Cardiorenal Syndrome

By

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AGENDA

- Definition.
- Classification of cardiorenal syndrome.
- Pathogenesis of cardiorenal syndrome.
- Diagnosis of CRS.
- Treatment of cardiorenal syndrome.
- Conclusion.

Definition

- **CRS** can be generally defined as a patho-physiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of one organ may induce acute or chronic dysfunction of the other.

Nephrol Dial Transplant 2011;26:62-74

CLASSIFICATION

:

- CRS type 1 : **Acute cardio-renal** syndrome.
- CRS type 2 : **Chronic cardio-renal** syndrome.
- CRS type 3 : **Acute reno-cardiac** syndrome.
- CRS type 4 : **Chronic reno-cardiac** syndrome.
- CRS type 5 :**Secondary cardio-renal** syndrome.

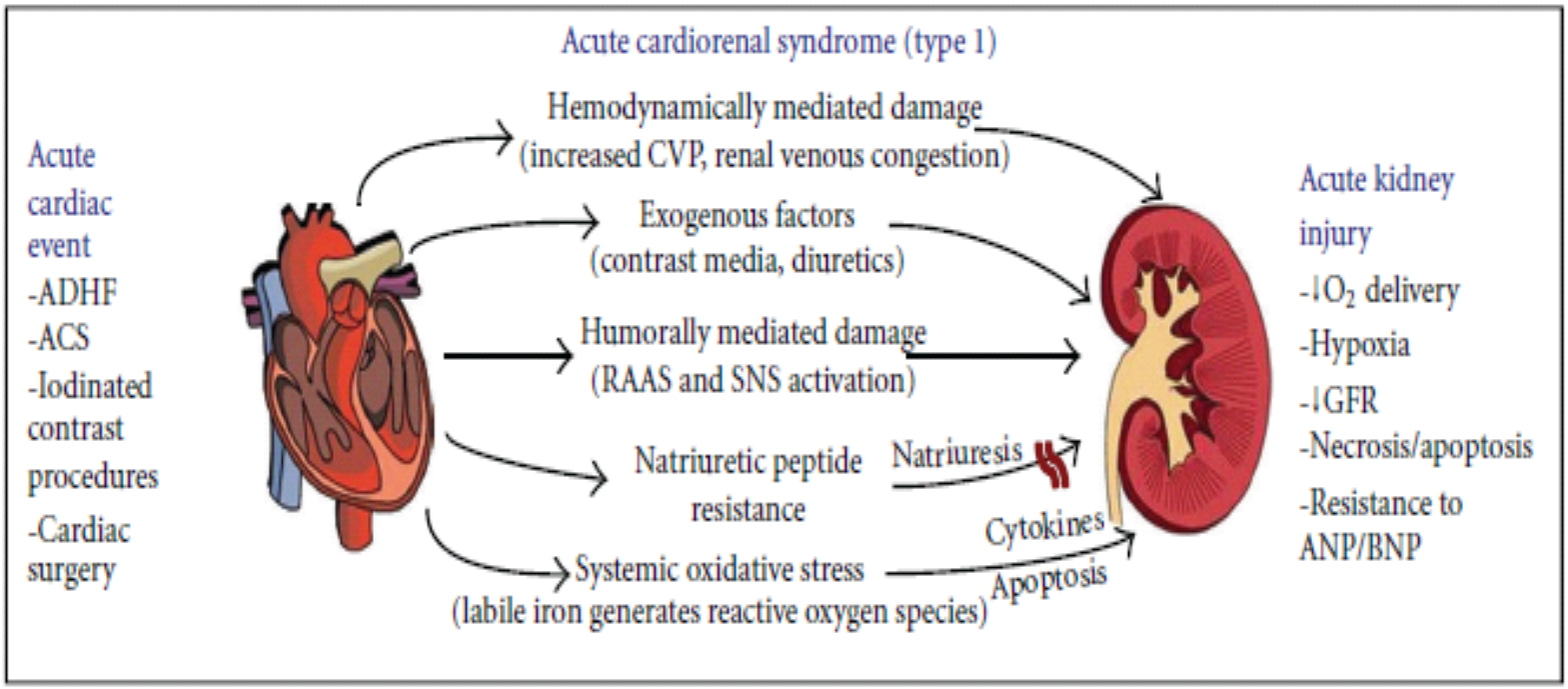
Nephrol Dial Transplant 2011;26:62-74

CRS Type I

- Rapid worsening of cardiac function, leading to acute kidney injury (AKI).

Circ J 2010; 74: 1274 – 1282

Type I: Pathophysiology



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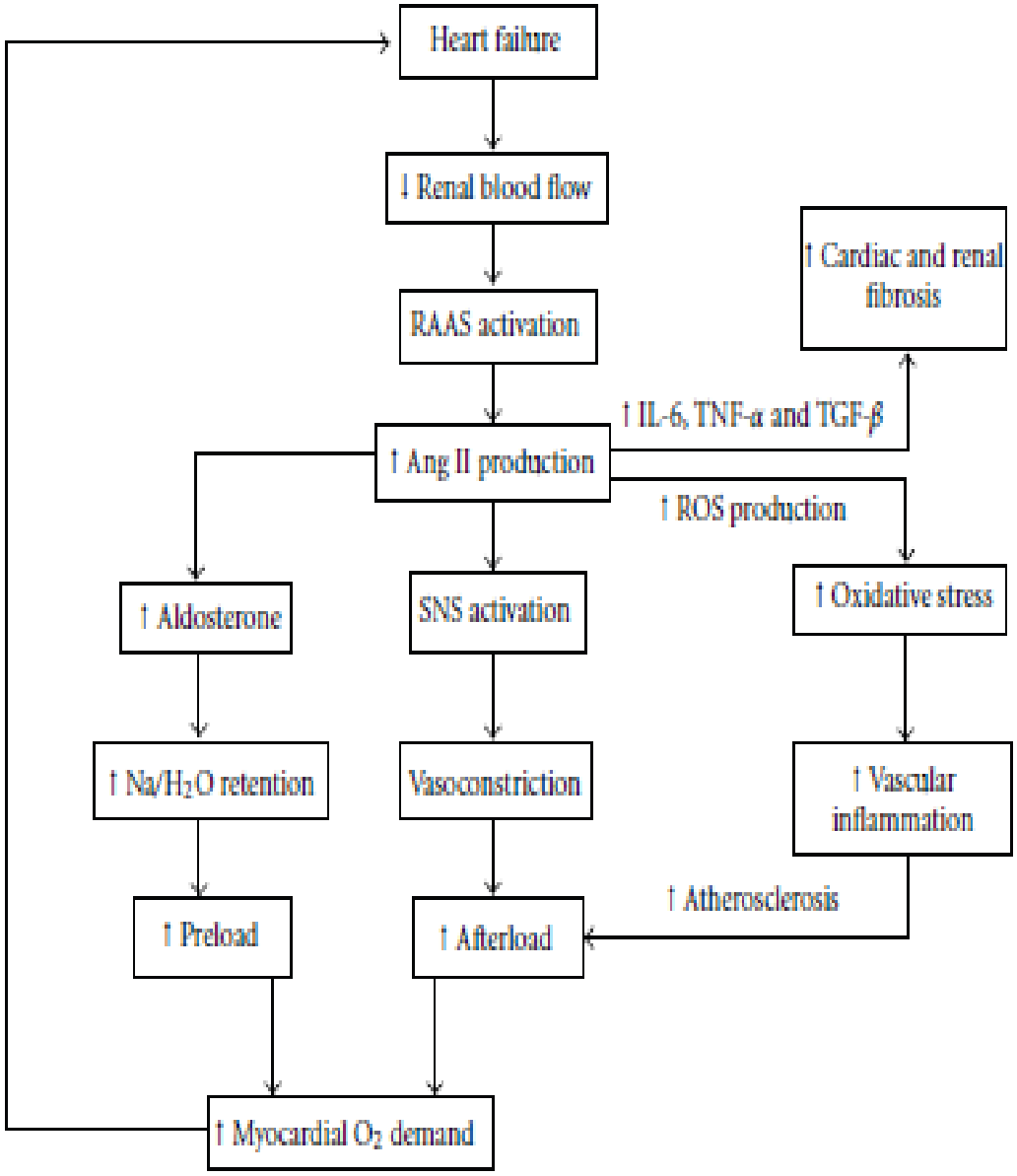
Heart failure
↓ Renal blood flow
RAAS activation
↑ Ang II production
↑ Aldosterone
SNS activation
↑ Oxidative stress
↑ Na/H2O retention
Vasoconstriction
↑ Vascular inflammation
↑ Preload
↑ Afterload
↑ Myocardial O2 demand
↑ Cardiac and renal fibrosis
↑ IL-6, TNF-α and TGF-β
↑ ROS production
↑ Atherosclerosis

CRS Type II

- Type II: Definition
  - Chronic abnormalities in cardiac function (e.g. chronic congestive HF) causing progressive chronic kidney disease…

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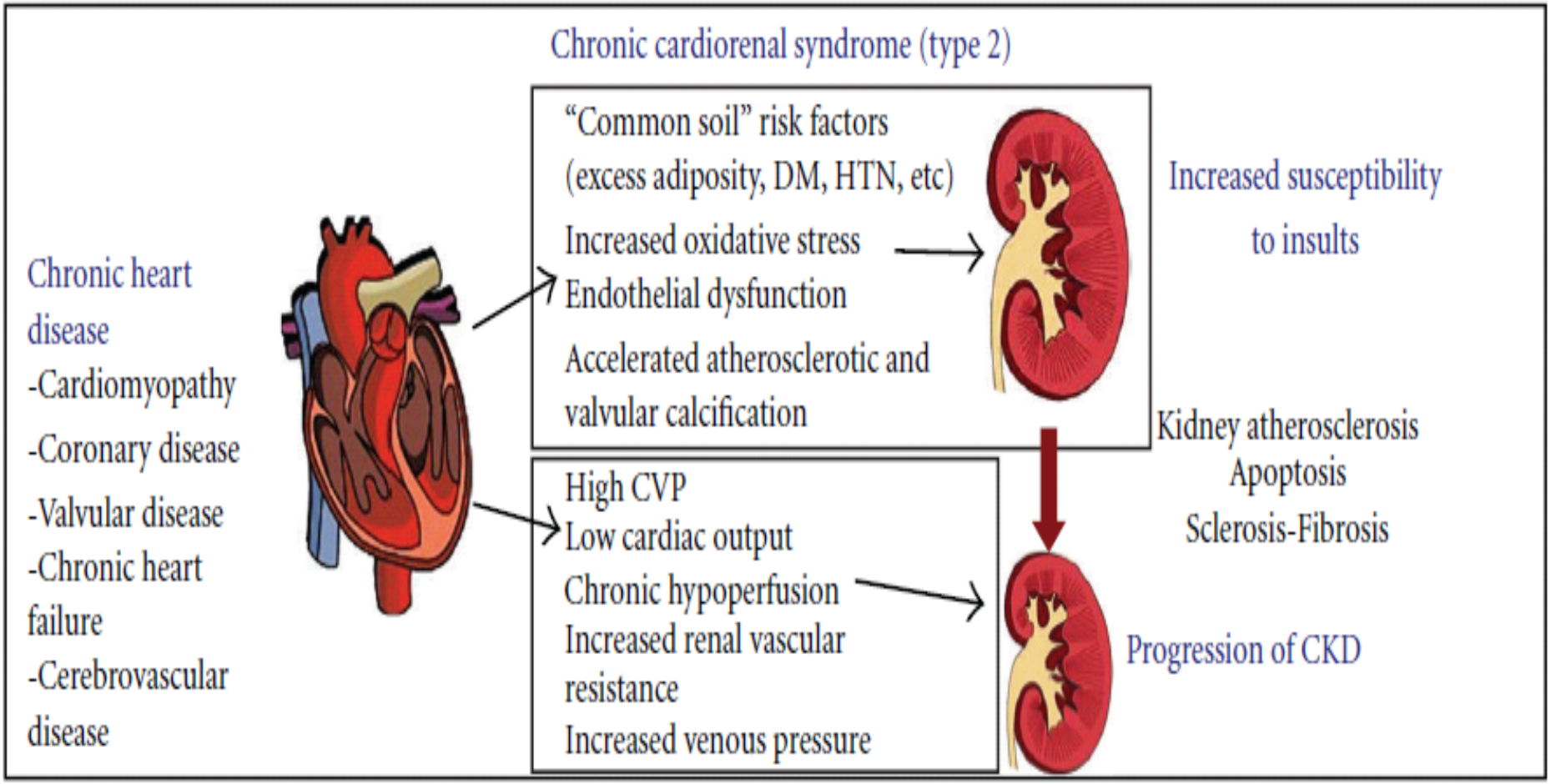
Type II: Pathophysiology



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CRS Type III

- An abrupt worsening of renal function (e.g. acute kidney ischaemia or glomerulonephritis) causing an acute cardiac disorder (e.g. HF, arrhythmia, ischaemia).

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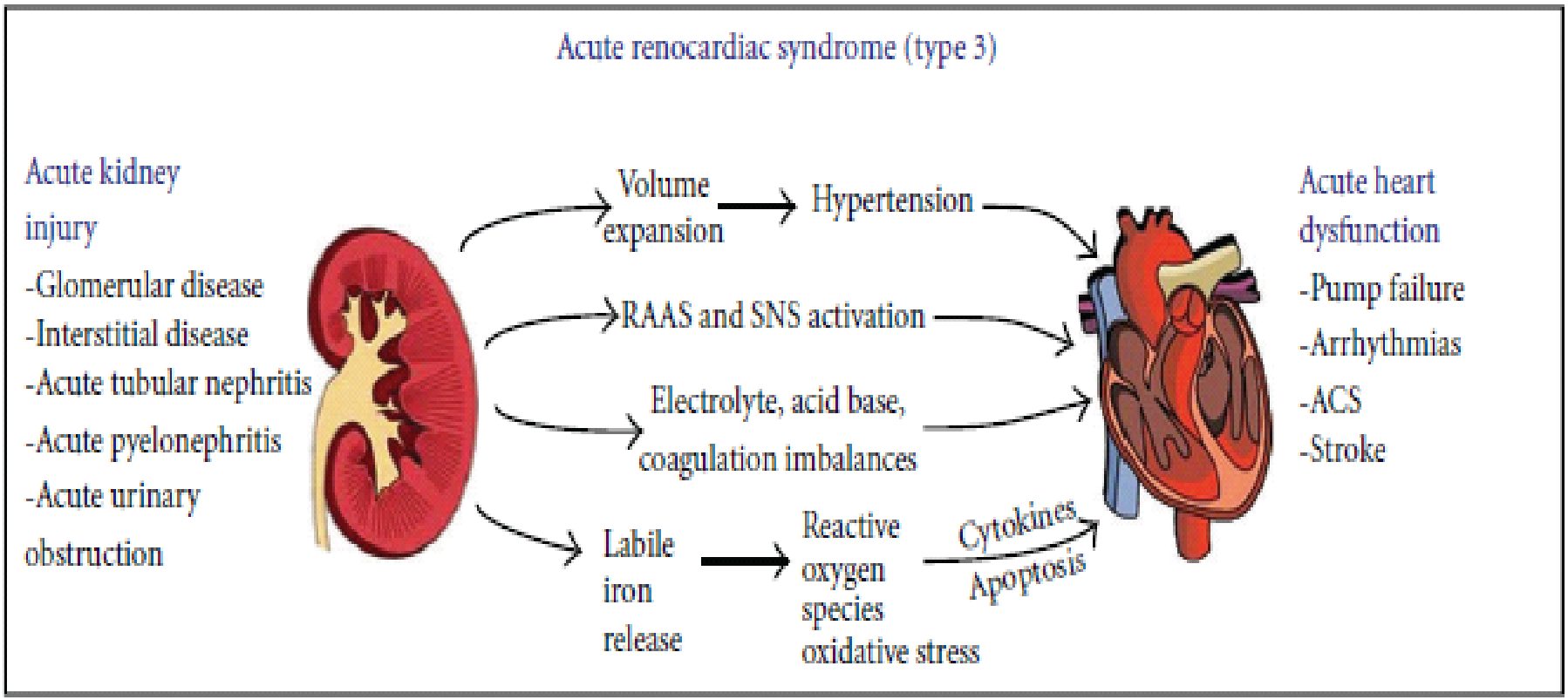
Type III: Pathophysiology



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CRS Type IV:

- State of chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events

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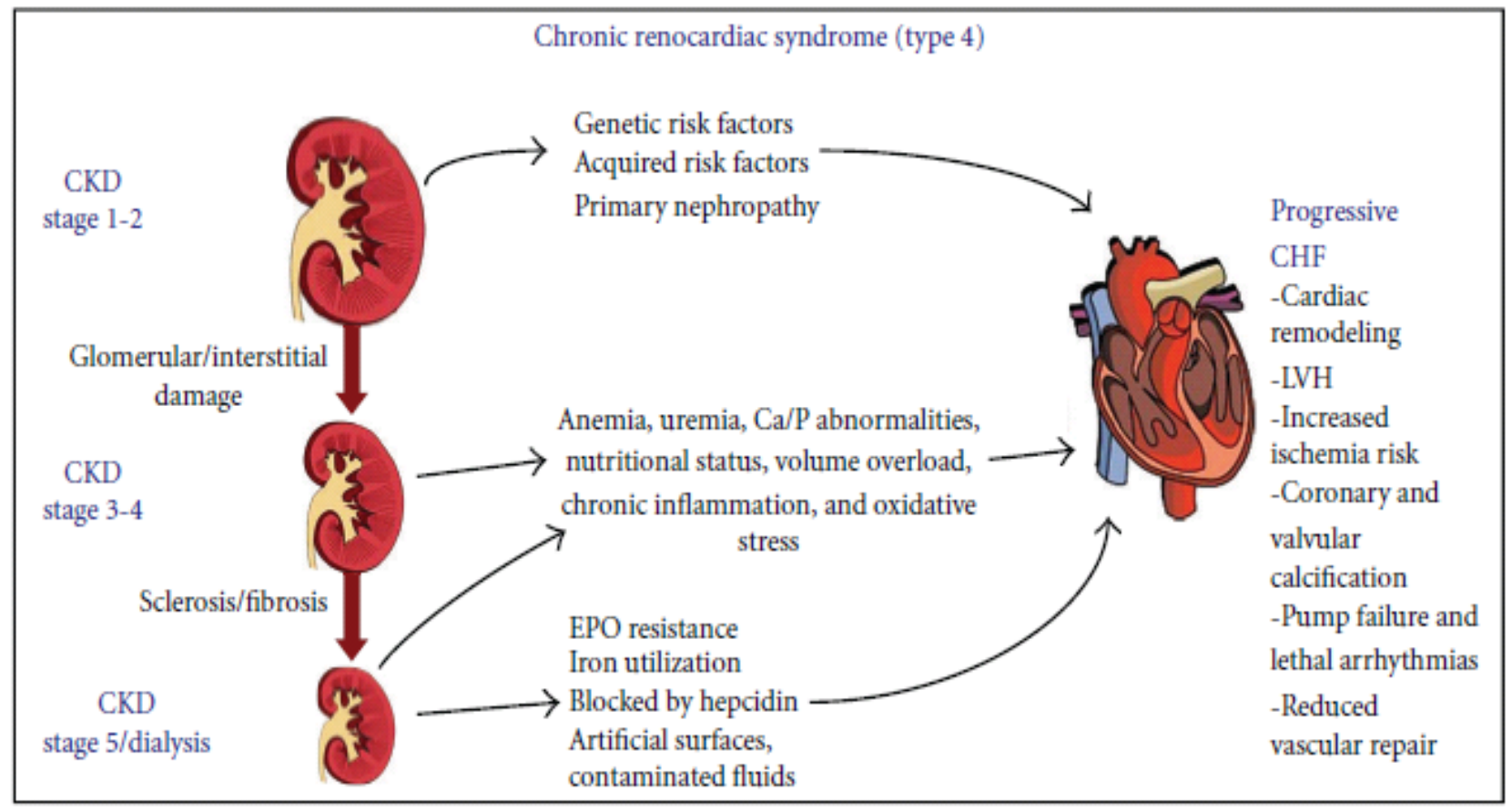
Type IV: Pathophysiology



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CRS Type V

- Systemic condition (e.g. sepsis) simultaneously causing both cardiac and renal dysfunction.

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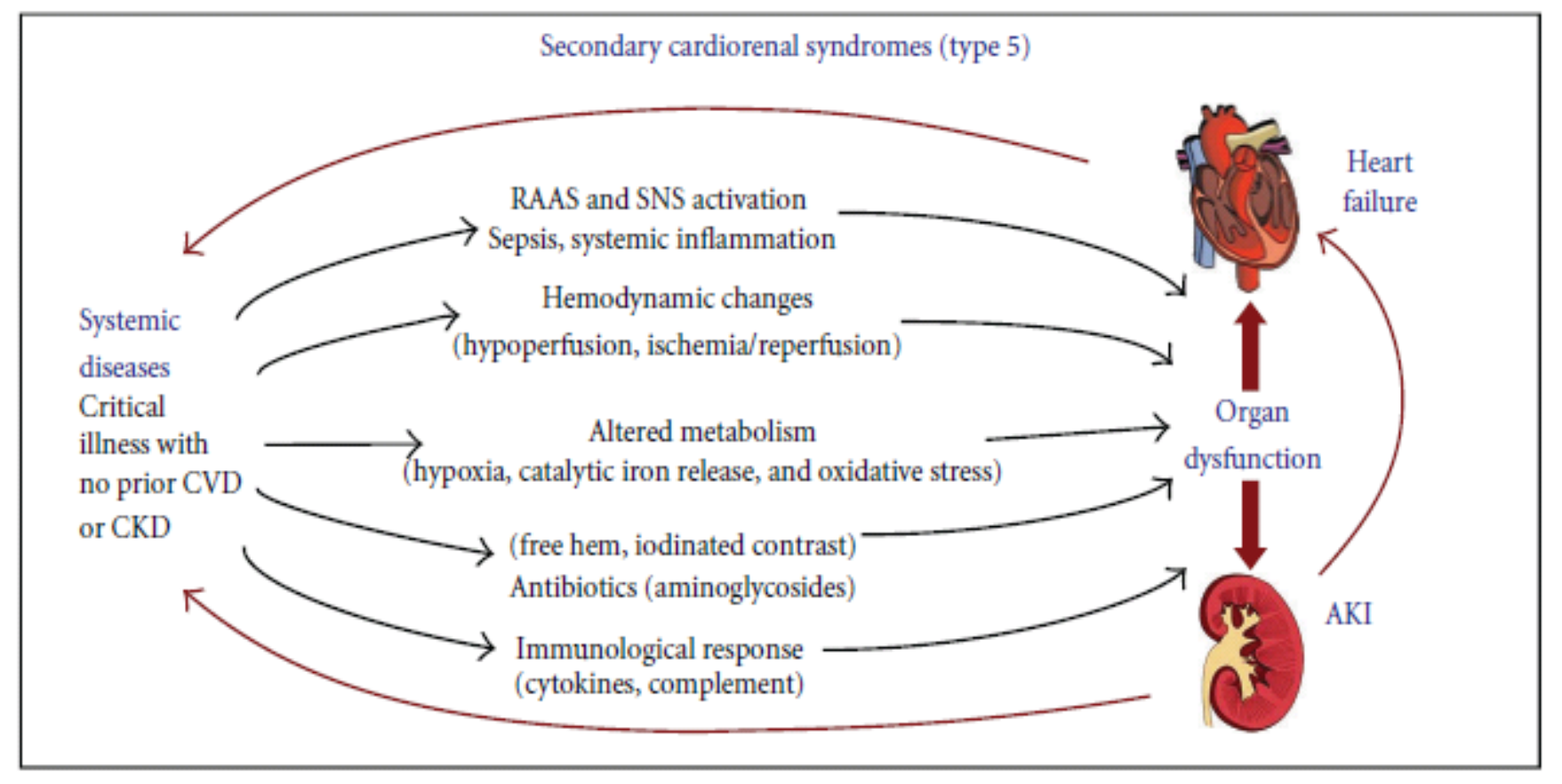
Type V: Pathophysiology



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- After discussing types and pathophysiology of CRS,
- We shall discuss few points of biomarkers for early detection of various CRS…

We need biomarkers that are:

- Sensitive(early appearance).
- Easy to detect.
- Specific(typical of organ injury).
- Correlate with severity(prognosis).

CARDIAC BIOMARKERS

Cardiac troponins

- Troponins T, I, and C are components of the contractile apparatus of muscle.
  - Specific forms of troponin T and I are present in the heart muscle, namely cTnT and troponin I (cTnI), and are released into the circulation with myocardial injury.
    - Thus, measuring circulating cTnT and cTnI level using high-sensitivity assays has become the gold standard approach in diagnosing acute myocardial necrosis.

Am Soc Nephrol 2008;19: 1643–1652

Cardiac troponins

- Levels of cardiac troponin are frequently elevated in the absence of acute coronary syndrome among patients with varying degrees of kidney disease, and
- cTnT is more frequently increased compared with cTnI in asymptomatic patients with ESRD

Am Soc Nephrol 2008;19: 1643–1652

Mechanisms of Elevated Cardiac Troponins in Patients with ESRD

- There is emerging evidence that
  - Increases in cTnT in asymptomatic patients with ESRD indicates subclinical myocardial necrosis or injury.

Am Soc Nephrol 2008;19: 1643–1652

BNP and NT-proBNP

- BNP belong to a family of vasopeptide hormones that have major role in regulating BP and volume through direct effects on the kidney and systemic vasculature and represent a favorable aspect of neurohumoral activation.
- Three different families:
  - A-type (atrial) natriuretic peptide.
  - B-type (brain) natriuretic peptide (BNP) .
  - C-type natriuretic peptide.

Am Soc Nephrol 2008;19: 1643–1652

BNP and NT-proBNP

- BNP is synthesized as an amino acid precursor protein and undergoes intracellular modification to a prohormone (proBNP) that
  - Comprises 108 amino acids and is secreted from the left ventricle (LV) in response to increased myocardial wall stress.
- On release into the circulation, proBNP is cleaved in equal proportions into
  - the biologically active 32–amino acid BNP, which represents the C-terminal fragment, and
  - the biologically inactive 76– amino acid N-terminal fragment (NTpro- BNP)

Am Soc Nephrol 2008;19: 1643–1652

BNP and NT-proBNP

- In the systemic circulation, BNP mediates different biologic effects through interactions with the natriuretic peptide receptor type A, causing intracellular cGMP production, and is eliminated from plasma by binding to the natriuretic peptide receptor type C or through proteolysis by neutral endopeptidases.
  - Although these enzymes are found in the kidney, glomerular filtration has only a minor role in the elimination of BNP.

Am Soc Nephrol 2008;19: 1643–1652

- Myeloperoxidase is a marker of altered myocyte metabolism, oxidative stress, and inflammation, especially in acute coronary syndrome.
- asymmetric dimethylarginine, plasminogen-activator inhibitor type 1, homocysteine, hs CRP, serum amyloid A protein, and ischemia-modified albumin are biomarkers whose levels correlate with cardiovascular outcomes in patients with CKD.

- Cytokines such as tumor necrosis factor (TNF),IL-1, and IL-6 may have a diagnostic role as early biomarkers of CRS, but also a pathogenic role causing myocardial cell injury and apoptosis and mediating myocardial damage in ischemic AKI.
- However, due to the non-specific nature of many of these cytokines as well as difficulty in measurement, they are not routinely used .

RENAL BIOMARKERS

1-Urine and serum NGAL(neutrophil gelatinase-associated lipocalin).

- early predictors of AKI. In these patients, an increase in creatinine is observed only 48 to 72 h later.
- Increased NGAL expression has been found in atherosclerotic plaque and failing myocardium in patients with CAD and heart failure . Its levels correlated with disease severity independent of coexisting renal injury (Yndestad A, etal,Eur Heart J 2009).
- It is a diagnostic and prognostic marker of cardiovascular outcomes in CKD (Iwanaga Y,etalCirc, J 2010).

2-Cystatin C

- predicts AKI and the requirement for renal replacement therapy earlier than creatinine .

- Higher levels of CysC have been demonstrated to be directly involved in the atherosclerotic process ;and are associated with increased LV mass.

(Ix JH, etal,Circulation 2007) .

3-N-Acetyl-β-(D)Glucosaminidase (NAG)

- NAG is a lysosomal brush border enzyme found in proximal tubular cells.
- It is a large protein (>130 kD) and is therefore not filtered through the glomerular membrane.
- It is a marker of AKI, reflecting particularly the degree of tubular damage.
- It is not only found in elevated urinary concentrations in AKI and CKD but also in diabetic patients, patients with essential hypertension and heart failure .

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4--Kidney Injury Molecule-1 (KIM-1): is a protein detectable in the urine after ischemic or nephrotoxic insults to proximal tubular cells and seems to be highly specific for ischemic AKI.

DIAGNOSIS OF CRS

- While making a diagnosis of CRS, it should be kept in mind that there is no correlation between serum creatinine and GFR.

- In addition, measurements of serum creatinine alone could also be misleading in terms of prognosis. Approximately two-thirds of patients admitted for acute exacerbations of CHF have decreased GFR or creatinine clearance, despite many of them having relatively normal levels of serum creatinine .

- Because of large renal reserve ,up to 50%of kidney function may be lost before serum creatinine rise.

- Serum creatinine level can vary widely depending on a large number of non renal factors(age,gender, muscle mass , hydration status).
- The estimation of GFR should be a part of the initial evaluation because GFR provides a general sense of prognosis.
- Moreover, GFR is helpful in the evaluation for planning a management strategy .

TREATMENT

Practical Recommendations

- Restrict fluid and sodium intake.
- Add Diuretics.
- Add inotrope or vasodilator (according to systolic blood pressure).
- Start ultrafiltration.
- RRT(hemodialysis,peritoneal dialysis)
- Insert intra-aortic balloon pump.

Diuretics:

- Loop diuretics need to be administered at frequent intervals in a high enough dose to achieve adequate drug levels within the glomerular filtrate.
- Coadministration of a long-acting thiazide diuretic can help maintain a natriuresis.
- In severe CHF, continuous low-dose infusion of a loop diuretic may be required.

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- More specifically, they lead to activation of the neuro-hormonal system, indirectly deteriorate the function of left ventricle, increase systemic vascular resistance, plasma renin, aldosterone activity, plasma neuro-hormonal level (arginine)

RAAS BLOCKADE DRUGS:

- They are the key component in the management of patients ;they improve survival in patients with heart failure and also prevent progressive renal insufficiency in diabetic nephropathy and other forms of chronic kidney disease.

BUT TAKE CARE!!

Of the side effects of ACEIs or ARBs.

Adenosine Antagonists:

- The elevated plasma adenosine levels observed in patients with heart failure can contribute to diuretic resistance and renal dysfunction.
- *A*1 adenosine receptor antagonists are novel agents that activate adenosine *A*1 receptors and improve renal blood flow, promote diuresis, and increase sodium excretion.
- The efficacy of an adenosine *A*1 receptor antagonist in the treatment of patients with heart failure is still unsettled.

Vasopressin Antagonists:

- Release of vasopressin by low cardiac output results in water retention and hyponatremia.
- EVEREST Clinical trial confirmed the efficacy of early administration of vasopressin antagonists.
- IT concluded that vaptans when used in the context of acute heart failure can modify kidney response to water retention. But still it does not favorably influence remodeling of the heart and kidney over the long term toward effects.

Vasodilators and Natriuretic Peptide

- Nesiritide, a synthetic BNP, is an effective vasodilator with a mild diuretic action. Its administration results in venous, arterial, and coronary vasodilatation, decreasing the cardiac preload and afterload, which in turn increases cardiac output without direct inotropic effects.

- These hemodynamic effects are accompanied by natriuresis and diuresis.
- Nevertheless, creatinine clearance was not improved by nesiritide, even in patients who showed satisfactory natriuresis and diuresis.

LOW DOSE DOPAMINE

- In clinical practice, low renal protective doses of dopamine are commonly used in combination with diuretic therapy, although available data do not clearly support favorable effects on renal function.
- A prospective, double-blind, randomized, controlled study to investigate the effect of low-dose dopamine concluded that it can worsen renal perfusion in patients with acute renal failure, which adds to the trend to abandon the routine use of low-dose dopamine in critically ill patients

- These agents should be given only for low cardiac output states, for a short term and under close monitoring, as they may increase the risk of arrythmias.

Anemia and Erythropoietin

- Cardio-renal anemia syndrome refers to the simultaneous presence of anemia, heart failure, and CKD that forms a pathologic triad with an adverse impact on morbidity and mortality.
- Every 1 gm/dl drop in mean hemoglobin increases the risk of cardiac failure by 25%, Increases LVH by 42%,increases death risk by 14%.

Several studies have shown that correction of anemia with subcutaneous EPO will increase aerobic metabolism, improved O2 peak utilization, improve skeletal muscle function, cerebral blood flow, and endothelial cell function.

Interventions

- Ultrafiltration:
  - PD
  - HD, hemofiltration
- Intraaortic balloon pulsation, ventricular assist devices cardiac resynchronization therapy (CRT).
- Cardiac transplantation.

ULTRA-FILTRATION

- Ultrafiltration can potentially manage worsening renal function and decreased urine output despite escalating doses of diuretics or diuretic resistance in severe heart failure.
- Ultrafiltration decreases levels of norepinephrine, aldosterone, and renin. In contrast to diuretics alone, UF also reduces systemic levels of inflammatory cytokines.

UF Therapy for Heart Failure: The New Era

- The advent of portable devices with newer technology rendered UF more appealing and led to a second generation of clinical trials.
- These simplified and user-friendly machines have the advantages of small size, portability,

  blood flow rates of as low as 40 ml/min, and an extracorporeal blood volume of<50 ml.
- They can provide UF rate within a large spectrum (0–500 ml/h), do not mandate admission to intensive care unit, and have been marketed with the ability of even using peripheral veins.

RENAL REPLACMENT THERAPYRT

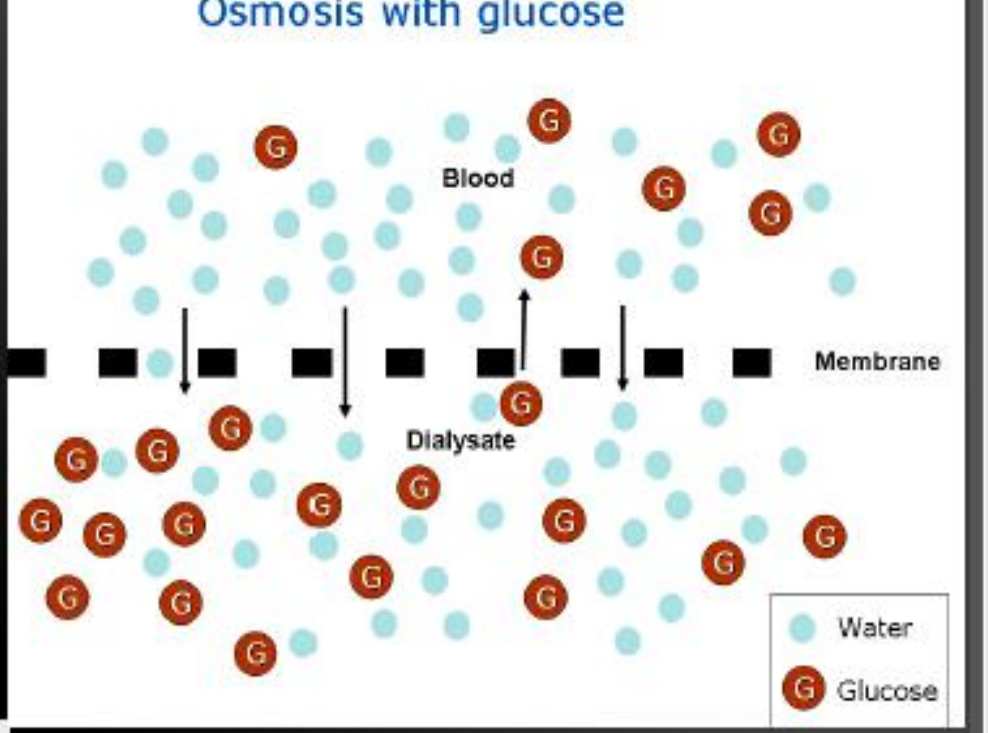
1-Intermittent HD:

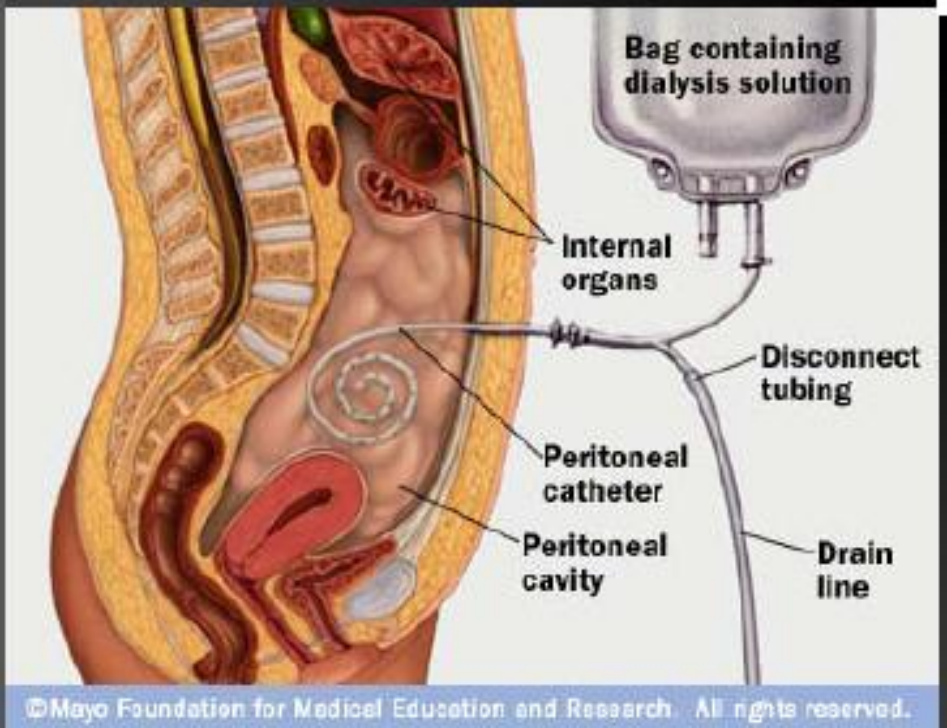
many unstable heart failure patients will not tolerate removal of 2 or more liters during typical 2- to 4-hour treatment times. Episodes of hypotension will not only prevent further fluid removal but can also induce acute kidney injury (AKI) and potentially make the patient dialysis dependent.

2-CRRT:

It can lead to substantial weight loss, improvement in pulmonary congestion, increased diuresis at lower diuretic doses.

What about PD?





3-PD:

Chronic PD in heart failure has had an acceptably low rate of complications but PD has to date not been associated with improved mortality in heart failure patients.

PROGNOSIS OF CRS

- As renal dysfunction radically worsens the prognosis of patients with heart failure, heart failure conversely worsens the prognosis of patients receiving dialysis, decreasing the probability of survival by as much as 50%

CONCLUSION

- The CRS has a unique and complex pathophysiology. Any degree of combination of renal insufficiency with heart failure makes patient management a great challenge and is associated with a poor prognosis.

- Most of the current therapies in use can have detrimental effects on renal function; hence, good clinical judgement is essential for proper patient management.

CONCLUSION

- Ultrafiltration and diuretic therapy are highly effective across a broad range of patients with ADHF and cardiorenal dysfunction.
- Although ultrafiltration may be helpful for fluid removal in acute decompensated HF in patients unresponsive to diuretic therapy, the available evidence does not establish ultrafiltration as first line therapy for ADHF.
- The 2009 AHA/ACC guidelines state that ultrafiltration is reasonable for patients with refractory congestion not responding to medical therapy.


Thank You