Cardio-Renal Syndrome in Heart Failure

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Cardio-renal syndrome (CRS)

- Definitions.

Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other

Nephrol Dial Transplant 2011; 26: 62–74

CRS: A cardiology Viewpoint

- **CRS Type 1 (AHF drives acute renal injury)**
  - Acute heart failure leading to AKI/WRF
  - Acute MI, cardiogenic shock, ADHF
- **CRS Type 2 (CHF drives CKD)**
  - Chronic heart failure leading to CKD
- **CRS Type 5**
  - Systemic disease (diabetes, hypertension, atherosclerosis, sepsis….) leading to heart and renal failure

Ronco C, DiLullo L. Heart Failure Clin 10 (2014) 251-280.

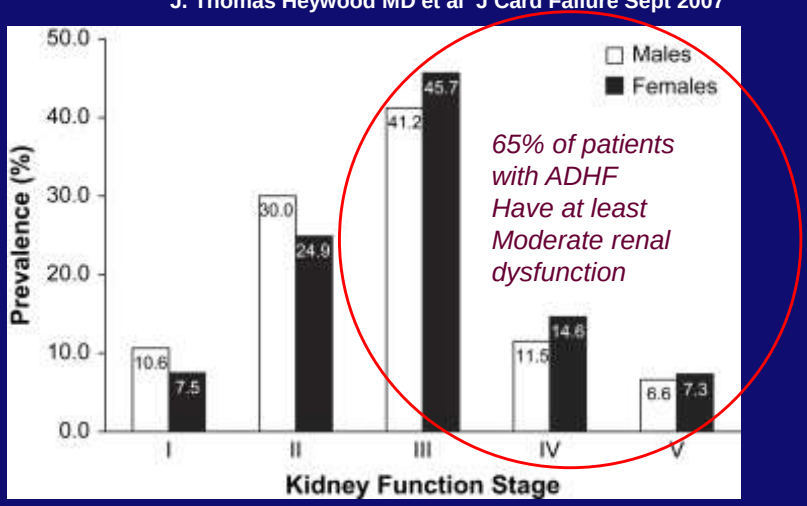
CRS in HF: Definition

Heart failure with…

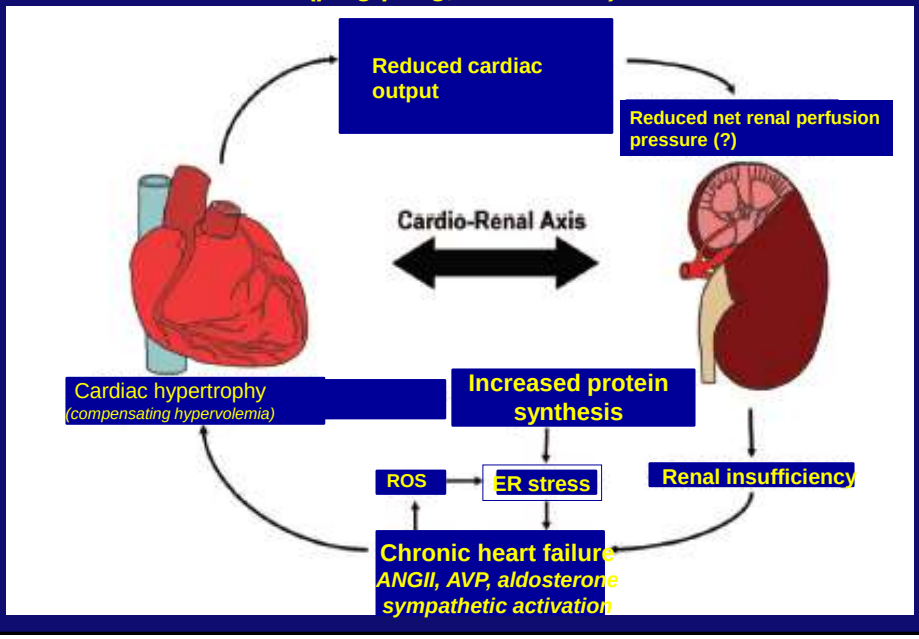
- Worsening renal function (> 25% increase in creatinine or a decrease in eGFR by 25%).
- Difficulty in diuresis without worsening renal function
- ACE intolerance due to hypotension or hyperkalemia

High Prevalence of Renal Dysfunction and Its Impact on Outcome in 118,465 Patients Hospitalized With Acute Decompensated Heart Failure: **A Report From the ADHERE Database**

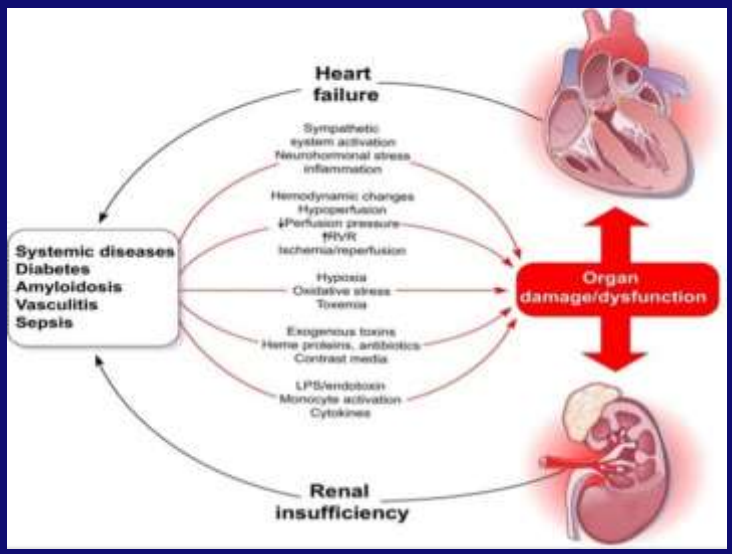
J. Thomas Heywood MD et al J Card Failure Sept 2007



Cardiorenal syndrome
(ping-pong, table tennis)



CRS Type 5 (Secondary CRS)



Inflammatory immune activation

- Neurohormonal and inflammatory immune activation
- CHF inflammatory cytokines :TNF and IL-6 (Anker et al, 2002)
- In ADHF: gut wall edema (secondary to elevated RA pressure) facilitates translocation of bacterial endotoxin (lipopolysaccharide) (Niebauer et al, 1999).

The net result → adversely impact on cardiac and renal function.

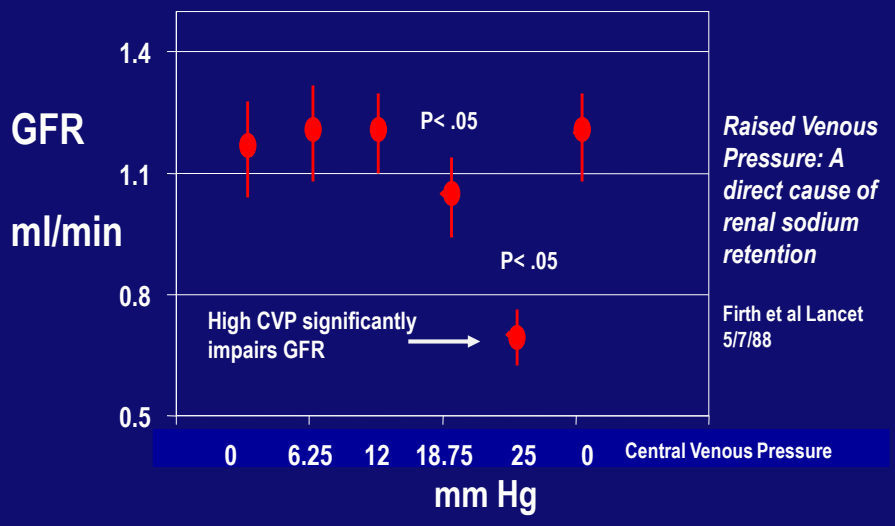
Risk factors

1. Advanced age, diabetes, pulmonary edema on chest X-ray on admission (Cowie et al, 2004)
2. Co-morbid vascular disease, higher level of baseline urea (Heywood, 2004)
3. HTN and lower SBP on admission.
4. Drugs (anti-inflammatory agents, diuretic , ACE inhibitors, ARBs)
5. Elevated cardiac troponins

Why is renal function abnormal in patients with heart failure?

1- Increasing central venous pressure

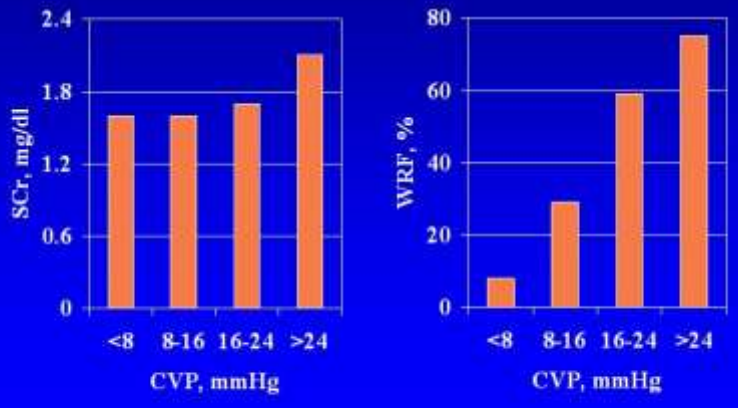
Effect of increasing CVP on GFR in dogs, constant BP



Raised Venous Pressure: A direct cause of renal sodium retention

Firth et al Lancet 5/7/88

Venous Congestion is an Important Hemodynamic Factor Driving WRF

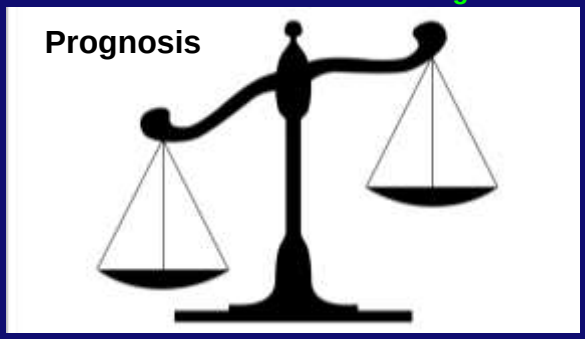


Mullens et al., J Am Coll Cardiol 2009;53:589

2- Bidirectional behaviour of Diuretic

Diuretic therapy → **Worsening renal function**

Diuretic therapy → **Improving Congestion**



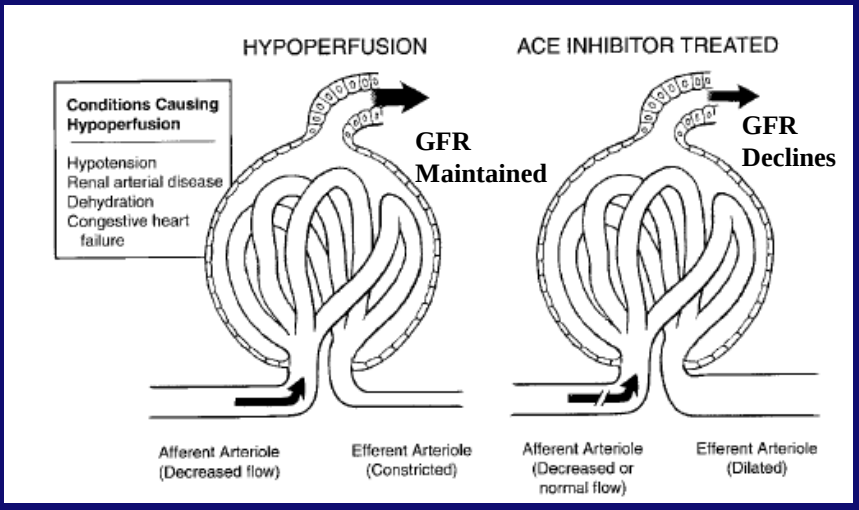
J Am Coll Cardiol 2011;57:2233-41

- High dose of IV diuretics associated with occurence of WRF (Felker et al. *NEJM 2011)*

ACEI play a complex role in renal function in HF

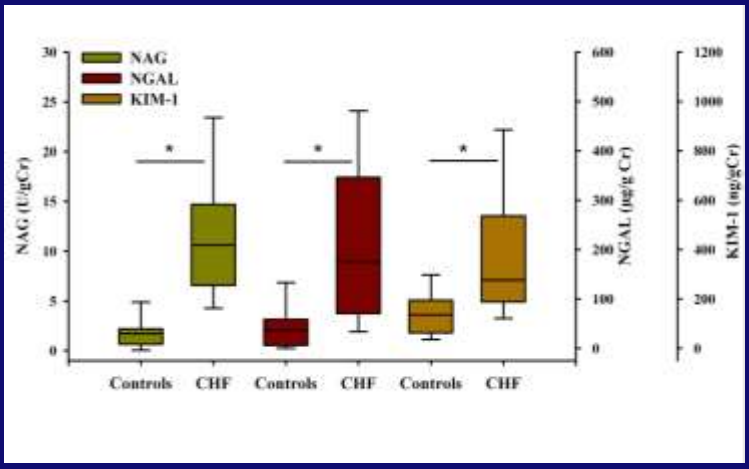
- May improve CO in some patient and hence increase effective renal perfusion
- ACEI may lower BP to the point where effective renal perfusion is impaired
- With chronic renal disease, there is hyperfiltration in the remaining nephrons. ACEI decreases efferent arteriole constriction and hence decreases glomerular capillary pressure which may preserve renal function longterm
- This may result in a 10-20% increase in creatinine, but over the long term renal function is preserved

3- ACEI intolerance in low CO, low SVR states



Circulation 2001:104:1985

4- Tubular Damage is prevalent in Heart Failure

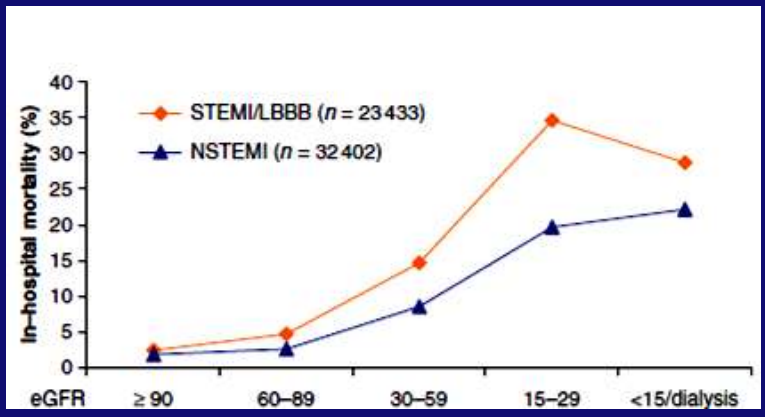


Damman et al. *Heart 2010*

5) Iatrogenesis should also be considered in the pathophysiology of type 1 CRS; pharmacological treatment of diabetes mellitus & other medications

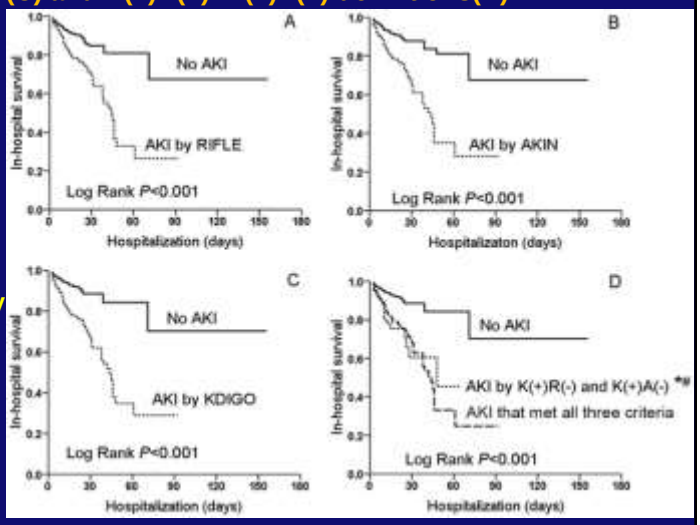
Impact of WRF

In hospital mortality according to eGFR
As regards admission ECG



Szummer, J.Intern.Med.(2010) 268:40

In-hospital survival of CRS type 1 according to RIFLE(A), AKIN(B), KDIGO(C) and K(+)R(−)+K(+)A(−) definitions(D).

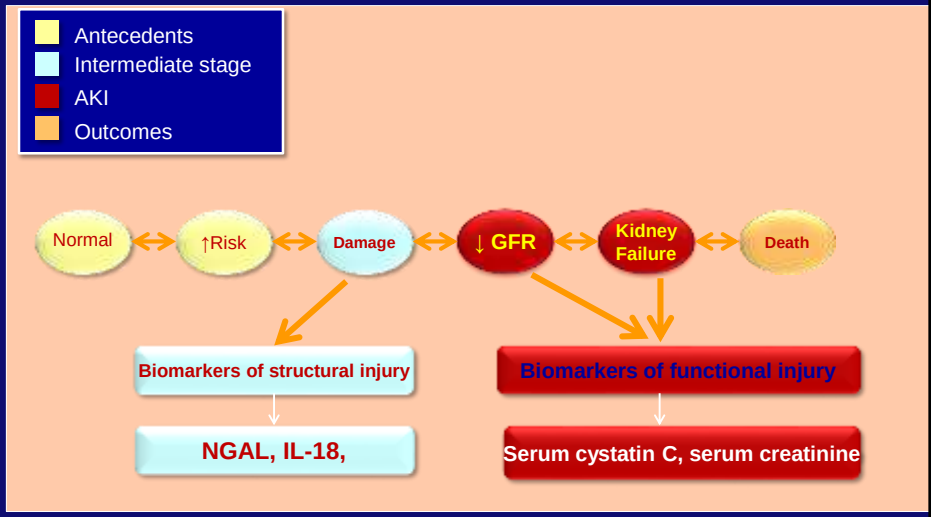


to RIFLE (risk, injury, failure, loss of kidney function, end?stage kidney disease)

Li Z, Cai L, Liang X, Du Z, et al. (2014) Identification and Predicting Short-Term Prognosis of Early Cardiorenal Syndrome Type 1: KDIGO Is Superior to RIFLE or AKIN. PLoS ONE 9(12): e114369. doi:10.1371/journal.pone.0114369

Diagnosis

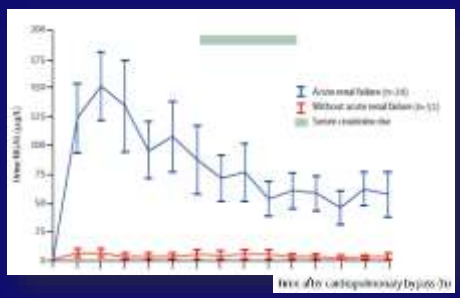
1) Biomarkers: for early diagnosis



Adapted from Murray, CJASN, 2008; 3: 864-868

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

- ✓Marked upregulation very early after ischemic or nephrotoxic AKI
- ✓May be measured in plasma or urine



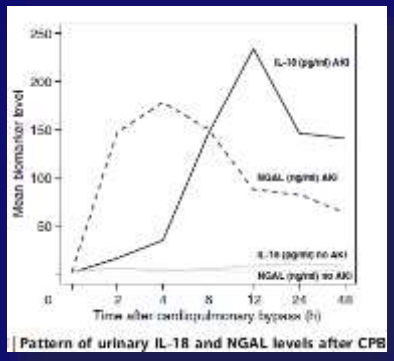
Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery

Joya Mishra*, Catherine Dent†, Ridwan Tarabishi*, Mark M Mitsnefes, Qing Ma, Caitlin Kelly, Stacey M Ruff, Kamyar Zahedi, Mingyuan Shao, Judy Bean, Kiyoshi Mori, Jonathan Barasch, Prasad Devarajan

Kidney International (2006) 70, 199–203

Interleukin 18 (IL-18)

- Low concentration at baseline
- **Easily detected in the urine after ischemic injury**
- **Levels correlate with outcomes**



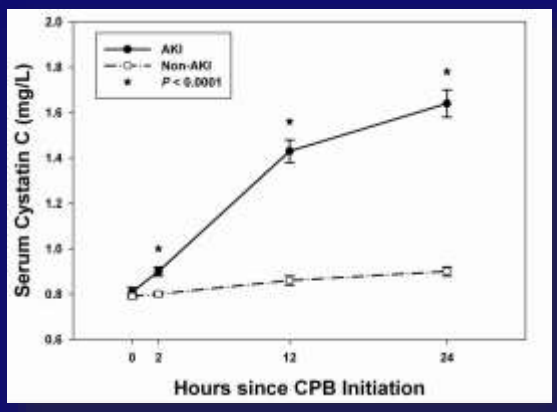
Pattern of urinary IL-18 and NGAL levels after CPB

Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery

CR Parikh[1], J Mishra[2], H Thiessen-Philbrook[3], B Dursun[4], Q Ma[2], C Kelly[2], C Dent[3], P Devarajan[2] and CL Edelstein[4]

Cystatin C

- Serum levels readily measurable using standard laboratory platform
- **Significant rise at 12h after CPB with peak at 24h**
- Can be measured in urine or plasma

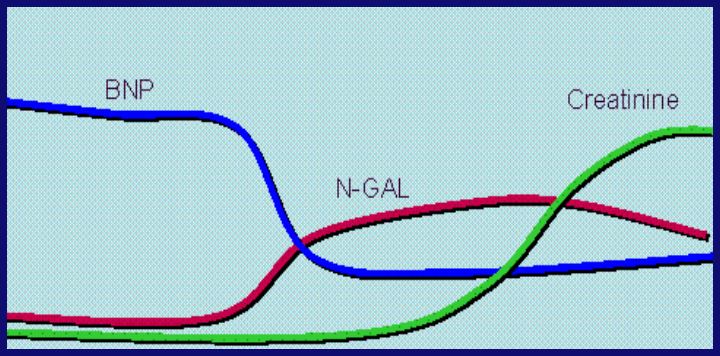


Cut-off value of 1.16 mg/dL at 12h predictive of AKI

Krawczeski et al, *CJASN 2010*

Coupling Cardiac and AKI Biomarkers

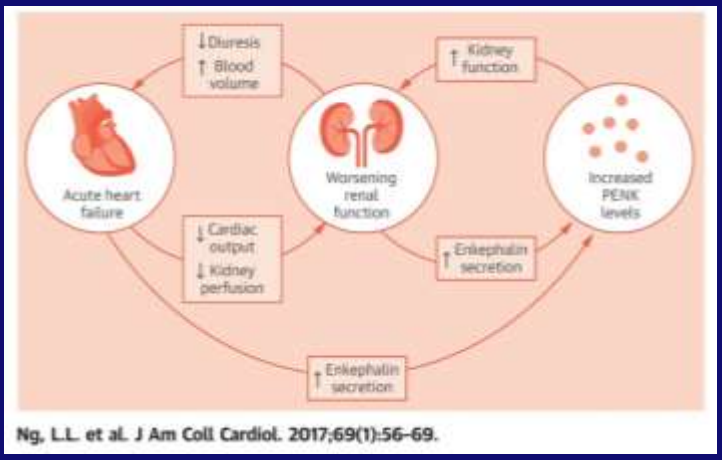
Addition of NGAL to known cardiac biomarkers (such as BNP) may allow full interpretation of fluid status in decompensated HF and direct clinical care



Ronco, et al

Contrib Nephrol. 2012;178:121-128. © 2012

Proenkephlin (PENK) in AHF



Ng, L.L. et al. J Am Coll Cardiol. 2017;69(1):56-69.

- PENK levels reflect cardio-renal status in acute HF and are prognostic for worsening renal function and in-hospital mortality as well as mortality during follow-up.

2) Ultrasound of the kidneys

- **Type 1 CRS:**
  1. Normal or larger dimensions with a preserved cortical-medullary ratio,
  2. Colour Doppler evaluation shows regular intraparenchymal blood flow, often associated with a raised resistance index (>0.8 cm/s)
- **Type 2 CRS:**
  - Reduction of cortical thickness, corticomedullary ratio and increased parenchymal echogenicity.

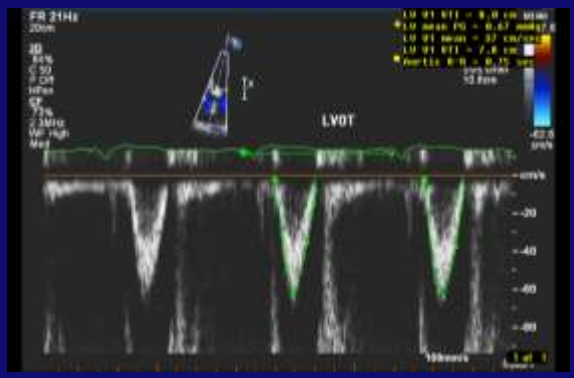
3) Echocardiography

- Echocardiography shows abnormal myocardial kinetics, valvular disease (calcific disease) ,….
- Increased atrial volumes, indices of volume overload, normal or decreased EF, right heart dilation & increased PAP, pericardial effusion, impaired RV function.
- **Type 5:** Early→ Low output myopathy late shift to high output myopathy.

Hemodynamic Echo- Noninvasive Evaluation

- Right Atrial pressure (Inferior Vena Cava)
- Pulmonary Artery Pressure (TR Velocity + RA)
- Estimated mean left atrial pressure (E/E')
- Cardiac Output (VTI x Area x HR)
- Systemic Vascular Resistance= **[(MAP-RA)x80/CO]**

Case example



Cardiac Output = *VTI x Area of Outflow Tract x Heart Rate*
8cm/sec x 3cm x 80 beats/min = 1920 ml/min, 1.9 L/min

SVR=[(MAP-RA)x80/CO]: 130/70 = Mean 130+140/3= 90 [(90-20) x 80/1.9= 5600/1.9] = SVR approx 2800 i.e. vasoconstricted

CHF: Risk Scoring for CRS in Hospital

Risk factor	Points	Hazard Ratio
History of CHF	1	1.3
Diabetes	1	1.4
SBP>160 mmHg	1	1.4
Creat. 1.5-2.5	2	2.1
Creat.≥2.5	3	3.5

Score= 0-3 → 10% risks
Score ≥ 4 → >53% risks

Treatment of the CRS

5 important questions…

1. What is the fluid status?
2. Is the BP adequate for renal perfusion?
3. What is the cardiac output?
4. Is there evidence of high central venous Pr?
5. Is there intrinsic renal disease?

CRS due to high central venous pressure

Too Wet!!!

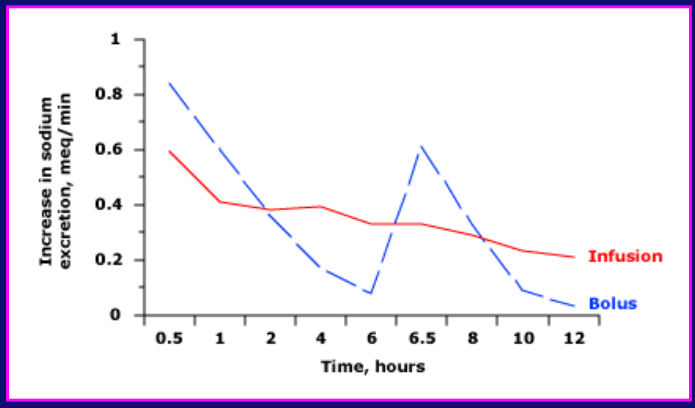
- Poor renal perfusion due to high central venous pressure
- Usually CVP > 15-20 mm Hg coupled with reduced BP

✓IV diuretics to reduce CVP add thiazides or metazolone

✓Ultrafiltration

IV Loop Diuretics: Bolus vs. Continuous Infusion

Rudy DW et al. Ann Intern Med 1991; 115:360



Metanalysis: Continuous Infusion Superior to Bolus Injection:

Total UO	P = 0.003
Increase in Sr. Creatinine	P < 0.00001
Length of Hospitaliization	P < 0.00001
All Cause Mortality	P = 0.00005

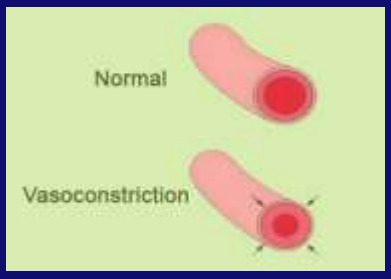
Salvador DRK et al. *The Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD003178.pub3. DOI: 10.1002/14651858.CD003178.pub3.

Hypovolemic Cardiorenal Syndrome

Too Dry!!!

- Overdiuresed or intercurrent illness results in volume loss and renal dysfunction
- Give fluids, stop diuretics and IV vasodilators
- Often a reluctance to give fluids to HF patients but it may be critical in this situation and time is of the spirit to avoid irreversible renal damage

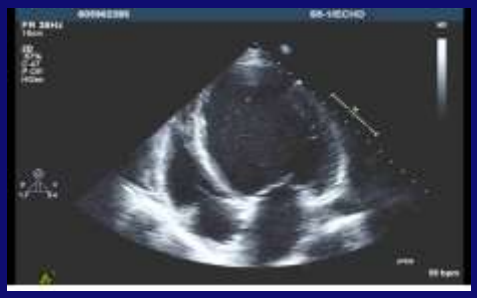
CRS with vasoconstriction



Clamped Down!!!

- Low CO and hence renal hypoperfusion due to HF mediated vasoconstriction (Ang II, endothelin induced increased afterload)
- CO is low and SVR high, often over 1800-2000
- ACEI and vasodilators very useful since CO can increase significantly if afterload normalized.
- Temporary inotropic support if SBP <80.

CRS with normal SVR but low CO or BP

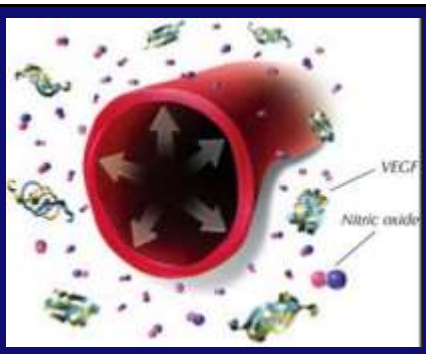


“ No Pump!!!”

- CRS due to inadequate renal perfusion because of low CO and/or BP, normal SVR!!!
- Inotropes, Pressors, Temporary circulatory support
- LVAD

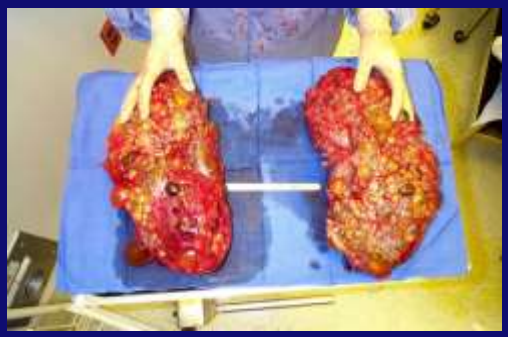
CRS with vasodilation

“Vasodilated!!”



- Renal hypoperfusion due to low perfusion; CO may be normal but SVR and BP low
- Vasodilators worsen BP and hence renal perfusion
- Stop of ACEI,
- Rule out sepsis
- Pressors, Inotropes, ? Vasopressin
- Consider transplant or ventricular assist device if renal dysfunction is felt to be reversible

CRS with normal CO and SVR



"It's the Kidneys, Not the Heart!!!!""

- Consider intrinsic renal disease (IRD) or diuretic resistance syndrome, renal artery stenosis
- Probable IRD when long hx of HTN and/or diabetes, look for proteinuria, renal artery stenosis
- Trial of loop diuretic infusion, combination with distal tubular diuretic
- Add nesiritide
- Consider ultrafiltration

Molecular approach: Histone Deacetylase Inhibition:

- It has been suggested as an approach to reduce the morbidity and mortality associated with cardiorenal syndrome.
- Valproic acid or Trichostatin A & 4-phenyl butyric acid

1. Reducing cardiomyocyte hypertrophy.
2. Reduce myocardial fibrosis
3. Affect protein folding through modifying the expression of ER stress response genes, including GRP78.

- Bush EW, McKinsey TA. Circ Res. 2010;**106**:272–284.
- Kee HJ, et al. Circulation. 2006;**113**:51–59.

Vasodilator: Nesiritide

Trial	Population	Intervention	Results
ASCEND-HF -O'Connor CM. NEJM 2011 -Randomized controlled trial	N=7141 Hospitalized with acute decompensated HF	-Assigned patients to placebo or nesiritide for 24 to 168 hours -Dose: 2ug/kg bolus then 0.01ug/kg/min	-No change in risk of worsening renal function compared with placebo. - No change in mortality risk -No major harm
- Yan B. Int J of Cardiol. 2014 -Systematic review and meta-analysis	N = 17271		No change in mortality rates

Inotropes

Trial	Population	Intervention	Results
ROSE AHF -Chen HH. JAMA 2013 Dec - Double blinded RCT	N = 360	Randomized to receive: -placebo, -dopamine (low dose: 2ug/kg/min), -Nesiritide (low dose: 0.005 ug/kg/min)	-No improvement of renal function or congestion
-Cuffe MS. JAMA 2002. - Prospective RCT	N = 951 NYHA class III or IV	Randomized to receive placebo or milrinone 0.5ug/kg per min x 48 hrs	Milrinone slightly increased mortality and new atrial arrhythmia.

Strategies to Overcome Cardiorenal Syndrome

1. Avoid Hypotension
2. Avoid “over diuresis” and allow adequate time for circulatory “refill”
3. Addition of thiazide-type diuretics should be considered when a progressive decrease in loop diuretic efficacy is observed; Add to block distal tubule
4. Improve RV function when possible: reduce PVR, support RV function
5. MRA: use natriuretic dose (> 25 mg spironolactone). Peak effect 48 hours; use with loop diuretic
6. Reduce Intra abdominal pressure: paracentesis