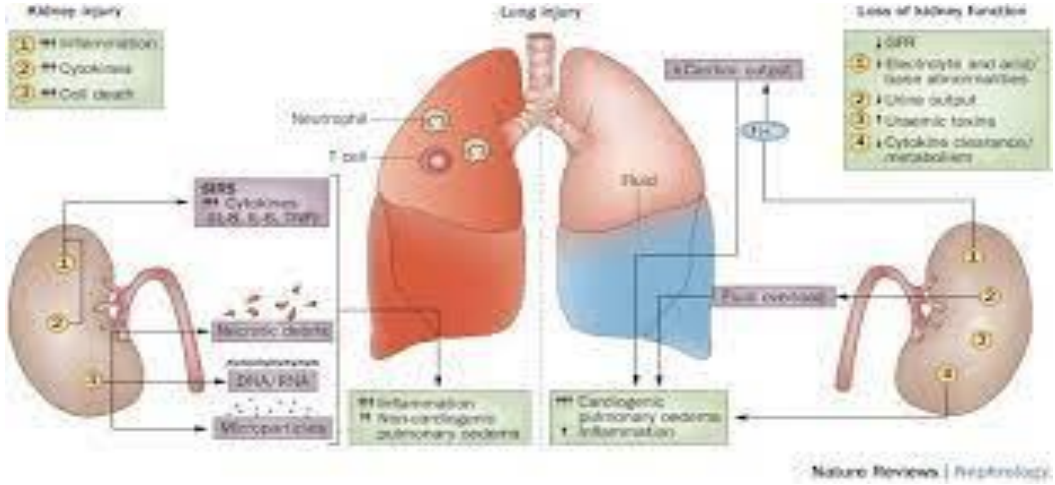
IN The Name Of God

Concomitant Lung and Kidney Disorders in Critically Ill Patients



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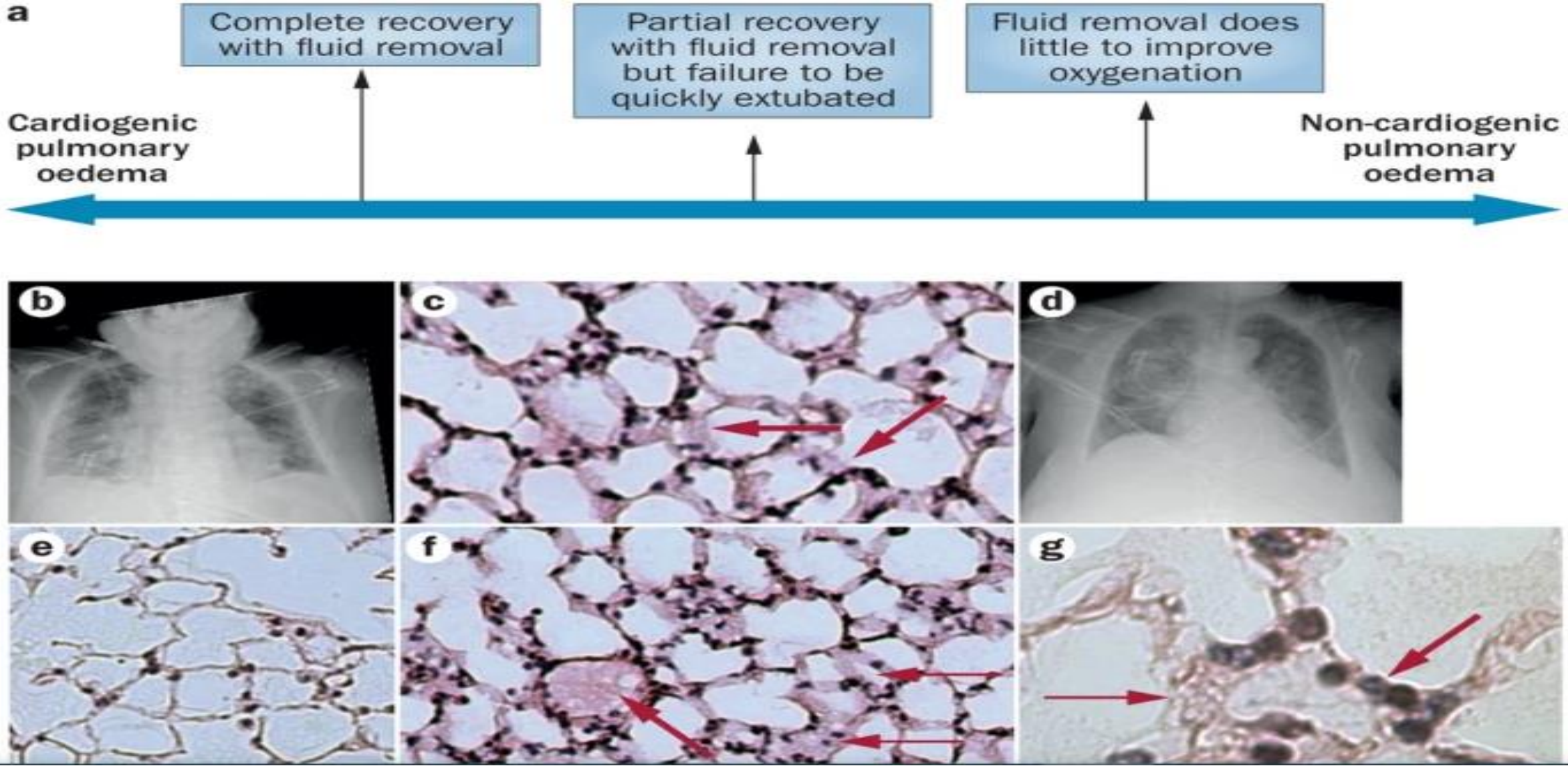
Outlines

- ALI After AKI
- Diffuse Alveolar Hemorrhage
- Heart Failure
- Acid-Base Disorders
- Venous Thromboembolism

Intruduction

- The lungs and kidneys are cooperative and interdependent organs that secure the homeostasis of the body.
- Volume and acid–base disorders sit at the nexus between these two systems.

Pulmonary oedema in AKI



Mechanisms and mediators of lung injury after acute kidney injury

- Respiratory complications are common after acute kidney injury (AKI) and are associated with increased mortality
- Cardiogenic (volume overload) and non-cardiogenic (lung injury with inflammation) pulmonary oedema can occur after AKI
- Animal data indicate that lung inflammation and lung endothelial apoptosis mediate non-cardiogenic pulmonary oedema after AKI
- Human and animal data suggest that IL-6, IL-8, TNF, NFκB, TNFR1 and caspase-3-mediated apoptosis, HMG-B1, and T cells mediate lung injury after AKI
- The high mortality associated with AKI might be due to both traditional (for example, electrolyte abnormalities) and non-traditional (for example, lung injury) complications of AKI

NATURE REVIEWS 2016

Box 3 | Indicators of lung injury after acute kidney injury

Very early (0–6 h)

Increased serum proinflammatory cytokines (for example, IL-6, IL-8, TNF)
Increased serum mediators (for example, HMGB1)
Increased lung NFκB
Increased lung chemokines (for example, MIP-2 and IL-8)
Increased lung adhesion molecules (for example, ICAM-1)
Increased lung markers of inflammation (for example, IL-1β)
Pulmonary oedema
Lung neutrophil accumulation

Early (24 h)

Lung T-cell accumulation
Increased lung endothelial apoptosis, caspase 3 activity, and lung TUNEL staining
Pulmonary oedema
Lung neutrophil accumulation

Late (7 days)

Increased lung IL-8
Lung neutrophil accumulation

Abbreviation: TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labelling.

NATURE REVIEWS 2016

Case 1

A 65-year-old woman with hypertension and diabetes is admitted to the ICU for **acute hypoxemic respiratory failure** requiring mechanical ventilation.

Vital signs :

T:37.9 C, HR: 75, BP: 106/68 mm Hg, RR: 22, PaO_2 :75 mm Hg

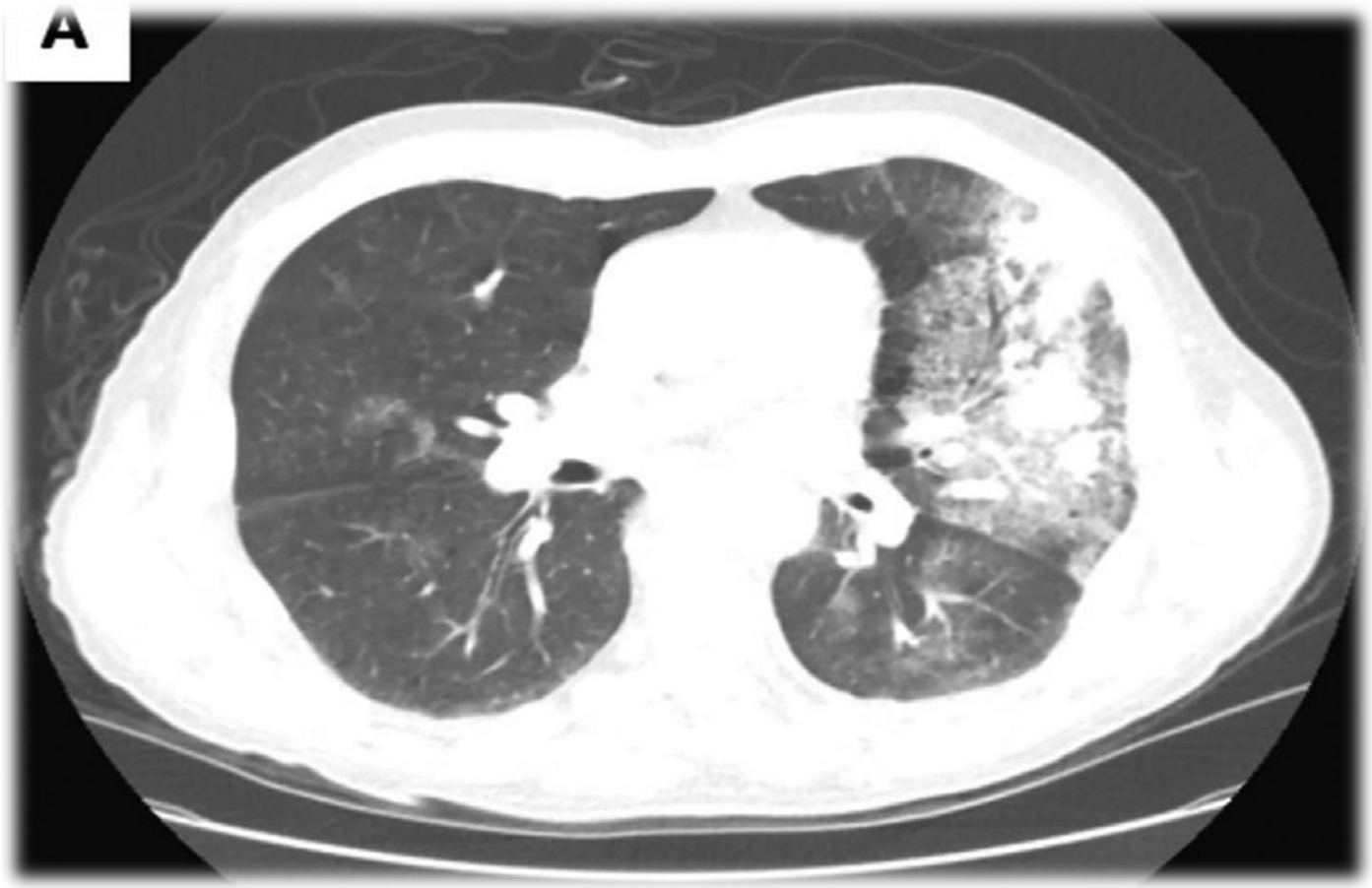
there is no saddle-nose deformity or nasal crusting.

She has coarse crackles on chest auscultation bilaterally without wheezing. She has no heart murmur, edema, or rash.

Suctioning through the endotracheal tube reveals pink sputum.

WBC: 16 × 10^3/µL, Hb:8.9, PLT:230 × 10^3/µL ,Scr: 2.9, U/A: 45 (RBCs) and proteinuria (3+).

noncontrast chest CT shows patchy groundglass infiltrate



Question 1

What should be the next step in management?

a. Transbronchial biopsy
b. Noncontrast CT of the abdomen
c. Bronchoscopy with bronchoalveolar lavage
d. Kidney biopsy

Cont…

the best answer to question 1 is c.

- Bilateral ground-glass infiltrates and blood-tinged sputum may be present in multifocal pneumonia, pulmonary edema, and ARDS.

- In this patient, the low hemoglobin level and active urine sediment with hematuria and albuminuria should prompt consideration of **DAH**.

- Confirmation of DAH requires bronchoscopy with sequential bronchoalveolar lavage.

Box 1. Causes of Diffuse Alveolar Hemorrhage With Glomerulonephritis

- ANCA vasculitis
- Anti–glomerular basement membrane antibody disease
- IgA vasculitis
- Drug-induced vasculitis (cocaine, hydralazine)
- Thrombocytopenia
- Systemic lupus erythematosus
- Infective endocarditis with septic emboli
- Cryoglobulinemia

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; Ig, immunoglobulin.

AJKD 2022

Question 2

Both PR3-ANCA and MPO-ANCA are often positive in which condition?

a. Eosinophilic granulomatosis with polyangiitis
b. Infective endocarditis
c. Drug-induced vasculitis
d. Anti-GBM disease

the best answer to question 2 is c.

- For the diagnosis of ANCA vasculitis, ELISAs for PR3 and MPO antibodies are the preferred tests because of the lack of standardization of ANCA immunofluorescence.

- The **sensitivity of the ELISA** test ranges from **70% to 90%** and correlates with disease activity.
- The **specificity of the ELISA** test is approximately **95%** for GPA and MPA.

- **ANCA positivity** has been **associated** with **endocarditis, inflammatory bowel disease, sarcoidosis, and almost all connective tissue disorders.**

- **The presence of both PR3- and MPO-ANCA strongly suggests a drug-induced vasculitis.**

- **Culprit drugs include levamisole, a contaminant of cocaine; and hydralazine, with which high-titer ANA positivity may also be seen.**

Cont…

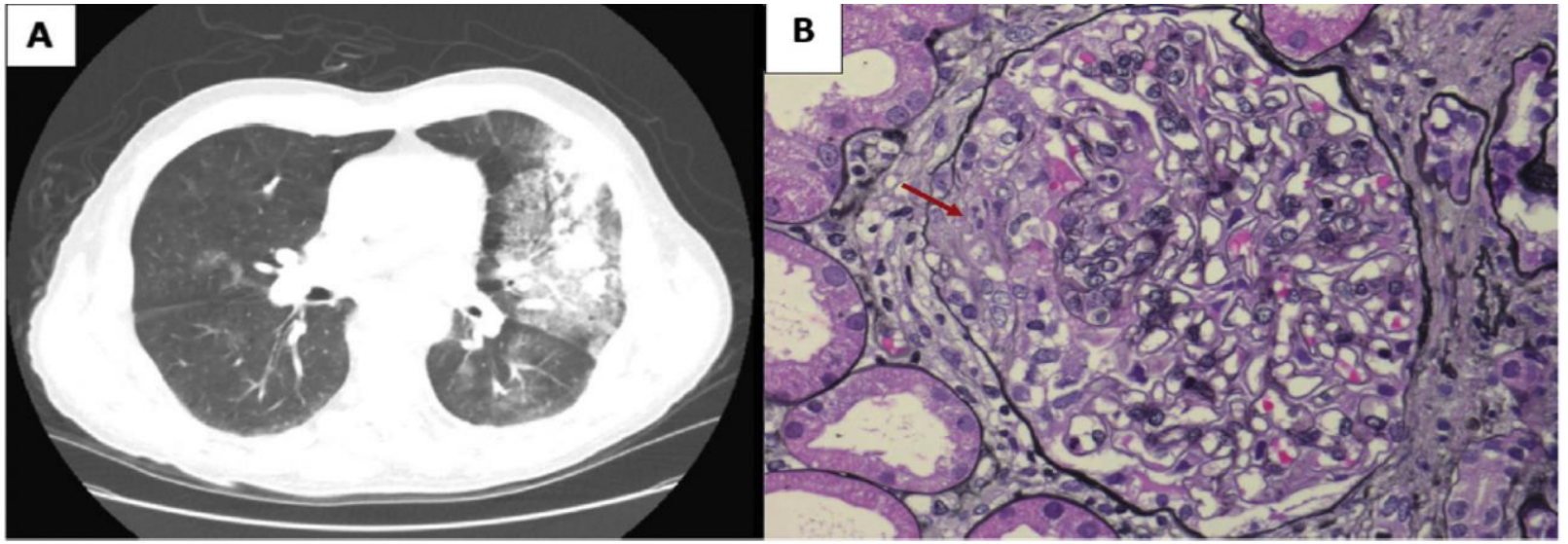
- Antibodies to GBM can be found in the serum of 90% of patients with anti-GBM disease. However, the sensitivity and specificity depend on the quality of the ELISA.

- **DAH** is a **rare complication of SLE** that occurs in **2%-5%** of people.

- Platelet count <50 × 10^3/uL is uncommon, suggesting the mechanism of hemorrhage is due to vasculitis rather than ineffective clotting.

- ANA is almost universally positive in this condition, The specificity of ANA in the setting of DAH has not been well studied.

Role of Tissue Biopsy



Histopathologic patterns on lung biopsy seen in DAH include pulmonary capillaritis, bland hemorrhage, or diffuse alveolar damage. **Pulmonary capillaritis is the most common finding** and may be accompanied by **palisading** granulomas in GPA, **linear** Ig G staining in anti-GBM disease, or **granular** IgA in IgA vasculitis.

A finding of pulmonary capillaritis alone is nonspecific.

Role of Tissue Biopsy

- **bronchoscopy** is still an important part of the workup to confirm the presence of DAH and to rule out infection beforebeginning immunosuppressive therapy.

Case 2

A 53-year-old man with CKD stage 3 and heart failure with reduced **EF: 35%**

has been hospitalized for a HF exacerbation and transferred to the ICU.

HR:90, BP: 126/79, RR :29, O_2 saturation: 91%, JVP: 12 cm H_2O, use of accessory respiratory muscles, bilateral crackles, and peripheral lower-extremity edema (1+).

During the previous 3 days, Scr 1.7 ⇨ 2.6 mg/dL BNP:3,500 pg/mL, and troponin is undetectable. Lactate :1.8 mmol/L K:6 mEq/L

Urinalysis is not performed because the patient has not produced urine.
As a result of his AKI, diuretic therapy(Fursemide 20 mg IV-TDS) was stopped 2 days earlier.

Calcium, insulin and glucose have been administered for hyperkalemia.

Question 3

What is your first step in management?

a. Start dobutamine infusion
b. Place a pulmonary artery catheter to guide management
c. Urgent dialysis
d. High-dose diuretic agents

the best answer to question 3 is d.

- His worsening kidney function is most likely due to renal venous congestion as evidenced by his elevated jugular venous pressure and peripheral edema.
- Among patients with ADHF, CVP correlates better with worsening kidney function than cardiac index.
- Furosemide also acts as a vasodilator to reduce excessive preload and enhances active alveolar fluid reabsorption, which can lead to an improvement in symptoms before diuresis ensues.
- **Loop diuretic therapy should be initiated intravenously at 2.5 times the total oral dose**.
- In the CARRESS-HF trial of patients with ADHF and worsening kidney function, ultrafiltration at 200 mL/h showed no benefit over diuretic agents in achieving a goal urine output of 3-5 L/d.

J Am Coll Cardiol. 2020
AJKD 2022

commentary

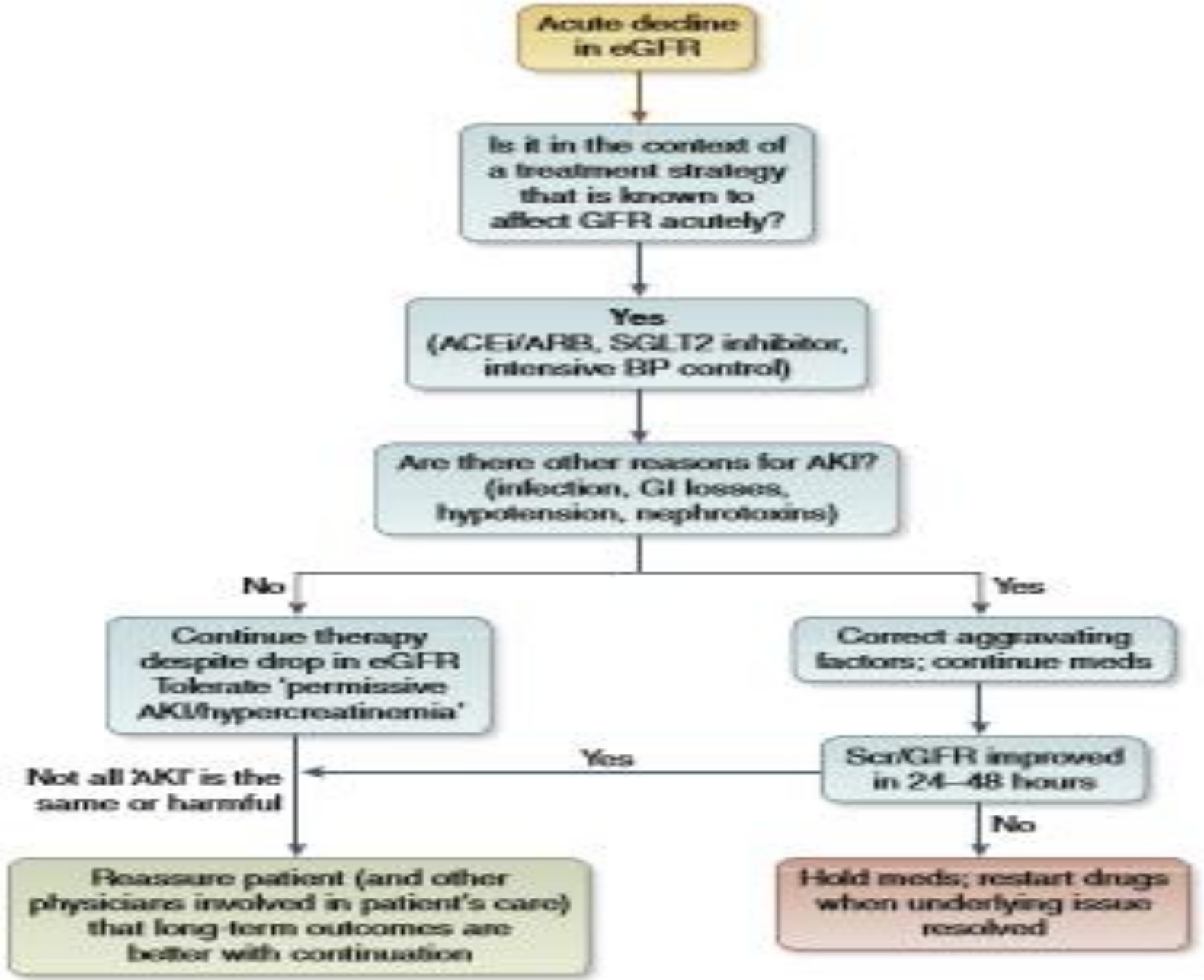
"Permissive AKI" with treatment of heart failure

Chirag R. Parikh[1] and Steven G. Coca[2]

Renin–angiotensin–aldosterone system inhibitors have proven clinical benefit in management of patients with heart failure with reduced ejection fraction. However, there are no guidelines to manage decline in kidney function that occurs with initiation and titration of renin–angiotensin–aldosterone system agents during management of heart failure. We discuss the complex interplay of kidney function and heart failure in the presence of renin–angiotensin–aldosterone system agents and suggest a clinical algorithm for management of acute decline in kidney function.

Kidney International (2019) 96, 1068–1072; https://doi.org/10.1016/j.kint.2019.07.003

Kidney International (2019)



Kidney International (2019)

Case 2 (continued)

High-dose furosemide is given, and a urine output of 80-100 mL/h is achieved.

On repeat check, his potassium level has decreased to 5.3 mEq/L.

Intravenous furosemide is titrated to 100 mg every 8 hours, but urine output continues to be only 100 mL/h.

BP:120/60,and he remains volume overloaded.

Question 4

Which of the following additions to his current treatment would be expected to augment urine output?

a. Nesiritide
b. Nitroglycerin
c. Metolazone
d. Dopamine

Cont…

the best answer to question 4 is c.

- This patient’s inadequate response to an optimized dose of loop diuretic agent can be characterized as diuretic resistance.

- Diuretic resistance may occur if renal venous congestion persists but is most often due to compensatory distal tubular sodium reabsorption.

Cont…

- Strategies that target these distal segments improve urine output but have not been shown to reduce symptoms or mortality in large studies.

- In the 3T trial, patients with diuretic resistance were randomized to adjunctive treatment with tolvaptan, intravenous chlorothiazide, oral metolazone.

- Weight loss and urine volume improved in all groups, but there was less natriuresis with tolvaptan.

- Because of its cost, lack of superiority to metolazone in altering sodium excretion, and potential liver toxicity, tolvaptan is not routinely used.

Diuretic Resistance

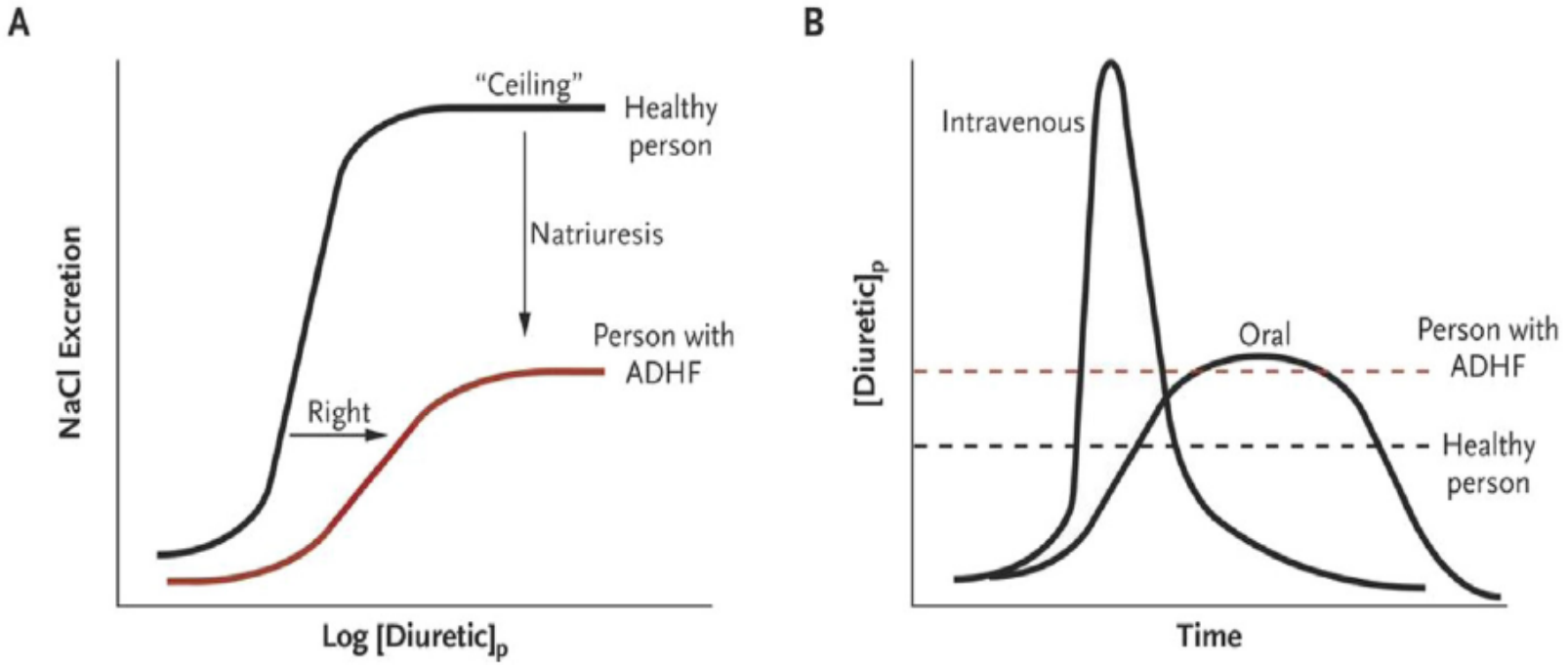


Figure 2. Loop diuretic pharmacodynamics. (A) The dose–response curve (plotted with diuretic concentration on the *x* axis) shifts to the right and has a lower ceiling in people with acute decompensated heart failure (ADHF). (B) Intravenous doses may achieve more time in range above the plasma threshold concentration (dashed lines). Graphic ©2017 Massachusetts Medical Society. Adapted from Ellison and Felker (*N Engl J Med.* https://doi.org/10.1056/NEJMra1703100) with permission of the copyright holder.

Cont…

- **Nitroglycerin**, in patients with stable condition, vasodilator therapy does not result in significant reductions in weight or N-terminal proBNP level.

- **Dopamine** and nesiritide, neither improved urine output at 72 hours when added to standard diuretic therapy in the ROSE randomized controlled trial.

- There are currently **insufficient data** regarding the effects of **aldosterone antagonists and carbonic anhydrase inhibitors** in the setting of diuretic resistance in ADHF.

Table 1. Adjunctive Medications and Outcomes in Patients Receiving Loop Diuretic Agents for Acute Decompensated Heart Failure

Medications	Dose	Mechanism of Action	Outcomes	Representative Studies
Metolazone, chlorothiazide	5 mg orally 2×/d, 500 mg IV 2×/d	Thiazide diuretic	Increased urine output and weight loss in diuretic resistant population	3T
Tolvaptan	30 mg orally 1×/d	V2 receptor antagonist	(1) Increased urine output and weight loss in diuretic resistant population; (2) no improvement in dyspnea	(1) TACTICS-HF; (2) 3T
Dopamine	2 µg/kg/min	Renal vasodilator	No increase in urine output in patients with decreased kidney function	ROSE
Nitroglycerin infusion	0.01 µg/kg/min	Systemic venodilator	(1) Decrease in pulmonary capillary wedge pressure; (2) reduced need for mechanical ventilation in severe pulmonary edema when added to furosemide	(1) VMAC; (2) Cotter et al[b]
Transdermal and sublingual nitrates	Dose titration to target SBP 90-100 mm Hg	Systemic venodilator	No increase in weight loss	GALACTIC
Spironolactone	100 mg orally 1×/d	Mineralocorticoid receptor antagonist	No improvement in dyspnea, urine output, or NT-proBNP	ATHENA-HF

Abbreviations: 3T, Comparison of Oral or Intravenous Thiazides vs Tolvaptan in Diuretic Resistant Decompensated Heart Failure; ATHENA-HF, Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure; GALACTIC, Effect of a Strategy of Comprehensive Vasodilation vs Usual Care on Mortality and Heart Failure Rehospitalization Among Patients With Acute Heart Failure; IV, intravenous; NT-proBNP, N-terminal pro–B-type natriuretic peptide; ROSE, Renal Optimization Strategies Evaluation; SBP, systolic blood pressure; TACTICS-HF, Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure; VMAC, Vasodilation in the Management of Acute Congestive Heart Failure.

[b]Cotter et al, 1998 (*Lancet*. https://doi.org/10.1016/S0140-6736(97)08417-1).

Case 3

A 48-year-old man with alcohol use disorder presented with fever, abdominal pain, and dyspnea several days after an episode of heavy drinking.

CXR:bilateral lower-lobe infiltrates.

increased potassium ,lipase and amylase levels.

ABG: pH 7.14, $PaCO_2$ of 73 mm Hg, PaO_2 .75 mm Hg, HCO3: 23.9 mM.

He was in hemodynamically stable condition, but intubated for ARDS because of pancreatitis and likely aspiration pneumonia.

The team considered administering sodium bicarbonate to improve his acidemia.

Question 6

What is an absolute indication for attempting correction of a respiratory acidosis?

a. Worsening hypoxemia
b. Increased intracranial pressure
c. Hyperkalemia
d. pH <7.25

the best answer to question 6 is b.

- ✓ In ARDS, in which hypercapnia arises from a combination of physiologic dead space and lung-protective ventilation, $PaCO_2$ in the range of 80-100 mm Hg is generally well tolerated.
- ✓ Considerable animal data in various lung injuries have shown that imposed respiratory acidosis decreases inflammation and improves lung compliance.
- ✓ **Severe respiratory acidosis generally does not cause an appreciable change in serum potassium**.
- ✓ **Its effects on other organ systems include renal vasoconstriction and cerebral vasodilation.**
- ✓ **In cases of increased intracranial pressure, respiratory acidosis should be corrected to reduce cerebral blood flow and intracranial pressure.**

Case 4

A 72-year-old woman with severe Copd and Heart failure with (EF= 40%) experienced increasing sputum, dyspnea, and cough combined with increasing peripheral edema .

On presentation, she had tachypnea with severe wheezing. With a face mask O_2 sat: 85%.

ABG: pH 7.29, $PaCO_2$:73 mm Hg, PaO_2 of 55 mm Hg, HCO3: 34 mM.

Despite treatment with methylprednisolone, frequently administered nebulized albuterol/ipratropium, and furosemide, she became somnolent and was intubated.

On hospital day 4, ABG: pH 7.47, $PaCO_2$ of 54 mm Hg, PaO_2 of 89 mm Hg, HCO3: 38.2 mM

Because of concern that her alkalemic pH was hindering her liberation from the ventilator, **the team considered the use of acetazolamide to facilitate extubation**.

Question 8

Which of the following is an expected effect of acetazolamide?

a. Decrease in airway resistance
b. Increase in serum bicarbonate level
c. Decreased time on the ventilator
d. Increase in tidal volume

the best answer to question 8 is d.

- **Acetazolamide** has a long history of use as a respiratory stimulant.
- Acetazolamide causes a decrease in serum bicarbonate level of 4-6 mM, with greater decreases in **elderly patients and those with CKD**; This effect may stimulate ventilation by reducing pH and subsequently **increasing tidal volume.**
- **Acetazolamide does not affect airway resistance**.

Risk of VTE in CKD

- The risk of **VTE** in CKD patients with an eGFR of 15-59 mL/min/ 1.73 m^2 is approximately 2-fold compared with those with an eGFR >90 mL/min/1.73 m^2.
- The increased risk attributable to CKD is similar to other risk factors such as bed rest, prolonged immobilization, and obesity.
- Mortality rates are significantly higher for persons with CKD (6.7%) versus those with normal kidney function (3.2%) in whom VTE develops.
- The median hospital stay is longer and rates of discharge to home are lower.

Clin Cardiol. 2019

Risk of VTE in CKD…

- CKD is a procoagulant state associated with abnormalities in the coagulation cascade due to **increased tissue factor, von Willebrand factor, factor XIIA, factor VIIa, and fibrinogen and reduced tissue plasminogen activator.**

- The phenotypes in kidney failure with KRT are heterogeneous, with some patients exhibiting increased bleeding risk and others typifying a prothrombotic state.

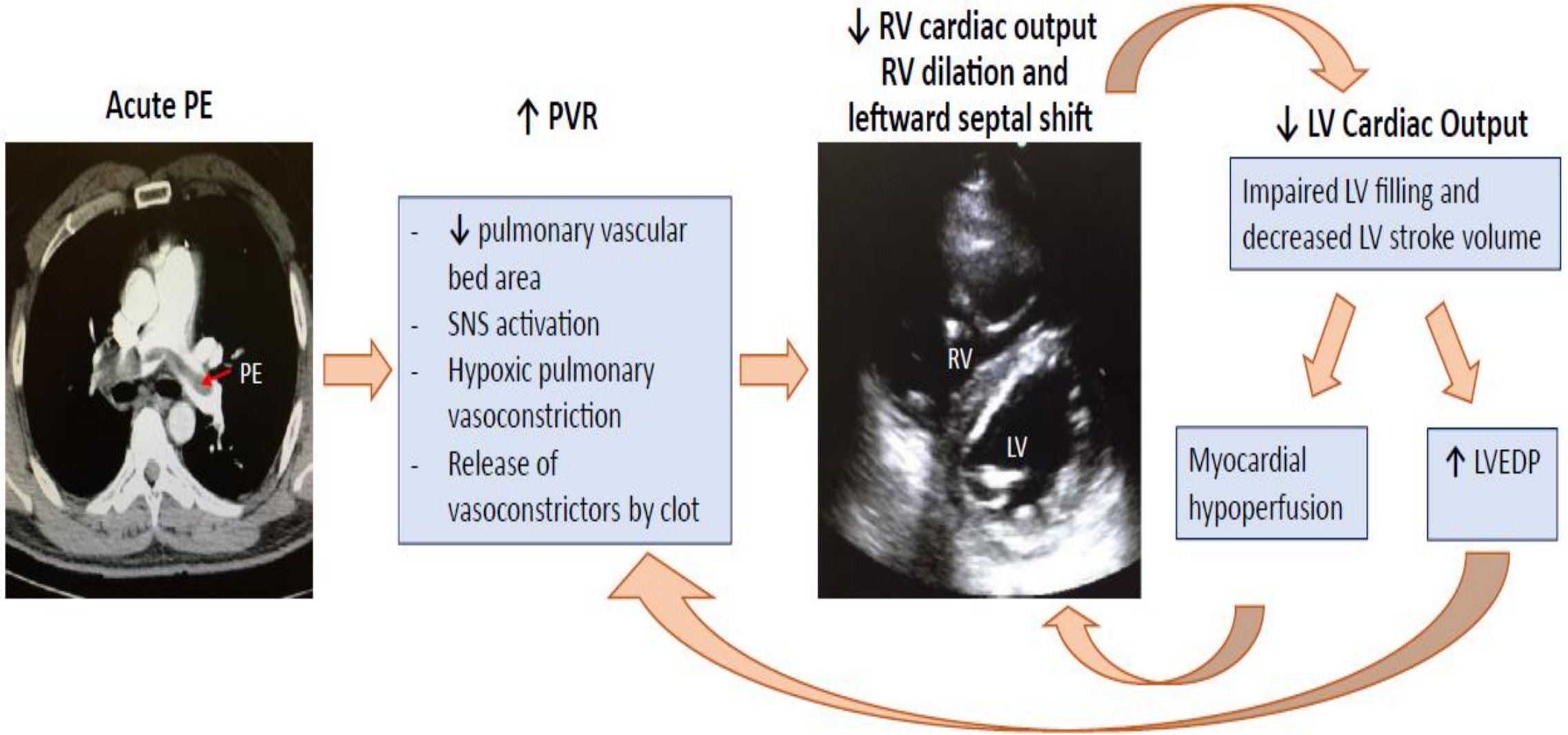


Figure 6. Mechanisms of hemodynamic compromise in acute pulmonary embolism. IVS, interventricular septum; LVEDP, left ventricular end-diastolic pressure; PVR, pulmonary vascular resistance; SNS, sympathetic nervous system.

Oral Anticoagulant Agents and Their Properties

- In the setting of decreased eGFR, vitamin K antagonists are recommended.
- **Direct oral anticoagulant agents were not considered as a first-line therapy in CKD population** because patients with an eGFR <30 mL/min were excluded from landmark trials in which they were studied.
- Pharmacokinetic data and retrospective studies suggest that direct oral anticoagulant agents are a reasonable therapeutic option when eGFR is >15 mL/min.
- **Enoxaparin** is renally cleared, and standard dosing results in increased factor Xa levels and an **increased risk of bleeding in patients with an eGFR <30 mL/min**.
- Adjusting the dose based on factor Xa levels may mitigate this risk, but we prefer to avoid the use of enoxaparin in this patient population.

Table 3. Oral Anticoagulant Agents and Their Properties

Oral Anticoagulant	Mechanism of Action	Metabolism	Dialyzable	Dose Adjustment
Warfarin	Vitamin K antagonist	Cytochrome P450 type 2C9	No	No
Dabigatran	Direct thrombin inhibitor	Renal excretion 80%	Yes	Yes
Rivaroxaban	Factor Xa inhibitor	Renal excretion 66%, 36% as unchanged drug	No	Yes
Apixaban	Factor Xa inhibitor	Cytochrome P450 type 3A4, renal excretion 27%	Partial	No
Edoxaban	Factor Xa inhibitor	Cytochrome P450 type 3A4, 50% renal excretion (unchanged)	No	Yes

Based on information in Jain et al, 2019 (*Clin J Am Soc Nephrol*. https://doi.org/10.2215/CJN.02170218).

Risks and Safety of Continuing ESA Therapy After VTE

- No study has answered the question whether ESAs can be safely restarted when a patient has begun therapeutic anticoagulation.

- It is thought that higher doses required for “ESA resistance” may be associated with cachexia and increased levels of inflammatory markers and may therefore contribute to the development of thrombosis.

Based on the available evidence, the decision to resume an ESA should be individualized based on patient factors :

(1) the level of hemoglobin at which symptoms develop
(2) the dose of ESA required
(3) kidney transplant candidacy

Summary

- Crosstalk between the lung and the kidney is based on the similarities that these organs share.

- The kidney-lung crosstalk in AKI and ARDS is a consequence of complex biological process which leads to dysregulation of cytokines/mediators and apoptotic signaling pathways.

- In patients with ALI, oxygen supply is decreased causing renal hypoxia. Besides, hypercapnia generated by ALI causes vasoconstriction in the renal vascular network and activation of the RAAS.

- Better understanding this relation can be a gateway to novel therapeutic strategies against AKI and decrease high mortality rate during AKI-related pulmonary failure.


Thank You
For Your
Attention