# The Cardiorenal Syndrome- a Nephrologist's Perspective

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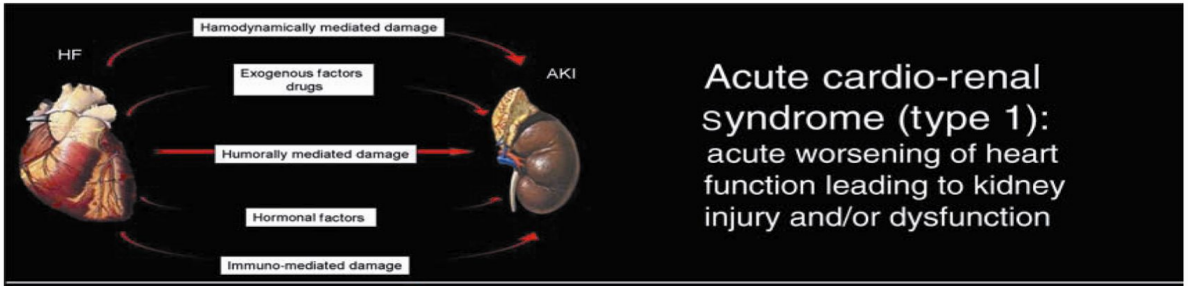
# Chronic cardiac and chronic renal failure-the common ground

- High cardiovascular mortality
- Cardiac fibrosis/sudden cardiac death
- Fluid overload: high morbidity and mortality
- Chronic inflammation, low albumin
- Neurohormonal activation: sympathetic nervous system and RAAS
- Rate of fluid removal (UFR→dialysis tolerance)-an important determinant of both Serious Adverse Effects and symptomatic relief
- Diuretics affect mortality (though differently)

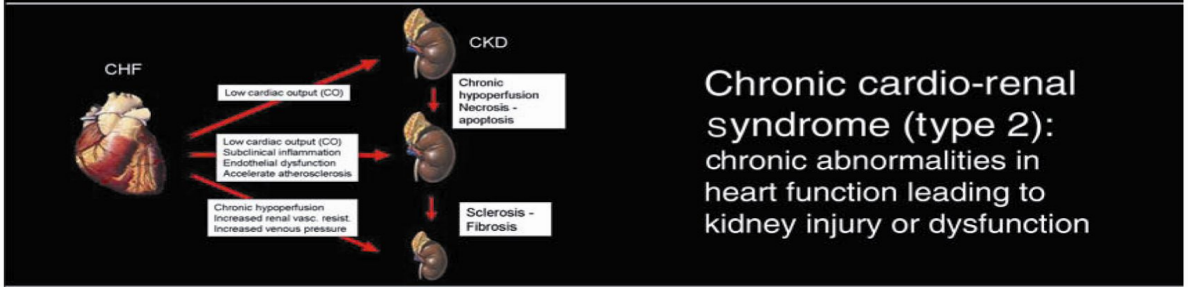
# The Cardiorenal Syndrome (CRS)
## Definition

Coexistent cardiac (acute or chronic) and renal failure (acute or chronic)

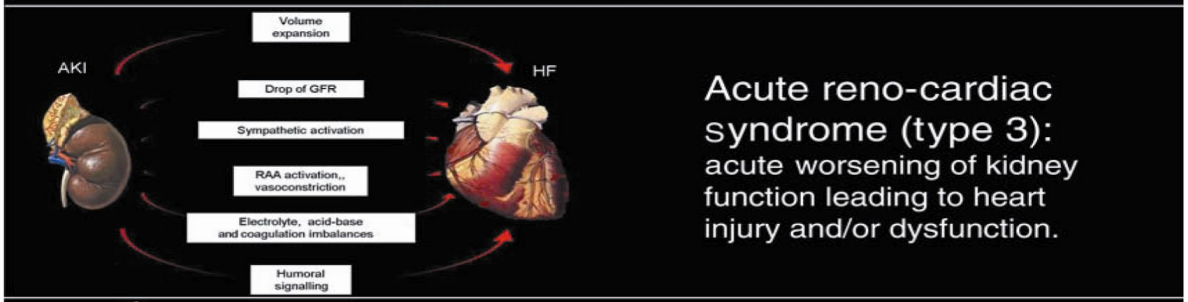
- Worsening renal function: > 25% increase in creatinine or BUN during treatment for acute decompensation
- Chronic kidney disease complicating chronic heart failure therapy
- Difficulty in diuresis without worsening renal function
- ACE intolerance due to hypotension/worsening renal dysfunction/hyperkalemia in severe heart failure



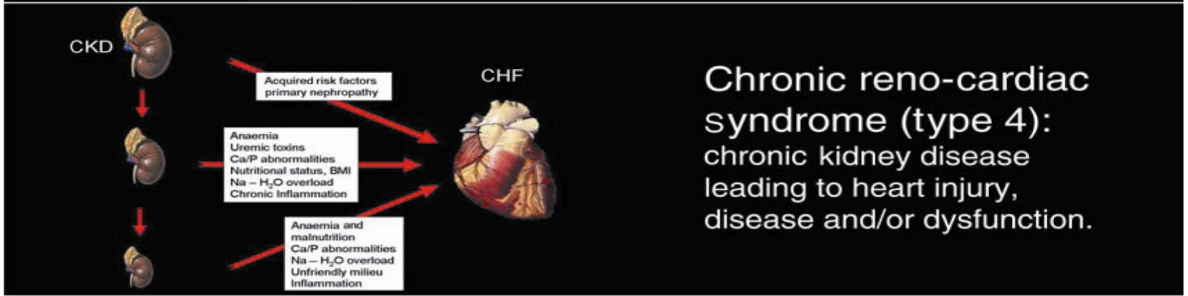

**Acute cardio-renal syndrome (type 1):** acute worsening of heart function leading to kidney injury and/or dysfunction



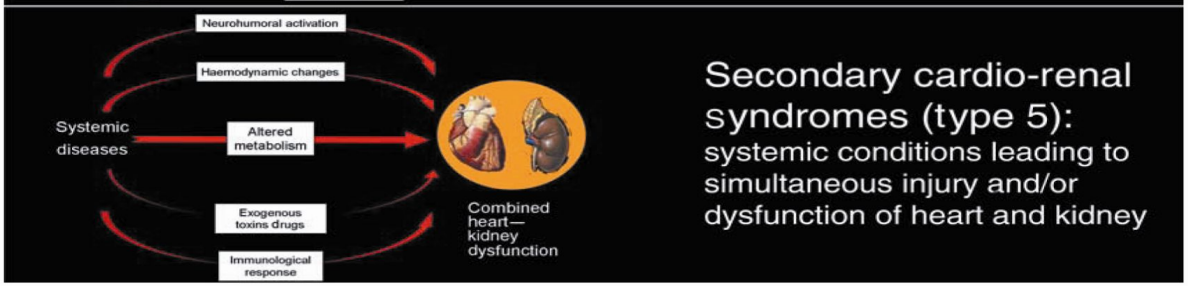

**Chronic cardio-renal syndrome (type 2):** chronic abnormalities in heart function leading to kidney injury or dysfunction




**Acute reno-cardiac syndrome (type 3):** acute worsening of kidney function leading to heart injury and/or dysfunction.




**Chronic reno-cardiac syndrome (type 4):** chronic kidney disease leading to heart injury, disease and/or dysfunction.




**Secondary cardio-renal syndromes (type 5):** systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney

- Type 1: loop diuretics, vasodilators, inotropes, UF, spironolactone
- Type 2: diet, ACE-I, ARB, β-blockers, diuretics, spironolactone
- Type 3 diuretics, UF, dialysis as necessary
- Type 4: diet, ACE-I, ARB, β-blockers, diuretics, UF, spironolactone
- Type 5: ICU support, treatment of underlying disorder

# Heart Failure and prevalence of eGFR< 60 ml/min/1.73 $m^2$

- SOLVD Prevention 21 %
- SOLVD Treatment 36 %
- SAVE 33 %
- DIG 46 %
- Atlanta, Georgia 38 %
- Alberta, Canada 56 %
- Sendai, Japan 43 %

SOLVD: Studies of Left Ventricular Dysfunction Prevention

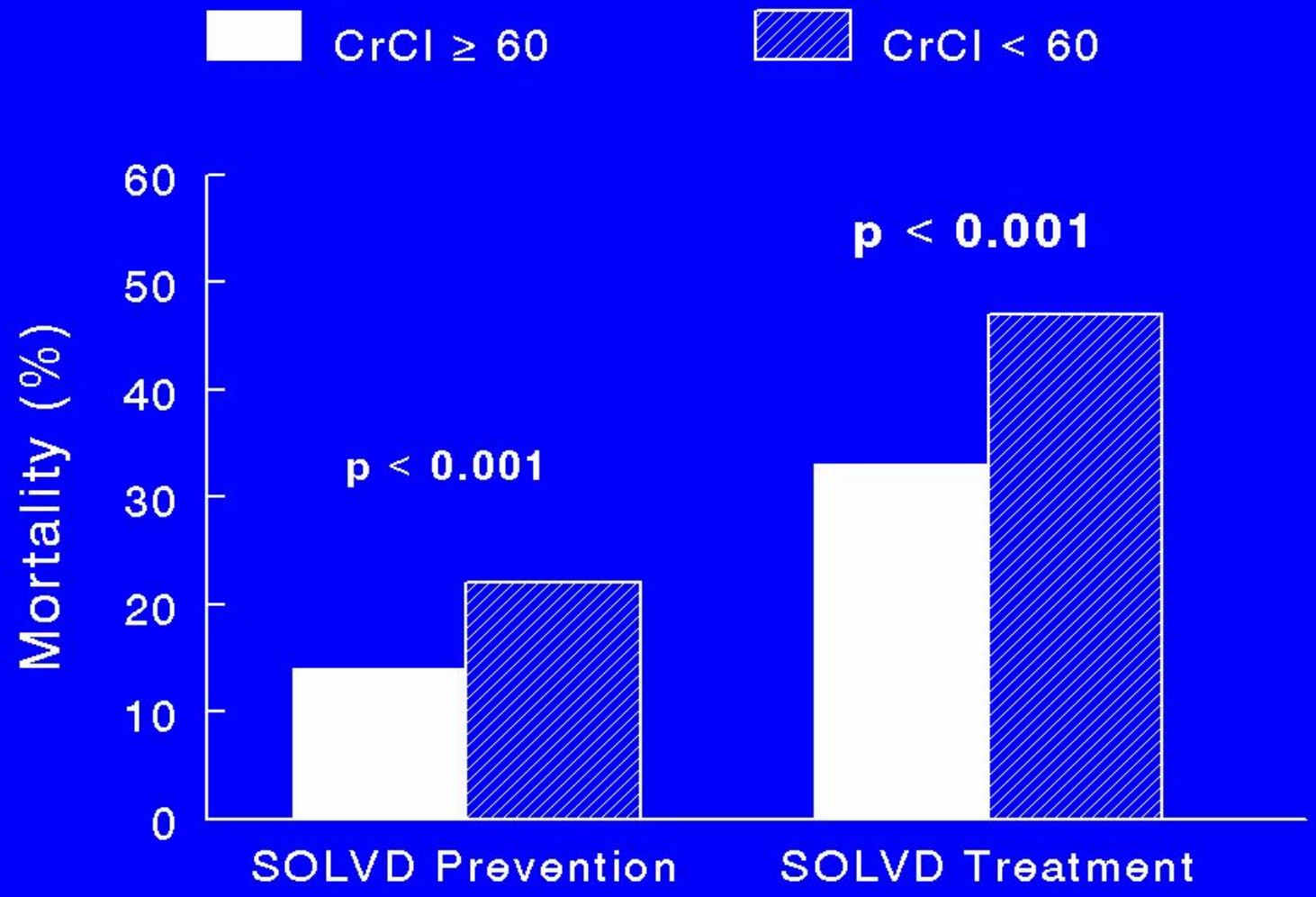
SAVE: Survival and Ventricular Enlargement Trial

DIG: Digitalis Investigational Group

M Givertz 2008

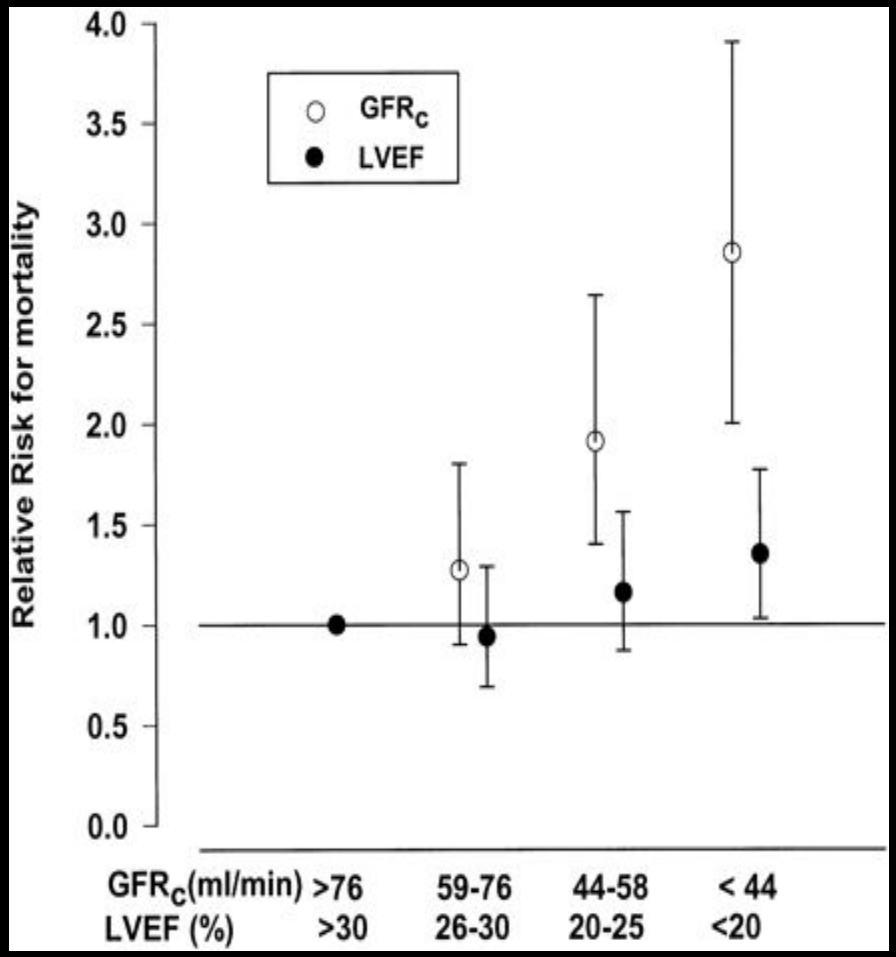
# Mortality In CHF

## Effect of Renal Dysfunction




Dries JACC 2000; 35:681

# Relation, in quartiles, of LVEF and GFRc to the risk of mortality using the multivariate proportional hazards regression




- eGFR is a powerful predictor of death in chronic heart failure

Hillage HL et al. *Circulation* 2000; 102:203-210

# Inpatient mortality from ADHERE Registry Based on admission BUN, creatinine and BP

- ≥BUN 43 vs <43: 8.35% vs 2.88%

  if ≥BUN 43 then

- ≥ Cr 2.75 vs <2.75: 19.76% vs 13.23%

Analysis of patients in the National Acute Decompensated Heart Failure National Registry (ADHERE)

BUN=blood urea nitrogen, Cr=serum creatinine

Fonarow GC et al. *J Cardiac Fail* 2003;9(suppl 1):S79.

# Causes of Cardiorenal Syndrome: The Cardiologist's Perspective

- Overdiuresis
- Diuretic resistance
- Hypotension (especially with high CVP)
- Neurohomonal (sympathetic activity, RAAS) activation causing low GFR and fibrosis
- Low Cardiac Index with high SVR
- Normal Cardiac Index with excessive vasodilation with shunting of blood away from kidneys

# Causes of Cardiorenal Syndrome: The Nephrologist's Perspective

## Heart failure→ reduced renal function

- Overdiuresis, underdiuresis, diuretic resistance= inadequate volume control (high volume=high mortality in AKI or CKD)
- Anything else that decreases either cardiac output or SVR (RBF)

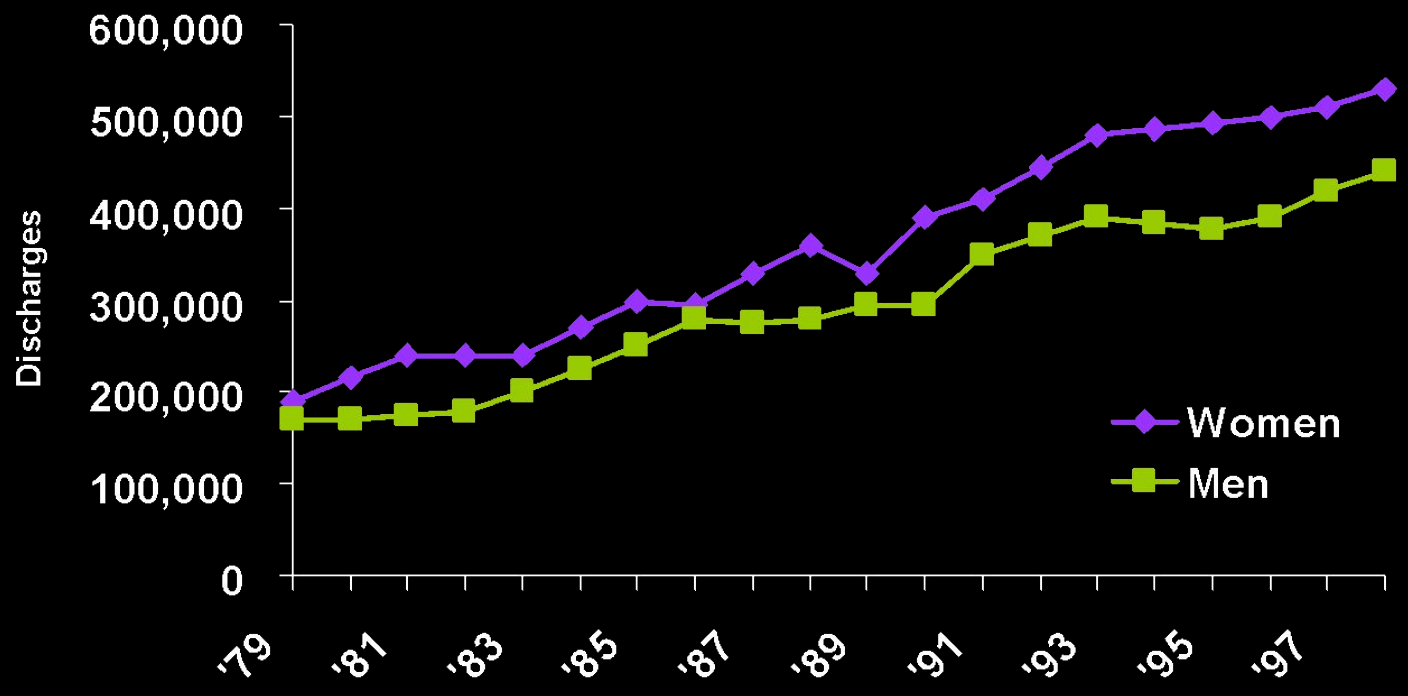
## Reduced renal function→ Heart failure

- inadequate volume control with sodium retention in CKD→ chronic hypervolemia→ resistant hypertension→ left ventricular hypertrophy→ diastolic dysfunction/cardiac fibrosis
- increased sympathetic activity/RAAS→resistant hypertension→ left ventricular hypertrophy→ diastolic dysfunction/cardiac fibrosis
- uremia/chronic inflammation→ accelerated atherosclerosis→ diffuse cardiovascular injury
- chronic maintenance dialysis with or without UF→ decreased myocardial perfusion, rapid electrolyte shifts, rapid fluid shifts, acute phase reaction→ repetitive insult to myocardium → ?diastolic dysfunction/cardiac fibrosis

# Cardiorenal Syndrome: Pathophysiology

| | Fluid status | CO | SVR | Proteinuria | Treatment |
|---|---|---|---|---|---|
| Hypovolemia: | dry | low | nml/high | none | fluids, d/c Acei |
| Vasocontriction: | wet,nml | low | high | none | Acei, nesiritide |
| Cardiogenic Shock: | wet,nml | low | high | none | inotropes, pressors, balloon pump, LVAD, Tx |
| Vasodilation: | wet,nml | nml/high | nml/low | none | stop Acei, Pressors, vasopressin, inotropes, VAD |
| Diuretic Resistance: | wet | nml | nml | none | cont diuretic infusion, comb diuretic, nesiritide, UF |
| Intrinsic renal disease: | wet | nml | nml | yes | diuretic, UF |

# Cardiorenal Syndrome: Hospitalizations over Time



# Cardiorenal Syndrome: Presentation, Symptoms at Hospitalization*

- Any dyspnea – 89%
- Pulmonary congestion (CXR) – 74%
- Rales – 67%
- Dyspnea at rest – 34%
- Peripheral edema – 65%

* ADHERE *(*Acute Decompensated Heart Failure National Registry*)*

- **Over 90% of All Hospitalizations for Acutely Decompensated Heart Failure (ADHF) Are Due to Fluid Overload[1]**

- **The Majority of These Patients Have Failed Treatment With Oral Diuretics[2]**

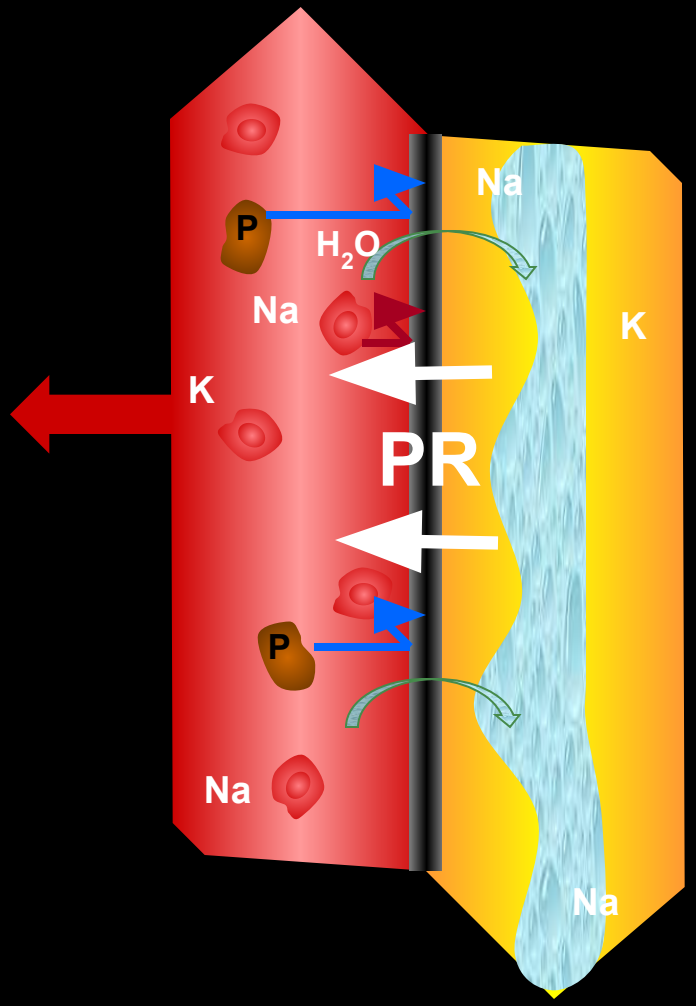

1. Aronson. *ACC*. 2000.
2. Adams et al. *Am Heart J.* 2005;149:209-216.

- Favorable aspects of diuretic therapy
  - Increases urine output; reduces total body volume in majority of patients

- Adverse aspects of diuretic therapy
  - Direct activation of renin-angiotensin-aldosterone system
  - Enhanced myocardial aldosterone uptake
  - Loss of K, Mg, Ca, secondary myocyte Ca loading
  - Indirect reduction of cardiac output
  - Increased total systemic vascular resistance
  - Reduced natriuresis and GFR
  - Associated with increased morbidity and mortality

# Fluid Removal by Ultrafiltration

- Ultrafiltration can remove fluid from the blood at the same rate that fluid can be naturally recruited from the tissue depending on vascular refill
- The transient removal of blood elicits compensatory mechanisms, termed *plasma* or *intravascular refill plasma* or *intravascular refill* (PR), aimed at minimizing this reduction[1,2]




1. Lauer et al. *Arch Intern Med*. 1983;99:455-460.
2. Marenzi et al. *J Am Coll Cardiol*. 2001;38:4.

# Plasma Refill Rates

- plasma refill rates in stable patients:

-Nephrotic syndrome 19.9 ml/min

-CKD 16.5 ml/min

-CHF 12.7 ml/min

- In acute decompensation may be much lower

# Ultrafiltration-Caveats

- plasma refill varies

-inter-individually (comorbidities etc)

-depending on the degree of neurohormonal activation

-based on volume status

-due to adverse effects of medications (vasodilators, sympathetic blockers)

-in time

- ULTRAFILTRATION RATE (rate of fluid removal, UFR) needs careful attention and has been shown a predictor of death in chronic dialysis patients
- Ultrafiltration may cause hemodynamic collapse when UFR is not appropriately individualized and adjusted to current clinical status
- Hyperkalemia may be a problem, especially if the patient has some underlying renal issues-some dialysis may be necessary to prevent this
- Frequent clotting with high UFR and peripheral lines can make cost prohibitive

# Favorable aspects of dialysis/ultrafiltration

-Removal of isotonic fluid

- Potential for tight regulation of speed of volume loss ( depends on UFR)

-Lack of neurohormonal activation

-Lack of major electrolyte disturbances (depends on close monitoring)

-hemofiltration may remove cytokines and “myocardial depressant factor”

# Adverse aspects of ultrafiltration/dialysis

-Need for vascular access (infection, hemorrhage, thrombosis, stenosis)

-Acute phase reaction (membrane, extracorporeal circuit)

-Potential for rapid fluid/electrolyte shifts (depends on treatment time, need for dialysis)

-Hyperkalemia (UF only)

-Potential for decreased myocardial perfusion (in intermittent dialysis)

-Need for anticoagulation

-Blood pressure drop (may depend on UF rate or rate of removal of osmoles)

-Excess fluid removal

-Acute hemorrhage, hemolysis

-Allergic reaction to the membrane

-Air embolus

# Diuretic Resistance

- Can be described as a clinical state in which the diuretic response is diminished or lost before the therapeutic goal of relief from edema has been reached

- Affects 20%–30% of patients with HF

# Causes of Diuretic Resistance

- Decreased renal function and distal Na+ delivery
- Variability in diuretic absorption (bioavailability)
- Neurohormonal activation (RAAS/SNS)
- Drugs/diet—increased sodium intake
- Noncompliance with medications
- Infrequent dosing (Lasix= lasts for six)

# Treatment of Diuretic Resistance

- Restrict daily fluid intake (1.0–1.5 L)
- Moderate restriction of daily salt intake (≤2 g)
- Avoid NSAIDs
- Institute and uptitrate ACE inhibitors and/or angiotensin receptor blocker
- Give short-acting loop diuretic orally in several divided (and increasing) doses, bolus, or continuous intravenous administration with close monitoring of electrolytes
- Use sequential nephron blockade via combination loop diuretic and thiazide diuretic- very high potential for hypokalemia with metolazone if given as outpatient
- Add small doses of spironolactone (12.5–25 mg)- potential for hyperkalemia in renal failure

# Trials: UF in diuretic resistance Euphoria

- Primary efficacy end point
  - Resolution of signs and symptoms of fluid overload permitting discharge in ≤3 days
- Primary safety end point
  - Feasibility of achieving the primary efficacy objective without symptomatic hypotension, renal insufficiency (≥25% increase in serum creatinine), or other adverse events

# Euphoria- Patients

- Age: 74 ± 8.5 years
- Gender: 75% male
- Race: 95% Caucasian
- Etiology of HF: 75% ischemic
- Left ventricular ejection fraction: 31 ± 16%

# Euphoria- Conclusions

- Early ultrafiltration in patients with fluid overload and diuretic resistance permitted the discharge of 60% of high risk ADHF patients in ≤3 days
- A treatment strategy to use ultrafiltration early* in patients with volume overload and evidence of diuretic resistance results in reduced length of stay and improved clinical status
- Improvements in clinical status are preserved for 30–90 days following hospitalizations

# UNLOAD

- UltrafiltratioN versus intravenous diuretics for patients hospitaLized fOr Acute Decompensated heart failure

http://www.clinicaltrials.gov/ct/gui/show/NCT00124137

http://www.chfsolutions.com/index.html

Costanzo, et al. JACC, 2007

- Inclusion Criteria:
  - Patients hospitalized with primary diagnosis of acute decompensated congestive heart failure (adCHF)
  - Evidence of fluid overload as indicated by:
    - pitting edema (2+) of lower extremities;
    - jugular venous distension;
    - pulmonary edema or pleural effusion;
    - ascites;
    - paroxysmal nocturnal dyspnea or 2-pillow orthopnea
- Exclusion Criteria:
  - Acute coronary syndrome
  - Creatinine greater than 3.0

  N=200

- Primary Outcomes:
  - Total weight loss during first 48 hours of randomization
  - Change in dyspnea score during first 48 hours of randomization
- Secondary Outcomes:
  - Change in global assessment
  - Change in quality of life (living with heart failure)
  - Changes in brain natriuretic peptide (BNP)
  - Changes in 6 minute walk test
  - Total fluid loss during first 48 hours of randomization
  - Changes in blood urea nitrogen (BUN) and creatinine
  - Changes in renin and aldosterone

# UNLOAD

- At 90 days following hospital discharge, UF group demonstrated:
  - 43% ↓ pts for HF re-admits
  - 50% ↓ total number of HF re-admits
  - 52% ↓ ED or clinic visits
  - 63% ↓ total days for HF re-admits
  - Only transient increase in creatinine with UF

    UF versus “standard care” (diuretics either bolus or IV drip in an un-blinded fashion)

# Criticism of UNLOAD

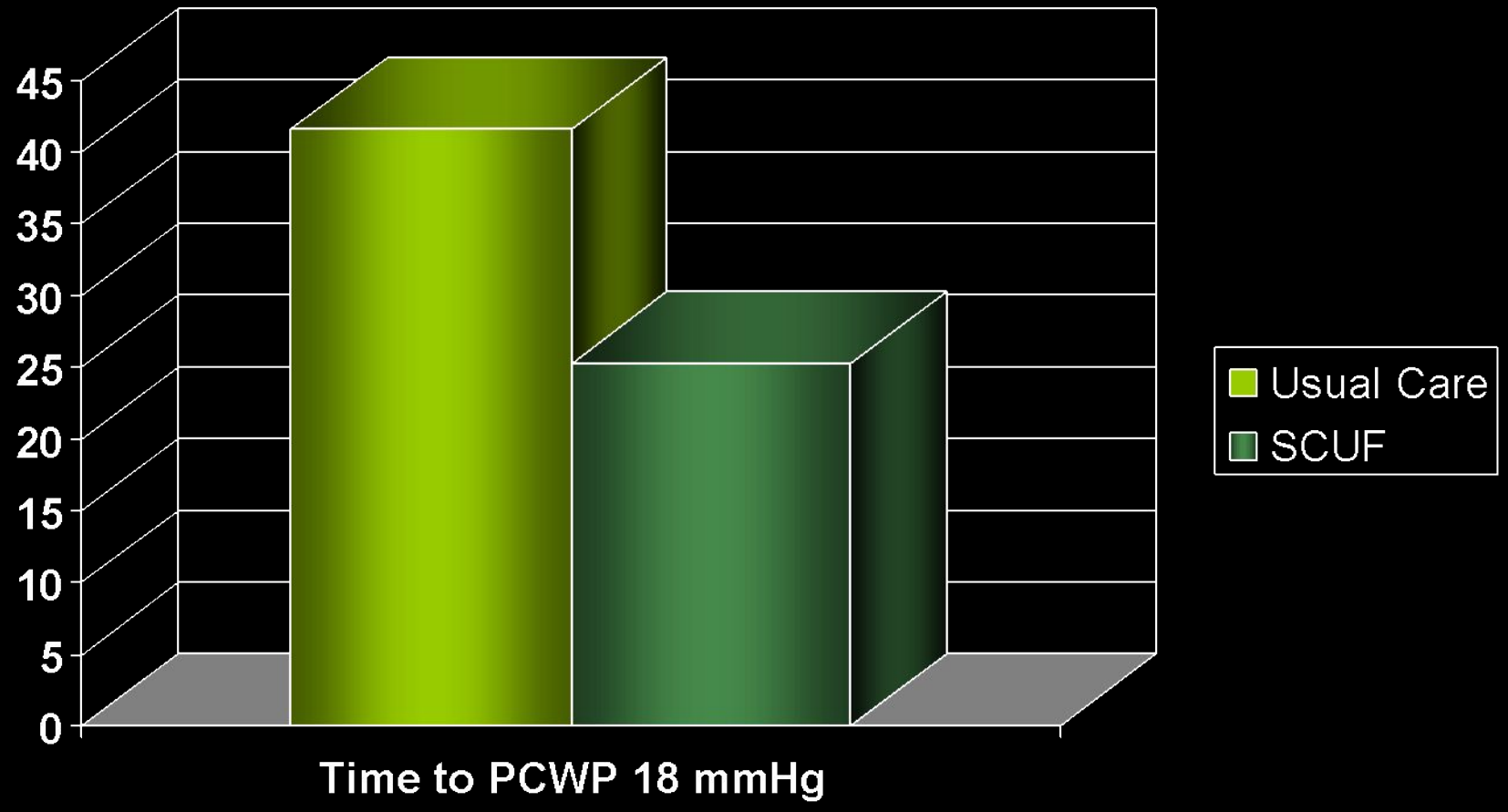
- Study population was more stable hemodynamically than typical ADHF patients. This favored the device used.
- The study groups were not controlled for the total amount of volume loss at the end of the treatment. This favored the device.
- Cost: $****/dialyzer is potentially excessive.
- Use of peripheral lines may result in problems with subsequent vascular access surgery.
- **NIH CARRESS-HF (Cardiorenal Rescue Study in ADHF):** randomized, multi-center study in 200 ADHF hospitalized patients.

Kazory et al J Am Coll Cardio 2007; 50:820

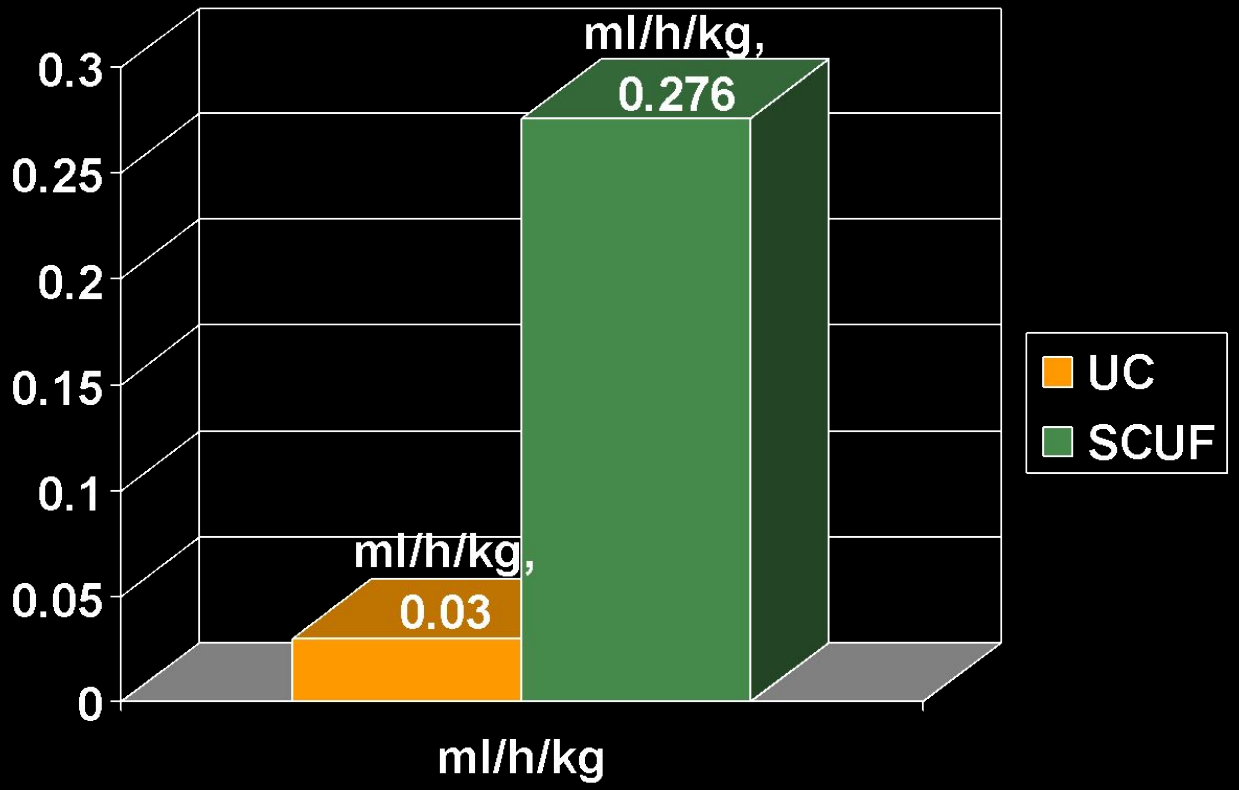
# Ultrafiltration vs. Customary Care for Patients Hospitalized with ***Severe*** Heart Failure at the Cleveland Clinic

- Prospective, open label, randomized, two arms
- N=36 patients in Heart Failure ICU
  - SG catheter with PCWP >20
- Stratified by renal function (MDRD 50 ml/min/1.73 $m^2$)
- Ultrafiltration vs customary care
- Primary endpoint
  - Time to achieve PCWP ≤ 18 for 4 consecutive hrs
- Secondary endpoint
  - Time in ICU / hospital
  - Total fluid removed
  - Urine output / renal f(x)
  - Cytokines, neurohormones
  - 90 day follow up
  - Minnesota QOL etc…

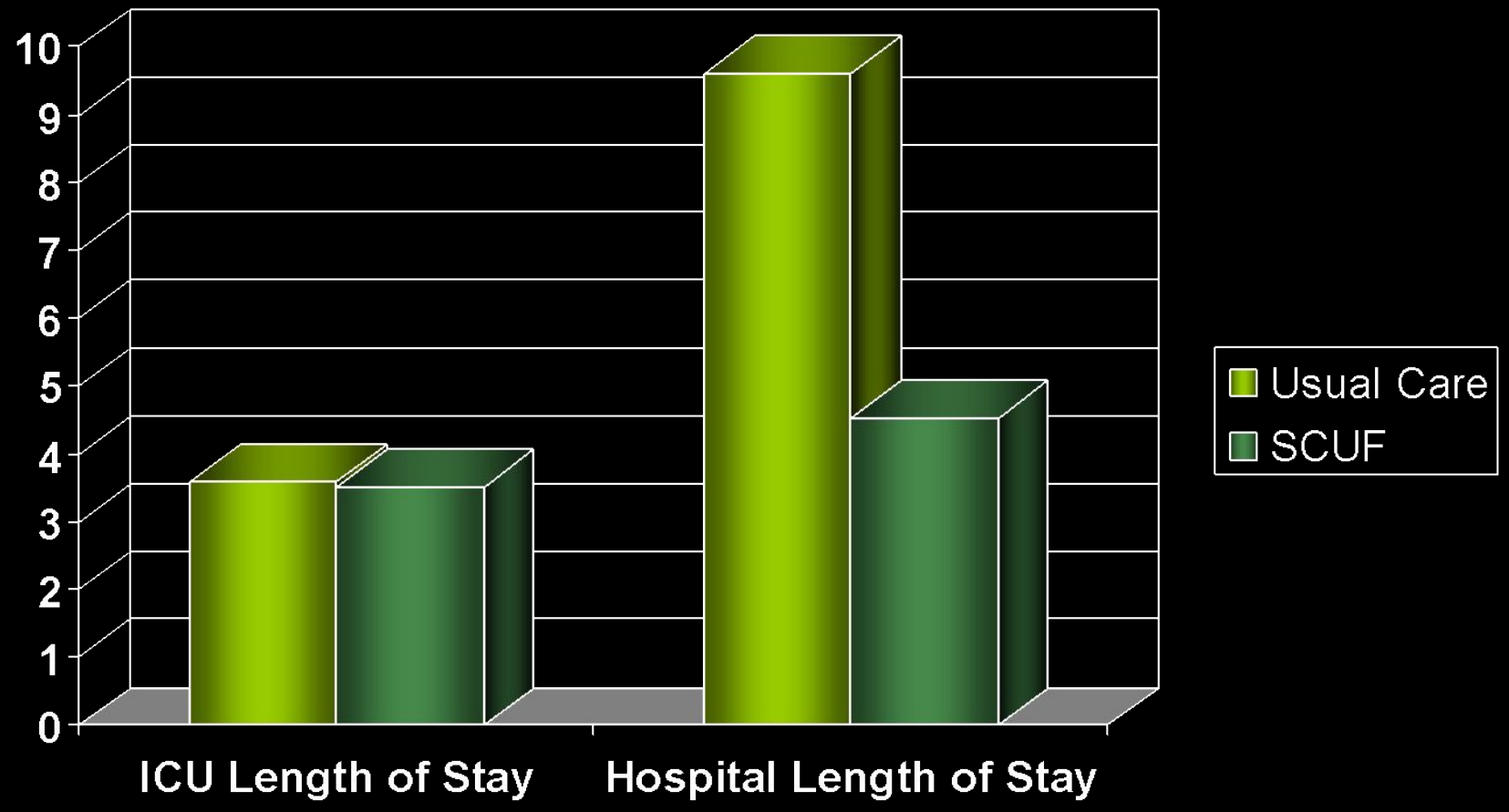
# Duration of Treatment to Achieve PCWP of ≤ 18 mmHg (Primary Measure)



# Total Volume Removal Rate
## (ml/h/kg)



# Length of Stay According to Treatment Group (Secondary Measure)



# Overall Outcome Data

# Cleveland Clinic Study Conclusions

- This population was much sicker than UNLOAD
- There is an advantage in fluid management
- There was no difference in SCr or Cystatin changes
- Cytokine and Neurohormonal changes were not different
- Markedly shorter hospital stay
- No real difference in overall mortality
- May be a disadvantage in re-admissions and ER visits

# Mayo Clinic Experience: Prospective Observational

Liang KY, et al. J Card Fail 2006

- **Complications with Therapy**
  - No SAE associated with UF
  - Increase S Cr to > 0.3mg/dl (45%)
  - Required HD for uremia or fluid (45%)
- **Mortality- 6 months**
  - 55%
- **Conclusions**
  - Sicker patients may not fair well
  - 45% had renal function deterioration
  - Only short-term goal effectiveness

# Diuretics versus Ultrafiltration: Summary

- Ultrafiltration and diuretics can both have side effects that sometimes can be alleviated by close monitoring and appropriate dosing/frequency (for diuretics) and frequent adjustment for UFR (for ultrafiltration)
- Ultrafiltration is an excellent option for short term symptomatic relief when diuretics (appropriately used) begin to fail and sometimes restore diuretic responsiveness
- Individualization of treatment based on the patient's current clinical situation and estimation of differential risk for typical side effects for either therapy should be instrumental in choosing therapy
- When making inferences from the results of randomized clinical trials, especially in a clinical syndrome with large inter-individual variability, careful assessment of potential differences between the study population/methods versus the given clinical scenario should be made

# Renal Replacement Therapy in ADHF

Udani, Murray  Seminars in Dialysis 2009

- **Intermittent Ultrafiltration**
  - Shortened time (3-4 hours) may induce cardiovascular instability as UFR is dependent on treatment time possibly best limited to when other modalities not available
- **Slow Continuous Ultrafiltration (SCUF) or Sustained Low Efficiency Dialysis (SLED)**
  - Both use conventional dialysis machine and dialyzers, lower blood flows (200 ml/min), 8-24 hr treatments, SLED can correct electrolytes and uremia
  - SCUF is just ultrafiltration with extended time
  - SLED also uses a dialyzate and removes uremic toxins and electrolytes in a concentration-dependent fashion; dialysis with extended time
  - Dialysis is often necessary in sicker patients as oliguria/uremia will eventually develop due to decreased renal perfusion; in these patients it can also prevent hyperkalemia

# Renal Replacement Therapy in ADHF

- **Continuous Venovenous Hemofiltration**
  - Typically restricted to ICU for unstable patients
  - 24 hr/day, low blood flow (150-200 ml/min); fluid replacement to correct metabolic abnormalities and treat uremia and to remove cytokines-sicker patients may have inflammation (observed in both chronic heart failure and chronic kidney failure) sometimes resulting in vasodilation and low blood pressure (rule out sepsis)
  - Hemofiltration (unlike dialysis) removes larger molecules including cytokines and “myocardial depressant factors” and may be especially useful when sepsis or SIRS are suspected

# Chronic Renal Replacement Therapy following ADHF

- **Peritoneal dialysis in refractory heart failure:**

**-may improve NYHA functional status**

**-may improve hospitalization**

**-may improve life expectancy**

**-may improve pulmonary arterial pressures (though not EF)**

**-now home hemodialysis 5-6x/week became available and might be an alternative option to relieve symptoms**

# The Nephrologist's Conclusion

- Renal and cardiac failure often coexist and share typical features and outcomes
- Reduced renal function is common in heart failure and when present predicts increased mortality
- Fluid overload is an important feature in both renal and cardiac failure
- Judicious use of diuretics or ultrafiltration often provides short term symptomatic relief
- When appropriately used, ultrafiltration may improve short term outcome in moderately sick patients
- Ultrafiltration is a good option in diuretic resistant cases

# The Nephrologist's Conclusion 2.

- Ultrafiltration needs to be escalated to renal replacement therapy if removal of uremic toxins, electrolytes or cytokines becomes necessary
- Hemofiltration has the advantage to remove cytokines
- Peritoneal dialysis or perhaps frequent home hemodialysis may be an option for symptomatic management of refractory heart failure

# Thank you for your attention!