Personalizing heart failure management in chronic kidney disease patients

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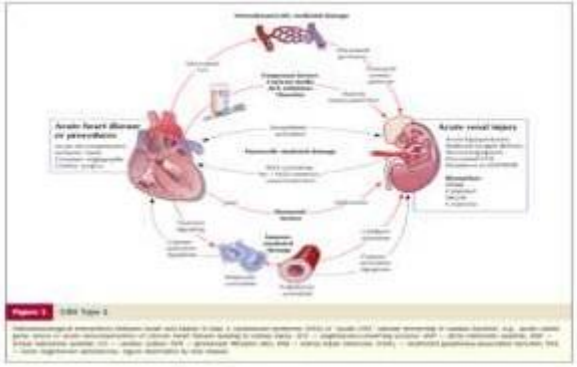
Cardiorenal Syndrome



Classification based on epidemiology Do not use it in clinical practice

Great for:

- Creating Awareness
- Popular term / Hype

However:

- Does not help to select the right treatment
- “CRS type I” very diverse
- Not every renal dysfunction in heart failure is equal (and visa versa)

Case

63 year old male

- Unremarkable medical History
- Works as welder in shipyard
- Active smoker past 45 years
- Negative Family History
- No Medication

- Presents with acute dyspnea, congestion, weight gain and low blood pressure in referral hospital

Case

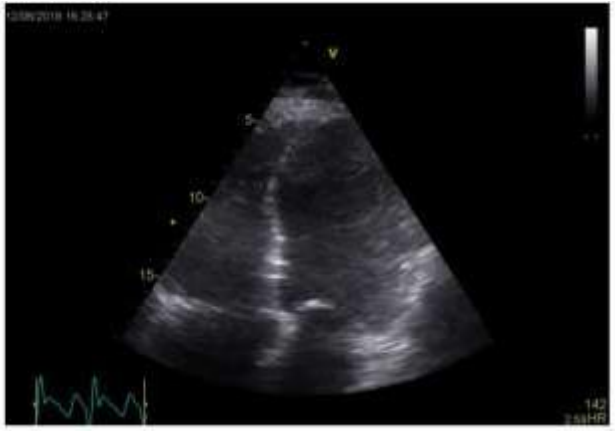
63 year old male

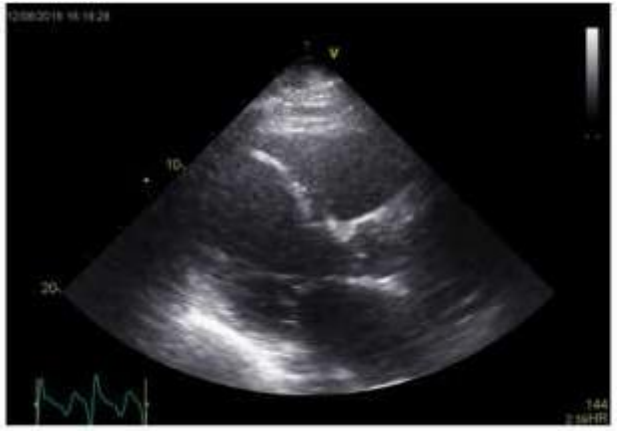
- Vitals: 98/44 mmHg, Afl, Resp Rate 27/min, Temp 35.9
- Height 185cm, weight 124 kg
- Physical: Rales ++, Edema ++, JVP R + 4
- ECG: Atrial Flutter, 150-200 bpm (later 110-130/min)
- Lab**: NTproBNP 17630 pg/mL, Creatinine 188 umol/L** (2.13 mg/dL), Potassium 5.4 mmol/L, Sodium 135 mmol/L
- Lactate 2.1 mmol/l

Case

63 year old male

- Echo: LVEF 15-20%, moderate RV Function, significant MR and TR. IVC dilated





Case

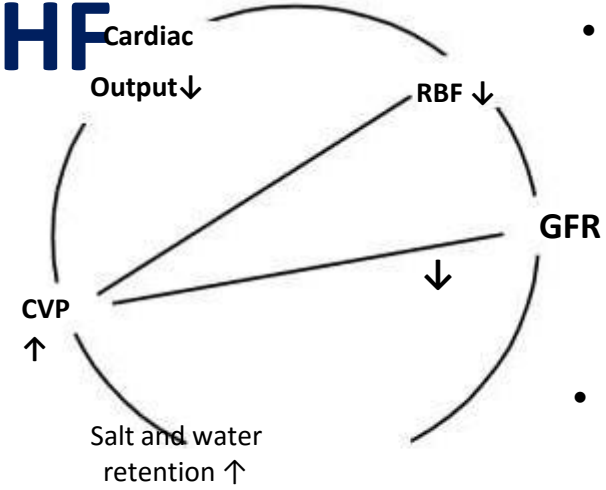
Cold and Wet Acute Heart Failure (de novo)
with Moderate renal impairment

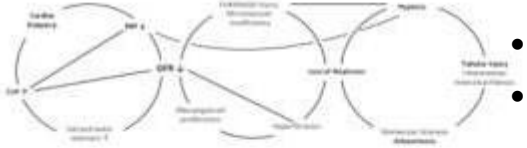
Question 2

What is True? Renal impairment in this case is most likely caused by:

A) Low Cardiac Output
B) Venous Congestion
C) A combination of both A and B
D) Pre-existent due to unknown renal disease

Pathophysiology of Renal Failure in HF

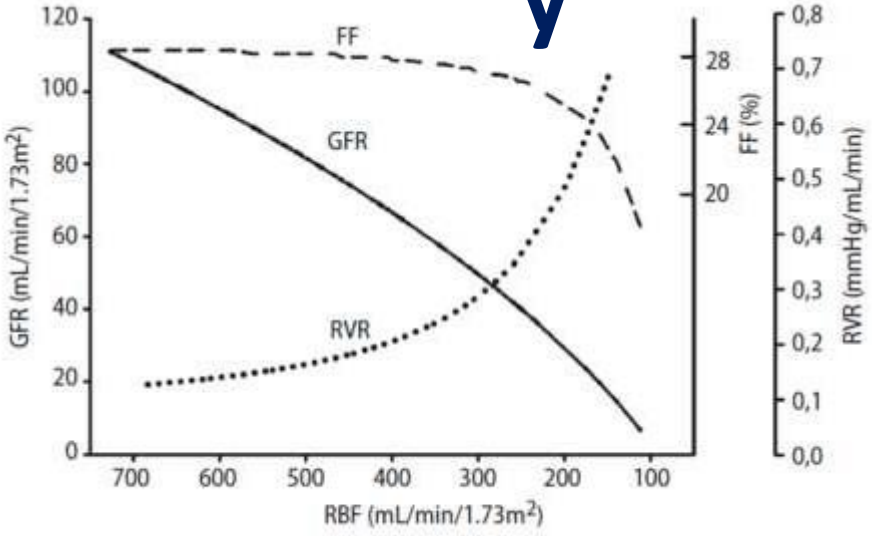


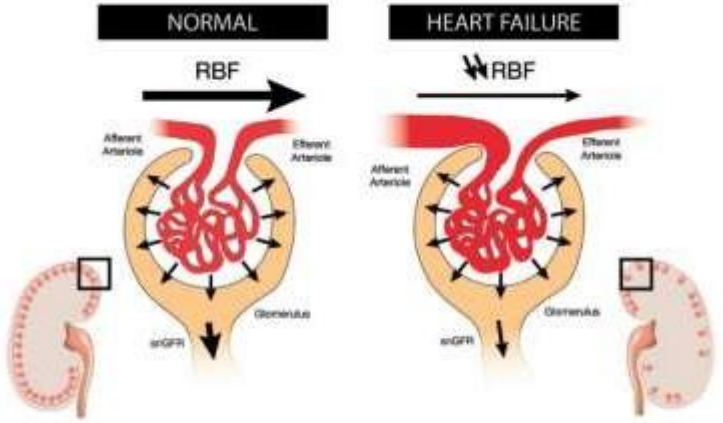


- **Interplay** between:
  - Comorbid organ dysfunction **(Susceptibility):**
    - Hypertension
    - Diabetes
    - CKD
    - Peripheral artery disease
  - **Hemodynamics (Direct cause) :**
    - Reduced Cardiac Output
    - Reduced Renal Blood Flow
    - Increased Renal/Central Venous Pressure
  - Intra-abdominal pressure **(Direct cause):**
  - Therapy **(Modulation):**
    - Inotropes / Vasodilators / Diuretics
    - RAASi

Damman et al Progr Cardiovasc Dis 2011

Pathophysiology



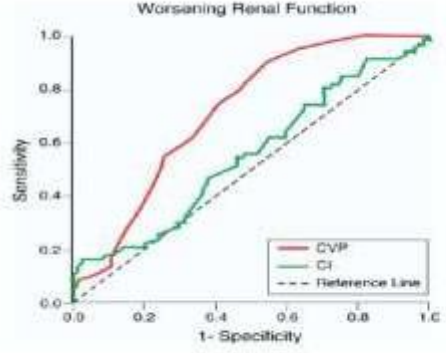


Smilde et al Clin Res Cardiol 2009 Mullens et al Eur Heart J 2017

Pathophysiology

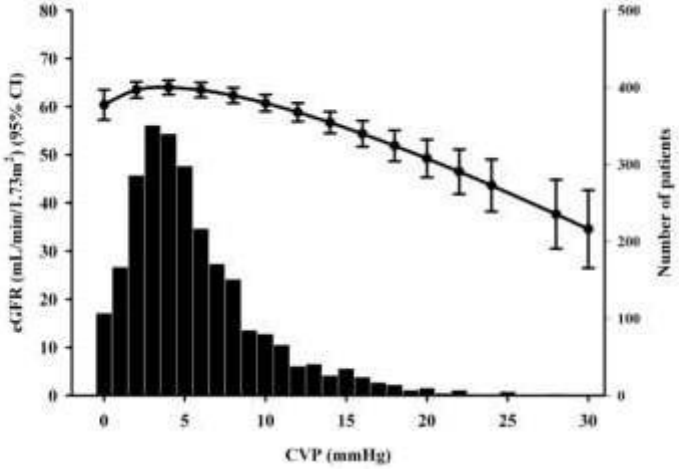
Relative Importance

CI/CVP For WRF

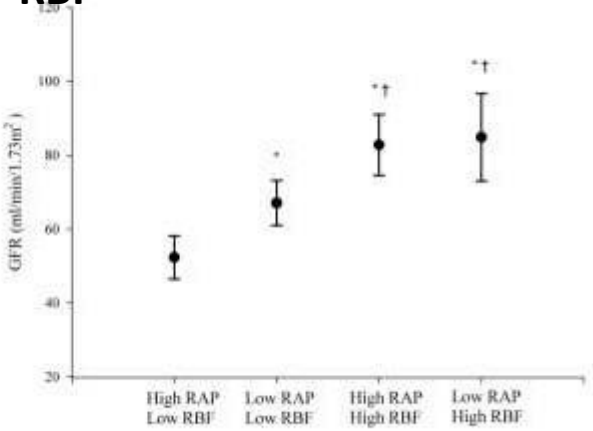


CVP associated with lower

eGFR in CV disease



CVP impacts GFR in low RBF



Mullens et al JACC 2009 / Damman et al JACC 2009 / Damman et al Eur J Heart Fail 2007

Renal Venous Pressure

Increased Renal Venous Pressure

↓

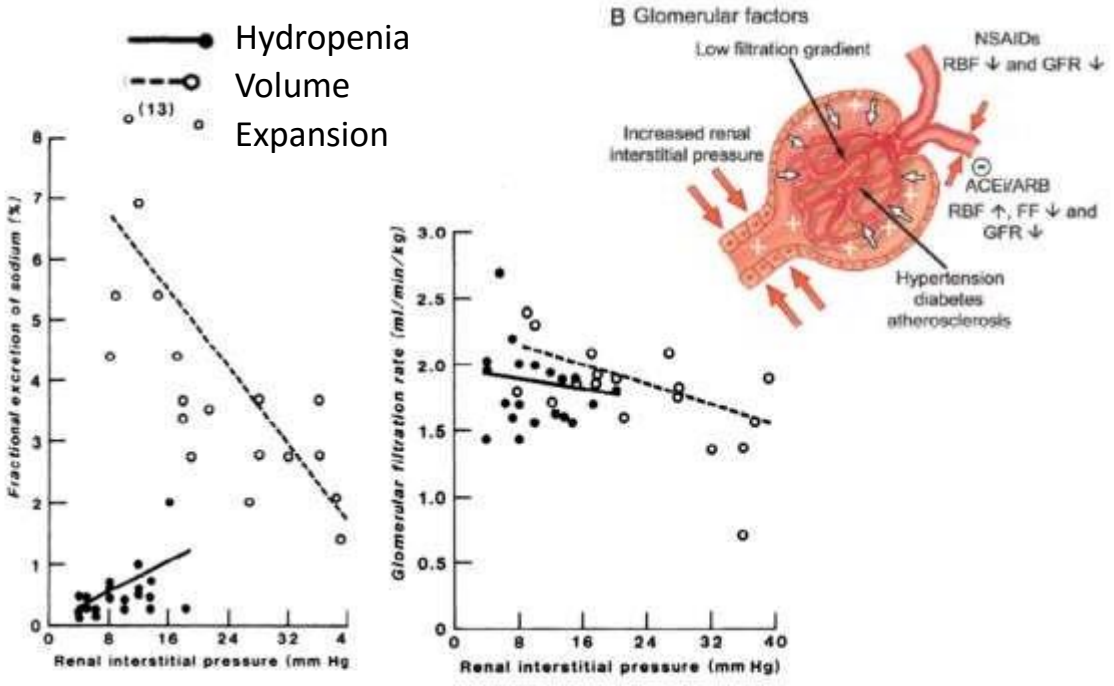
Increased Renal Interstitial Pressure (> tubular hydrostatic P)

↓

Collapsing of tubules → Increasing tubular hydrostatic P

↓

Decrease filtration, decrease in net ultrafiltration pressure



Joles JACC 2009, Boberg Am J Physiol 1985, Burnett Am J Physiol 1980

Case

Cold and Wet Acute Heart Failure (de novo)
Moderate renal impairment

- CVL, arterial line, CAD (SvO2 50%)
- Dobutamine
- Loop Diuretic: Furosemide / Bumetanide / Torsemide → What dose and route?

- → Consider eGFR!!

Case

Cold and Wet Acute Heart Failure (de novo)
Moderate renal impairment

- Bumetanide bolus 3 mg i.v. followed by continuous infusion 10 mg/24 hours i.v.

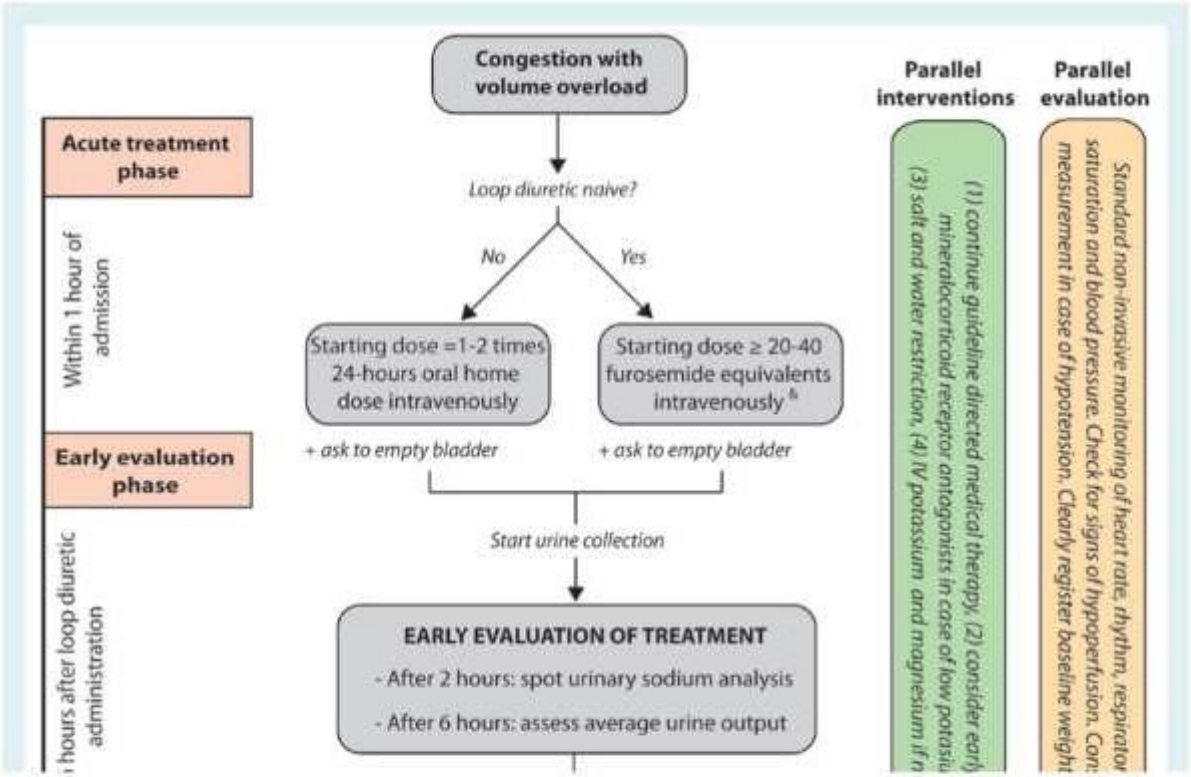
- Its 17.49 hours admission day… you go home… See about effect tomorrow… right?

Question 3

How do you evaluate the effect of your initial therapy?

A) Signs and Symptoms only
B) Signs, Symptoms and Weight change
C) Signs, Symptoms and Quantitative Urine Output
D) Signs, Symptoms and Qualitative Urine Output
E) Signs, Symptoms and Biomarkers (Natriuretic Peptide,

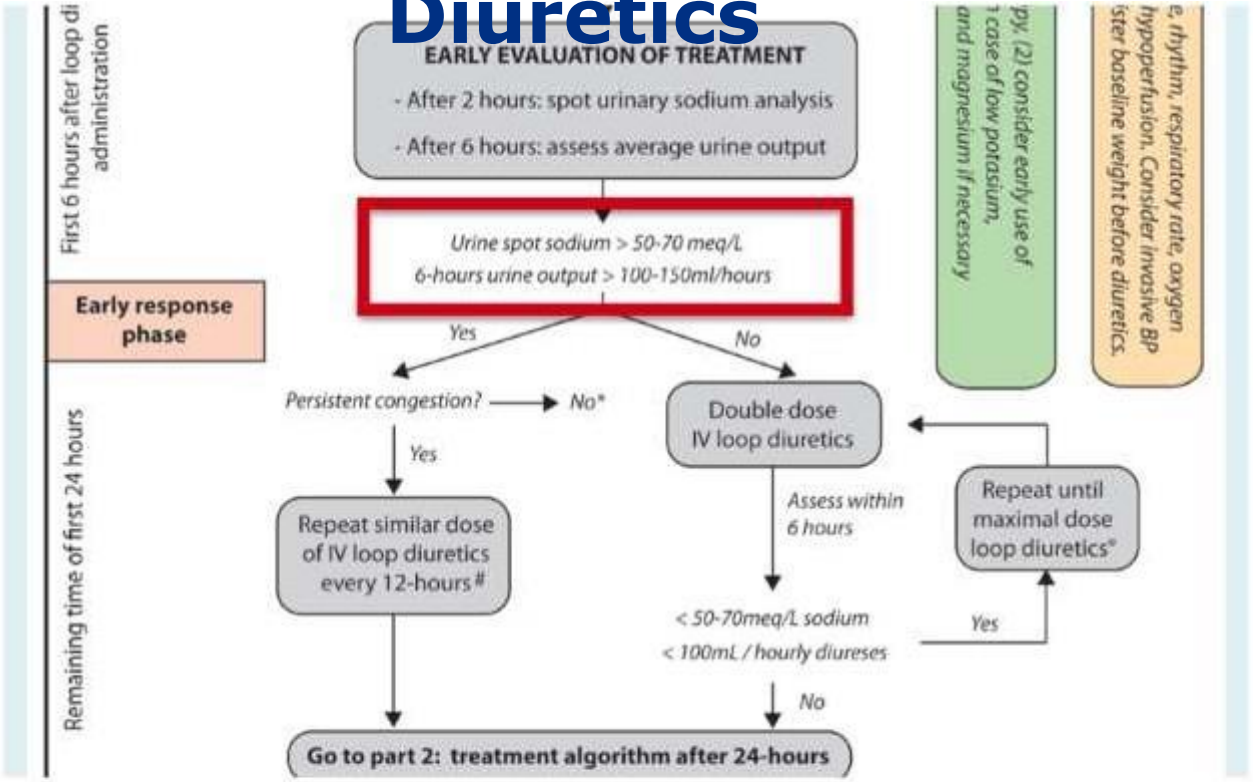
New Consensus Diuretics



&Higher dose should be considered in patients with reduced glomerular filtration rate

Mullens, Damman et al Eur J Heart Fail 2019

New Consensus Diuretics



Mullens, Damman et al Eur J Heart Fail 2019

Diuretic Response - Case

6 Hours

Total 6 hour volume: 300 mL Total Urinary Sodium: 8 mmol

Urinary sodium concentration: **28 mmol/L**

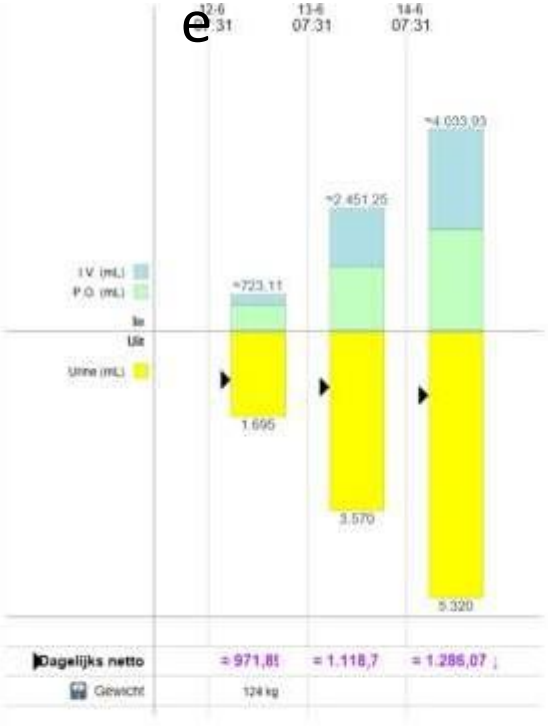
6-24 Hours

Total 6-24 hour volume: 1800 mL Total Urinary Sodium: 130 mmol

Urinary sodium concentration: **72 mmol/L**

Case

Cumulative



What is the Diuretic Response?

- In 56 hours:
  - Diuresis 5320 mL (net weight loss 1 kg)
  - Bumetanide 25 mg
    - (1 mg Bumetanide ~ 40 mg Furosemide)

Diuretic Response =
5320 / 25 = 213 ml/40 mg Furosemide

Case – Renal Function

Change in Serum Creatinine (188 to 303 umol/L):

What change in Renal Function would you normally expect?

What change would change your therapy?

Case

Following days:

- Dobutamine 3 ug/min/kg and added Milrinone 0.5 ug/min/kg
- Amiodarone
- Bumetanide 15 mg/24 hours + Spironolactone 50 mg
- Due to persistent Diuretic Resistance: added HCT 25 mg

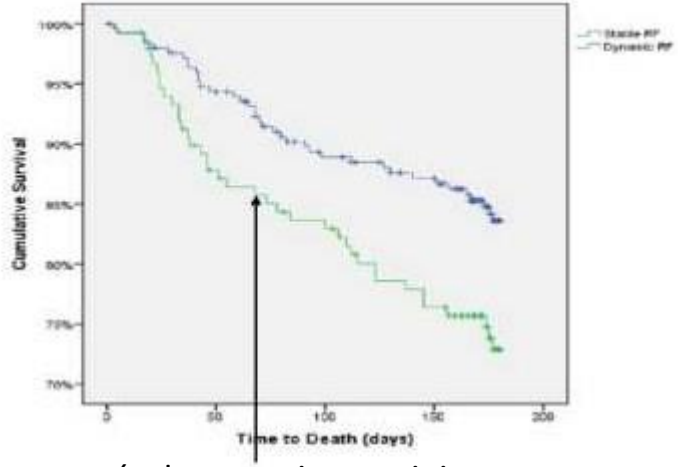
18 days:
- 47 liter urine -
14 liter neg fluid balance
- 15 kg net weight loss

WRF in (acute) HF

- Significant increase in serum creatinine (WRF) occurs in around 20-25% of patients with acute HF
- In a similar proportion, a decrease in serum creatinine is observed
- **Definition(s):**
  - > 26.5 µmol/L (0.3 mg/dL) ánd > 25% increase in serum creatinine
  - > 20/25% decrease in eGFR

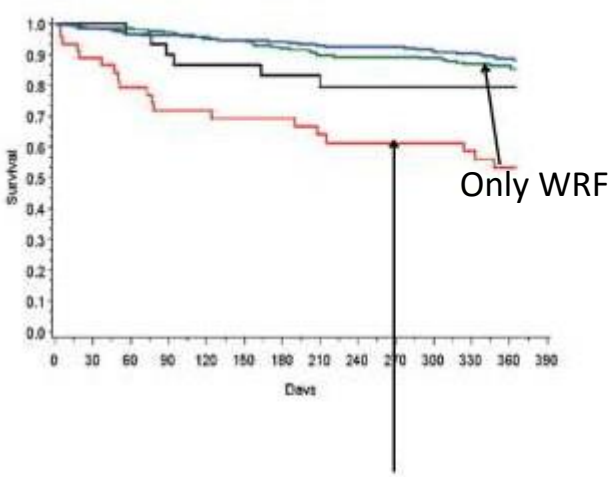
WRF in (acute) HF

Any change



Increase ór decrease in creatinine

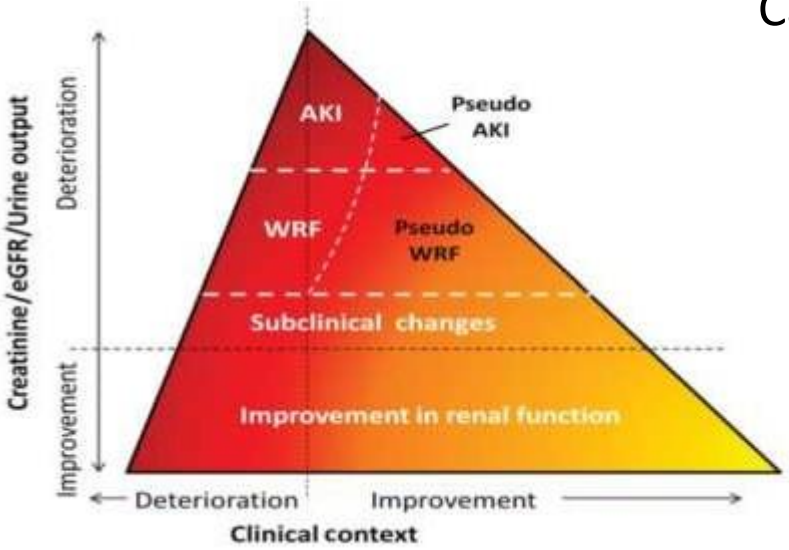
(no) residual congestion



WRF ánd residual congestion

Testani et al AJC 2010, Metra et al Circ HF 2012

WRF in (acute) HF



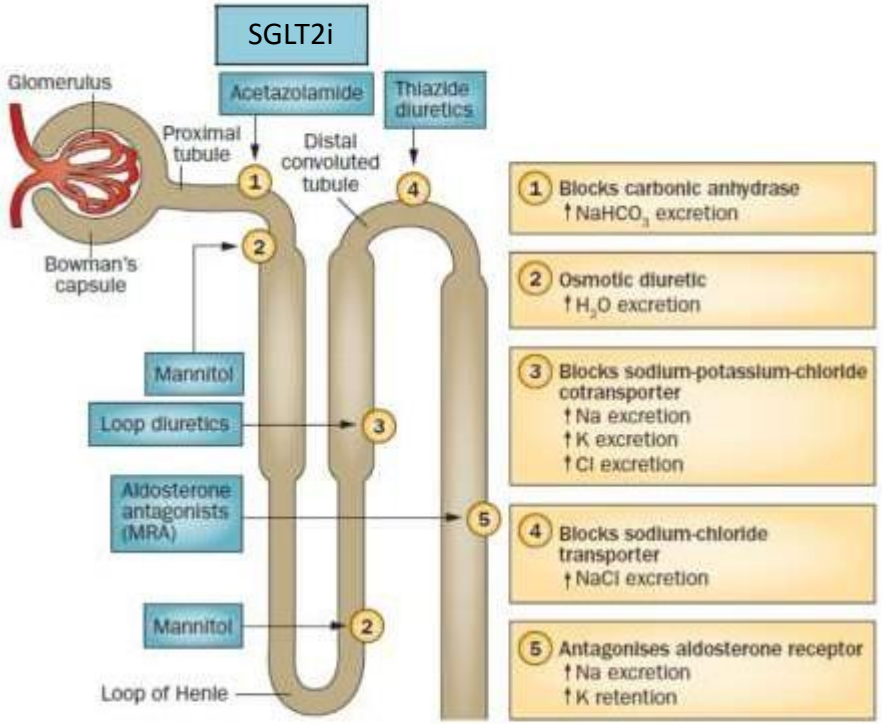
Causes:

- Not entirely known
  - **Persistently increased CVP / Worsening Heart Failure**
  - Intravascular depletion
  - Change Intraglomerular hemodynamics
  - Direct effect (loop) diuretics

Not associated with worse outcome if Diuretic Response is favourable!

Damman et al. Eur Heart J 2014

Combinational Diuretic Therapy



Proximal Tubular Blockade now being tested:

ADVOR (Acetazolamide vs Placebo)

- N = 494
- NCT03505788
- Recruiting

EMPA-RESPONSE-AHF (Empagliflozine vs Placebo)

- N = 80
- NCT03200860
- Recruiting

Conclusions

- Renal Impairment frequently complicates acute heart failure
- Worsening Renal Function acceptable if Diuretic Response is favourable
- Both Congestion and low cardiac output predispose to (worsening) renal failure
- Dose Diuretics adequately in patients with low eGFR
- Evaluate Diuretic response!
- If Diuretic Resistant with monotherapy, consider sequential nephron blockade

A 60-year old male patient

CAD RF: HTN , DM

Post CABGs

And case of CKD (the values associated to renal function amounting to 1.4 mg/dl .

presenting the following symptoms:

severe lower limb edema, orthopnoea, DOE F0C III-IV, significant decrease in exercise tolerance during the last month.

The initial physical examination showed the following data:

generalized pallor,

peripheral oxygen saturation of 82%,

warm central cyanosis,

blood pressure of 180/90 mmHg, pulse of 110 bpm, abnormal JVP,

gallop rhythm, basal bilateral crackles ,

hepatomegaly, ascites.

severe edema in the upper third of the thigh.

The laboratory indicated the following:

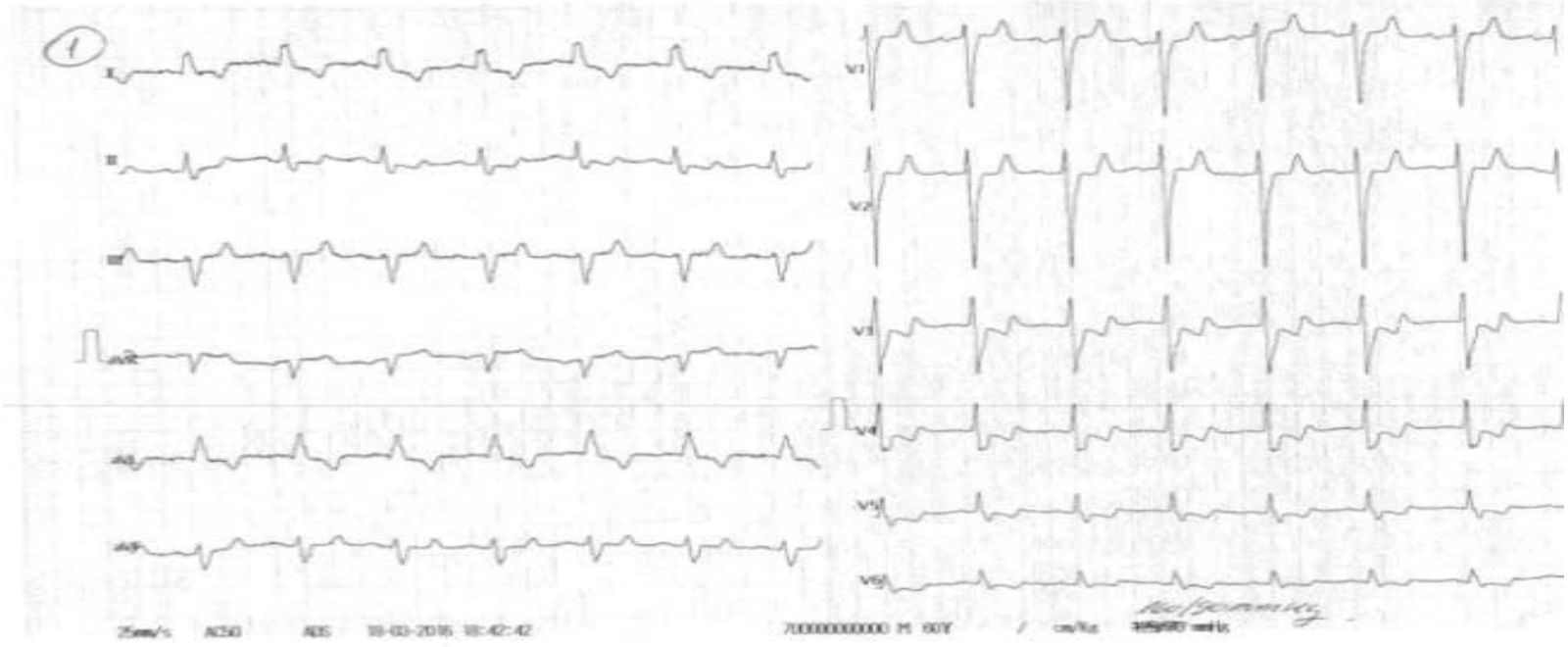
leukocytosis (leukocytes 12000/µl),

anemia (hemoglobin 9.3 g/dl , serum iron of 35 mg/dl, transferrin saturation of 15%, ferritin of 75 ng/ml, peripheral smear with normochromic, normocytic appearance,

glycosylated hemoglobin 7.9%,

NT pro BNP 20000 pg/ml,

serum creatinine of 3.1 mg/ dl, urea nitrogen of 152 mg/dl, hyperkalemia (K 6.3 mmol/l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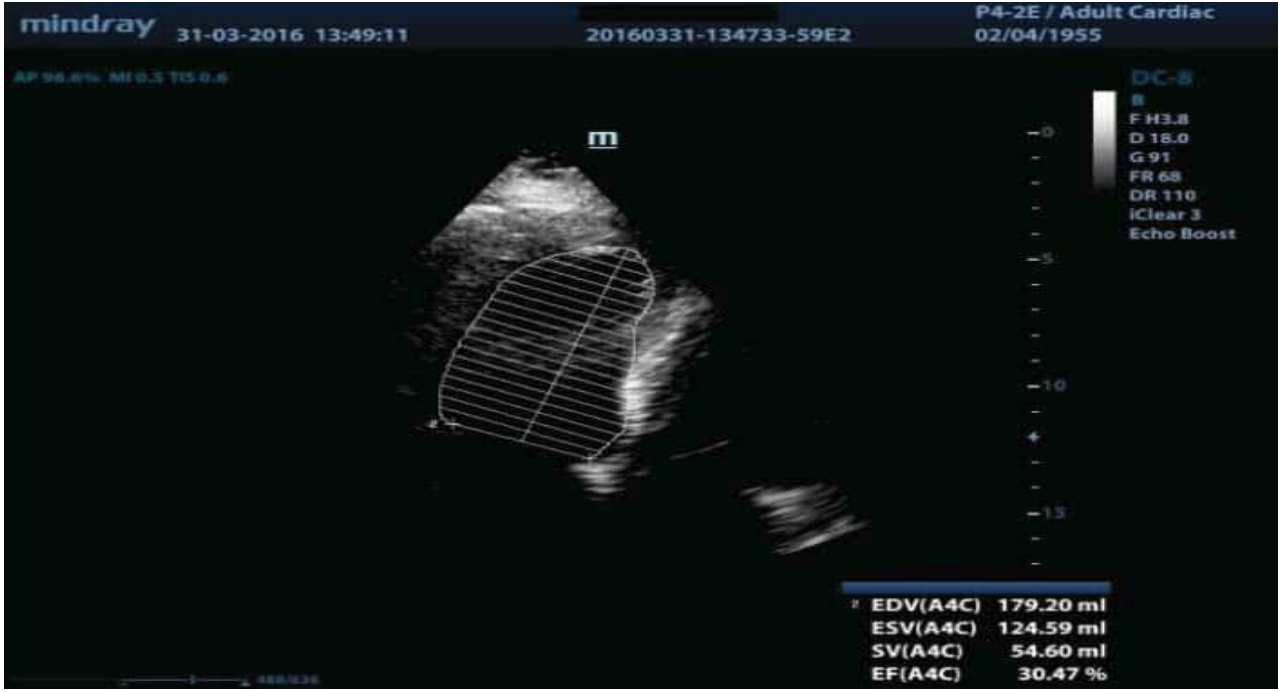
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G 91
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DR 110
iClear 3
Echo Boost
EDV(A4C) 179.20 ml
ESV(A4C) 124.59 ml
SV(A4C) 54.60 ml
EF(A4C) 30.47 %

Please let me know your views :

(ADHF , high BP ,ascites , anemia , cr =3.1)

- ✓ ***High dose of diuretics***
- ✓ ***Hemodialysis***
- ✓ ***Rapid lowering of BP***
- ✓ ***Abdominal paracentesis***

Renal dysfunction is the most important predictor of mortality in heart failure patients , and worsening renal function is associated with increase hospital stays , cost of complications and mortality at 5 years.

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Because many early heart failure trials excluded patients with renal dysfunction , much of the data about cardiorenal syndrome comes from retrospective studies where worsening renal function was found in patients hospitalized for ADHF.

Several definitions have been used for worsening renal failure:

Increase in Cr equal to or more than 25%

An increase in serum Cr equal to or more than 0.3 mg/dl

cardio renal syndrome as a "pathophysiologic disorder of the heart and kidney whereby acute or chronic dysfunction of 1 organ may induce acute or chronic dysfunction of the other.(In 2008 Ranco , et al.)

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classification:

1-Acute of worsening of cardiac function(ACS , cardiogenic shock , ADHF) leading to AKI.

2-Chronic abnormality in cardiac function causing progressive CKD.

3-Acute kidney injury (ischemia or glomerunephritis leading to cardiac dysfunction.(ischemia , arrhythmia ,…)

4- Chronic kidney disease that lead to chronic cardiac dysfunction.(decrease in cardiac function , LVH , diastolic dysfunction or increase in CV morbidity)

5-Systemic condition causing simultaneous heart and kidney dysfunction.(sepsis , SLE , drugs , toxins , Wegner granulomatosis , DM , sarcoidosis , amyloidosis)

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Epidemiology:

The incidence of CRS varies by its type.

Because CRS (V) is a newly recognized entity that may occur in different pathological process , its incidence , prevalence ,and outcome are not well defined.

We know that acute worsening of renal dysfunction occurs in 25-45% of patients with ADHF , specially during the first 3 days after admission.

ADHERE(Acute Decompensated Heart Failure National Registery):

That had more than 105,000 patients with ADHF ,renal dysfunction was found in 30% and 21% had a serum Cr >2

And in stage III CKD(CRS IV) , defined as GFR<60 ,has been present in up to 60% of patients with chronic CHF.

Pathophysiology :(focus on CRS type I)

1- low cardiac out put

2- vascular congestion

3- increase in intra abdominal pressure

4- neurohrmonal activation

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Low CO:

(especially those with systolic dysfunction and related hypovolemia)

Activation of arterial and intrarenal receptors in the kidney

Non-osmotic release of arginine vasopressin

Activation of renin-angiotensin-aldosterone

Activation of sympathetic nervous system

Water and sodium retention

Increased renal arteriolar resistance

Renal ischemia

Decreased GFR

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Vascular congestion:

(Mullen et al ,): obsereved that patients admitted with ADHF had CVP higher than 18 mmHg at admission.

This increased CVP transmitted to the renal vein(demonstrated by intrarenal Doppler ultrasonography)with a subsequent decrease in GFR and an associated

decrease in renal flow and an increase in renal interstiatial pressure that is associated with tissue hypoxia.

In addition , the authors found a limited contribution of impaired CI at admission in the development of worsening renal function in these patients(similar to ESCAPE trial)

ESCAPE:193 patients treated with pulmonary artery catheter-based therapy , although the CI improved in this patients , there was no significant improvement in renal function.

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Increase in intra abdominal pressure:

An increase in intra abdominal pressure equal to or higher than 8 mmHg has been associated with worsening renal function in patients with ADHF.(Mullens et al : showed that removing intra abdominal fluid either by ultrafiltration or paracentesis is linked to improvement in renal function without a significant alteration in hemodynamic parameters.)

APP(Abdominal perfusion pressure):

Is the difference between mean arterial pressure and intra abdominal pressure

APP=MAP-IAP

Patients with ADHF associated with congestion and who have low MAP but experience an increase in IAP , resulting in reduced perfusion in abdominal organ.

An APP of at least 50 mmHg was shown to be a good predictor of survival .

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Immune response and oxidative stress imbalance:

Significantly higher monocyte apoptosis and activation of Caspase cascade

Higher level of inflammatory cytokines (IL-16 ,IL 18 , TNF alpha)…promote renal tubular epithelium injury and death …

Decrease NO , increase in vasoconstrictor molecules(thromboxane A2)

…loss of normal epithelial cell function.

Diagnosis:

Measuring the GFR (is not reliable in acute states)

Serum Cr(are influenced by several factors :age , sex , muscle mass)

New biomarker: N-GAL neutrophil gelatinase-associated lipocalin (indicates accumulation of nephrotoxins and renal ischemia 48-72 h before the increase in serum Cr) ,

cyctatin C(cyctein protease inhibitor produced at a constant rate for almost all nucleated cell ,freely filtrated by the kidney due to its low molecular weight and it is neither secreted nor reabsorbed in the kidney) ,

and several markers of inflammation (myeloperoxidase , cytokines , urine IL-18).

The most important tool for diagnosis CRS remains the clinical assessment.

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Management:

Because patients with cardiorenal syndrome have been excluded from many heart failure trials , literature supporting appropriate management and treatment cardiorenal syndrome is lacking and remain largely empirical .

Most treatment plans focus on improving hemodynamic abnormalities and congestion.

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Congestion relief:

Evaluation of cardiac filling pressure and intra-vascular volume

There is a disconnection between cardiac filling pressure and intra-vascular volume.

In the patients who presented with no significant increase in weight but with a significant increase in filling pressures , likely secondary to change in the splanchnic venous pool. These changes are caused by a persistent sympathetic activation that leads to vasoconstriction of the venous pool with the subsequent volume shift to the systemic circulation and an increase in filling pressures.

Several volume control strategies have been attempted in patients with ADHF:

1-diuretic:

Loop diuretics remain the most-used therapy for patients with ADHF.(based on ADHF registery)

DOSE trial (is probably the only large randomized clinical trial that evaluated the use of diuretics in HF patients , this trial failed to show any difference in symptoms or in change in renal function between patients who received continuous vs .bolus of diuretics and those who received high dose vs. low dose.

CARRESS trial (diuretics was as effective as ultrafiltration in managing congestion

2-ultrafiltration

RAPID trial and UNLOAD trial , showed that UF can safely remove more fluid than high dose diuretics , and with more weight loss and decrease in admission for HF at 90 days , neither therapy showed a significant clinical benefit in terms of dyspnea or renal function

and it was associated with a higher incidence of transition to renal replacement therapy and high in-hospital mortality despite improvement in hemodynamics.

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3- Vasopressin receptor antagonist:

V1a and V2 receptors: (V1 receptors are located in the peripheral vasculature and V2 receptors are located in the distal tubules and collecting ducts)

Tolvaptan , V2 receptor antagonist ,was tested in ACTIV in CHF and EVEREST trials , showed a benefical effect on body weight loss , dyspnea , and edema as well as improvement of hyponathremia . there was no difference in primary end point.

Conivaptan , V1a /V2 receptors antagonist , increase of diuresis in patients with ADHF without significant effect on blood pressure and HR.

Neither Tolvaptan nor Conivaptan has been approved for use in ADHF patients.

5-Nateriоretic paptid:

Brain nateriоretic peptid (nesiritide) , commonly use for diuretics resistence .

ASCEND HF trial ,found a lack of impact on death , rehospitalization , or renal function in patients hospitalized for ADHF.

interest in natriuretic peptides remain high in light of their combination of vasodilatory and natriuretic properties.

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Improvement of hemodynamics:

As important as relieving congestion , improving the patient's hemodynamics avoid worsening renal failure and breaks the vicious cycle that perpetuates kidney damage.

Decreasing intra abdominal pressure ***(paracentesis in patients with ADHF presenting with ascities has been associated with improvement in renal function)***

Avoiding hypotension and intra vascular volume:

Avoid of hypotension ***(avoid MAP below 65mmHg)***

Adequate capillary refill(titrated decongestion therapy)

History of chronic HTN(they require higher BP to maintain autoregulatory mechanism)

Increasing CO with maintenance of an appropriate effective circulatory volume is critical to restore organ perfusion and improve GFR:

Afterload reduction by vasodilators , improvement in contractility with inotropic therapy , (if tolerated , vasodilator should be used as the first line therapy , inotropes have been associated with increased mortality and poor short prognosis)

Serelexin (a recombinant human relaxin-2 , vasodilatory and end-organ protective effects has shown rapid relief of congestion in ADHF , improvement in marker of cardiac , renal and liver function and clinical outcome)

Low dose of dopamine (has failed to show a beneficial effect in ADHF and tachycardia and hypotension could be deleterious in patients with renal dysfunction).

use of mechanical circulatory support (while naver indicated based solely on the presence of cardiorenal syndrome- has shown improvement in renal function.


Thank
you