ULTRAFILTRATION

Managing Congestion
in Advanced Decompensated Heart Failure
13th Annual Meeting of the
Heart Failure Society of America
Monday, September 14, 2009

Maria Rosa Costanzo, M.D., F.A.C.C., F.A.H.A
Medical Director, Midwest Heart Specialists Heart Failure and Pulmonary Arterial Hypertension Programs
Medical Director, Edward Hospital Center for Advanced Heart Failure

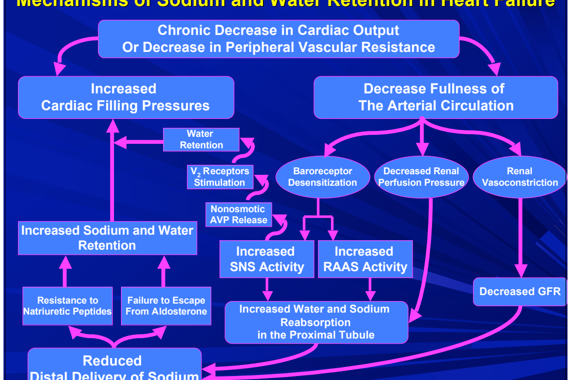
Maria Rosa Costanzo, MD, F.A.C.C., F.A.H.A.

Disclosure Information
Symposium IV:
"Managing Congestion in Advanced Decompensated Heart Failure"
Presentation Title: Ultrafiltration

- I will not discuss off label use and/or investigational use in my presentation.

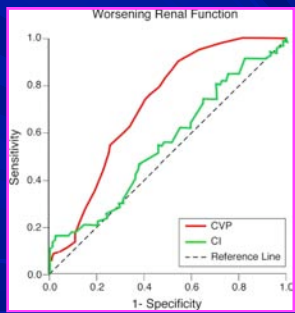
- I have financial relationships to disclose:
- Employee of: Midwest Heart Specialists
- Consultant for: CHF Solutions, St. Jude Medical, Medtronic
- Stockholder in: None
- Research support from: St. Jude Medical, Paracor Medical, CardioMems
- Honoraria from: CHF Solutions, St. Jude, Gilead

Mechanisms of Sodium and Water Retention in Heart Failure



Adapted from Schrier RW: J Am Coll Cardiol 2006; 47:1-8

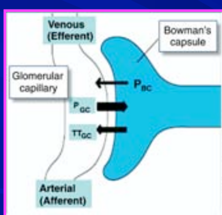
ROC Curves for CVP and CI on Admission for the Development of WRF



Mullens, W. et al. J Am Coll Cardiol 2009;53:589-596

JACC

Impact of Venous Congestion on Glomerular Net Filtration Pressure



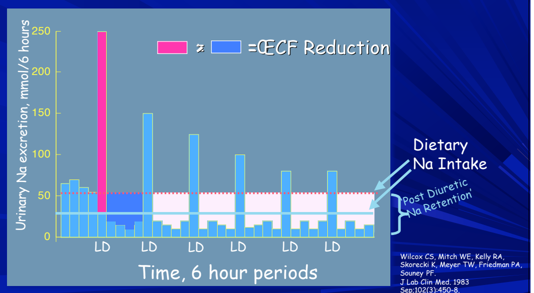
Forces	Normal: Afferent end of glomerular capillary (mmHg)	Normal: Efferent end of glomerular capillary (mmHg)	↑ RA pressure: Afferent end of glomerular capillary (mmHg)	↑ RA pressure: Efferent end of glomerular capillary (mmHg)
1. Favoring Filtration				
Glomerular-capillary hydrostatic pressure, P_{GC}	60	58	55	63
2. Opposing Filtration				
a. Hydrostatic pressure in Bowman's capsule, P_{BC}	15	15	15	15
b. Oncotic pressure in glomerular capillaries, π_{GC}	21	33	21	33
Net filtration pressure (1-2)	24	10	19	15
Filtration pressure:	*14 mmHg*		*4 mmHg*	

Jessup M and Costanzo MR. J Am Coll Cardiol 2009; 53:597-9

Causes of Diuretic Resistance

- Inadequate Dose
- Patient Non Compliance
  - Not taking drug
  - High NaCl Intake
- Poor Absorption
- Impaired Secretion
  - Chronic Kidney Disease
  - Old Age
  - Kidney Transplant
  - Chronic Heart Failure
  - Drugs
    - NSAIDs
    - Probenecid
- Proteinuria
- Hypoproteinemia
- Hypotension
- Drugs-Direct Inhibitors
  - NSAIDs
  - ACE/ARB **
- Diuretic Tolerance (Structural/Functional Adaptation)
- Neurohormonal Activation
- 'Cardiorenal Limit'

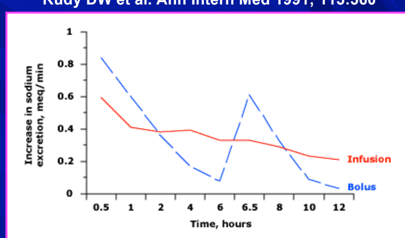
Excessive Dietary Sodium Intake



Wilcox CS, Mitch WE, Kelly RA, Skorecki K, Meyer TW, Friedman PA, Souney PF.
J Lab Clin Med. 1983 Sep;102(3):450-8.

IV Loop Diuretics: Bolus vs. Continuous Infusion

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

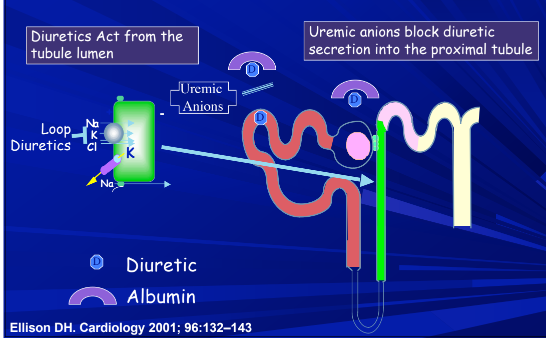


Metanalysis: Continuous Infusion Superior to Bolus Injection:

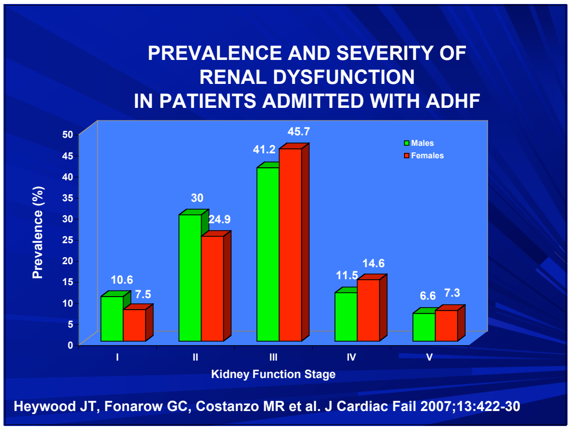
Total UO	P = 0.003
Increase in Sr. Creatinine	P < 0.00001
Length of Hospitaliization	P < 0.00001
All Cause Mortality	P = 0.00005

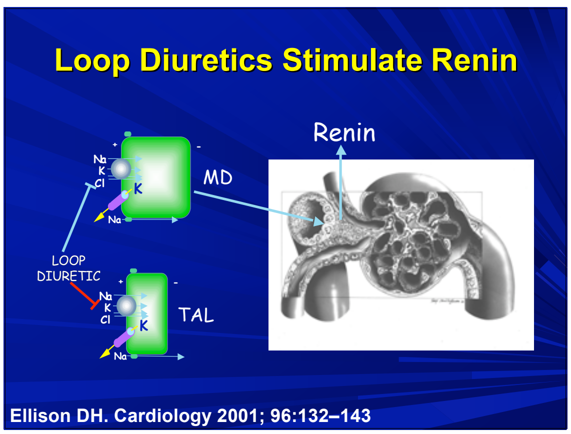
Salvador DRK et al. *The Cochrane Database of Systematic Reviews* 2005, Issue 3.
Art. No.: CD003178.pub3. DOI: 10.1002/14651858.CD003178.pub3.

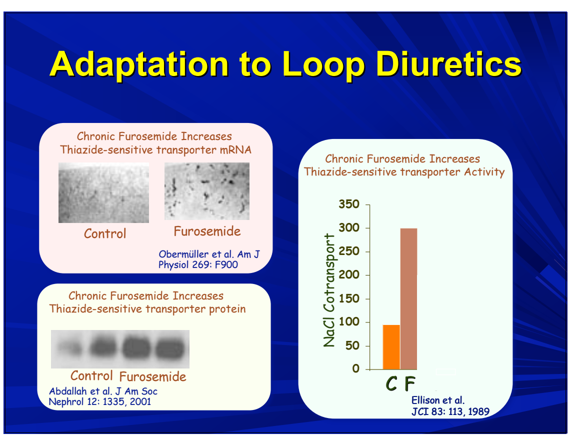
Diuretic Secretion Is Impaired in CKD



Ellison DH. Cardiology 2001; 96:132–143


PREVALENCE AND SEVERITY OF
RENAL DYSFUNCTION
IN PATIENTS ADMITTED WITH ADHF
Prevalence (%)
50
45
40
35
30
25
20
15
10
5
0
10.6
7.5
30
24.9
41.2
45.7
11.5
14.6
6.6
7.3
I
II
III
IV
V
Kidney Function Stage
Males
Females
Heywood JT, Fonarow GC, Costanzo MR et al. J Cardiac Fail 2007;13:422-30


Loop Diuretics Stimulate Renin
Renin
Na
K
Cl
K
Na
MD
LOOP
DIURETIC
Na
K
Cl
K
Na
TAL
Ellison DH. Cardiology 2001; 96:132–143

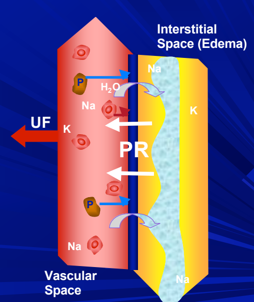

Adaptation to Loop Diuretics
Chronic Furosemide Increases
Thiazide-sensitive transporter mRNA
Control
Furosemide
Obermüller et al. Am J
Physiol 269: F900
Chronic Furosemide Increases
Thiazide-sensitive transporter protein
Control Furosemide
Abdallah et al. J Am Soc
Nephrol 12: 1335, 2001
Chronic Furosemide Increases
Thiazide-sensitive transporter Activity
NaCl Cotransport
350
300
250
200
150
100
50
0
C F
Ellison et al.
JCI 83: 113, 1989

Therapeutic Approaches

- Block Adaptive Processes
  - Post Diuretic Na Retention
    - Chronic infusion
    - Long-acting diuretics (thiazides, spironolactone)
  - Structural Adaptations
    - DCT diuretics (thiazides, spironolactone, ACEI/ARBs)
    - CD diuretics (spironolactone, ACEI/ARBs)
  - Neurohormonal Activation
    - ACE Inhibitors
    - Spironolactone
    - Beta blockers
    - Nesiritide
- Ultrafiltration

Fluid Removal by Ultrafiltration

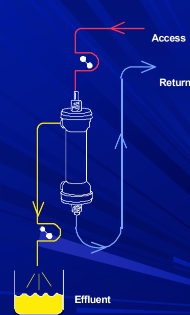
- Ultrafiltration can remove fluid from the blood at the same rate that fluid can be naturally recruited from the tissue
- The transient removal of blood elicits a compensatory mechanism, called *plasma* or *intravascular refill* (PR), aimed at minimizing this reduction[1,2]



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

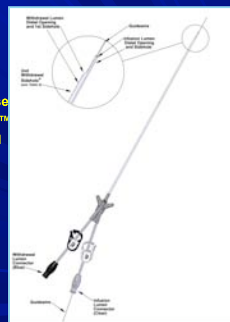
Simplified Veno-Venous Ultrafiltration

- **0.12 m2 polysulphone filter**
- **Blood flow adjustable (10-40 ml/minute)**
- **Total extracorporeal blood volume 33 ml**
- **Peripheral, midline, or central venous access**
- **Anticoagulation with heparin recommended**



dELC Overview

- **Name:** dELC
- **Length:** 20 cm
- **Size:** 6 French, reverse taper
- **Blood Flow:** 20-30 ml/min
- **Average UF rate:** ≤ 250cc/hour
- **Use:** Designed specifically for use with the Aquadex FlexFlow™
- **Features:** Minimizes recirculation and maximizes performance
- **More Info:** Dual lumen
  - Polyurethane
  - Radiopaque
  - Sterile by ethylene oxide
  - Non-pyrogenic
  - Single-use
  - Latex free
  - Female luer connectors
  - Offset tip with side holes



dELC Best Practices

- ***Blood flow*** **is 20-30 ml/min**. Decreased from 40 ml/min.
- ***Placement***:
  - insertion point **above the antecubital area.**
  - in the **basilic vein.**
  - **catheter tip should avoid the shoulder area**.
    - 1-2 cm below the shoulder, or
    - **midclavicular**
- Very obese or very edematous patients may be challenging.
- Catheter placement can be guided by ultrasound.
- Maintain catheter per hospital policy (e.g. heparin flush q 8)

Ultrafiltration versus IV Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure: A Prospective Randomized Clinical Trial

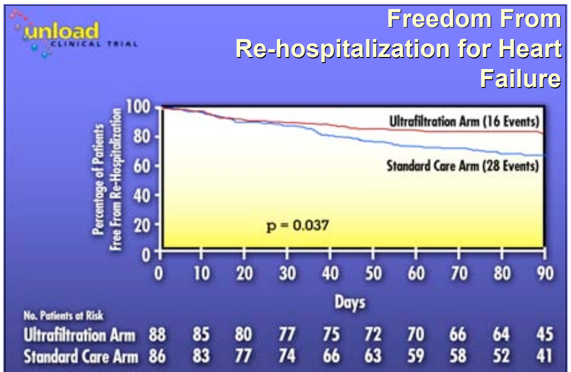
UNLOAD Trial

Principal Findings

- At 48 h after randomization early Ultrafiltration compared with IV Diuretics produces:
  - greater weight loss
    (5.0 ± 0.68 Kg vs. 3.1 ± 0.75 Kg; p= 0.001)
  - greater fluid loss
    (4.6 ± 0.29 L vs. 3.3 ± 0.29 L; p= 0.001)
  - similar changes in sCr
    (0.12 ± 0.42 mg/dL vs. 0.07 ± 0.41 mg/dl; p=0.356)

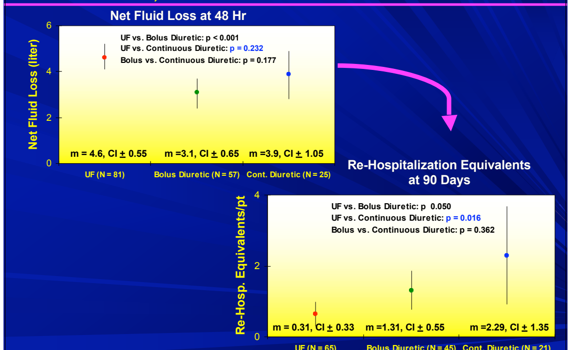
Costanzo MR, Guglin ME, Saltzberg MT et al. J Am Coll Cardiol 2007; 49:675-83

Freedom From Re-hospitalization for Heart Failure



Costanzo MR, Guglin ME, Saltzberg MT et al. J Am Coll Cardiol 2007; 49:675-83

Differential Oucomes after Ultrafiltation, Bolus IV Diuretics and Continuous IV Diuretics

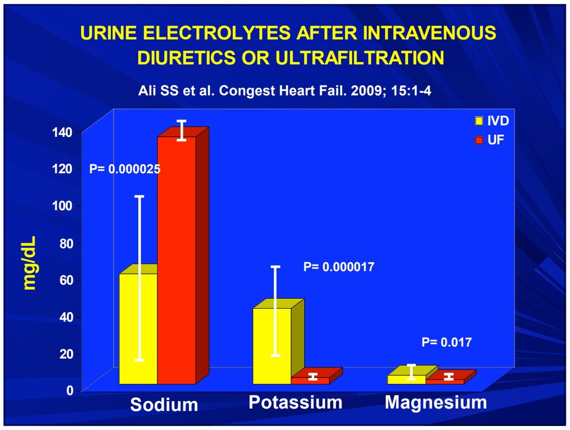


Costanzo MR et al. J Am Coll Cardiol 2007: 49 (Suppl.): 56 A

Enhanced Sodium Extraction with Ultrafiltration Compared to Intravenous Diuretics

- 15 hospitalized ADHF patients with presumed diuretic resistance and clinical evidence of volume overload.
- Urine electrolyte concentrations measured after a dose of IVD.
- UF was then begun and ultrafiltrate electrolyte concentrations were measured 8 hours later and compared to the initial urine values.

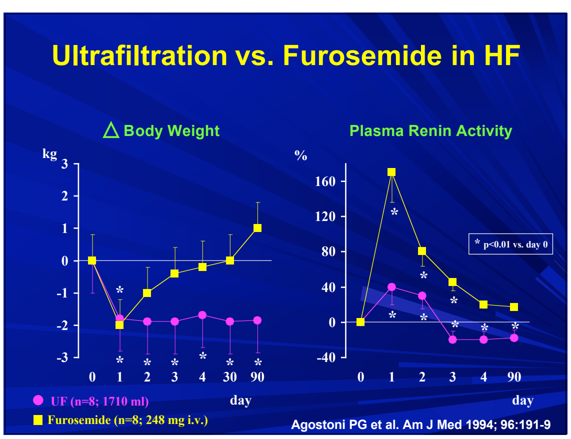
Ali SS et al. Congest Heart Fail. 2009; 15: 1-4



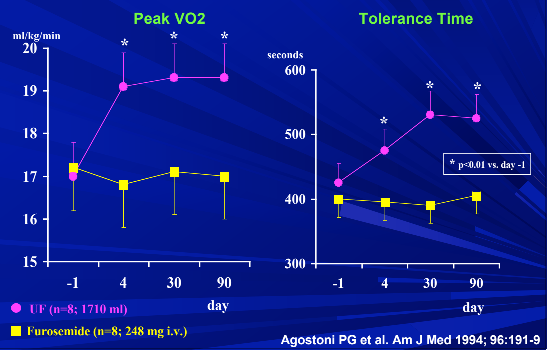
Sustained Improvement in Functional Capacity after Removal of Body Fluid with Isolated Ultrafiltration in Chronic Cardiac Insufficiency: Failure of Furosemide to Provide the Same Result

Agostoni P. et al. The American Journal of Medicine 1994; 96: 191-199

- 16 stable, NYHA II-III chronic HF patients matched by age, gender and peak VO_2
- Randomized to isolated ultrafiltration (500 cc/h) or IV furosemide
- Removal of the ***same amount of fluid*** in both arms (≈ 1,600 cc)
- Measurement of hemodynamics, peak VO_2, NE, PRA and Aldosterone at baseline, end of treatment and 3 months



Ultrafiltration vs. Furosemide in HF



Agostoni PG et al. Am J Med 1994; 96:191-9

Guidelines for the Use of UF in the Management of HF

Expert Group	Comment
ACC/AHA[1] Updated based upon UNLOAD data	Ultrafiltration is reasonable for patients with refractory congestion not responding to medical therapy (578). (Class IIa, Level of Evidence: B) If the degree of renal dysfunction is severe or if edema becomes resistant to treatment, ultrafiltration or hemofiltration may be needed to achieve adequate control of fluid retention. This can produce clinical benefits and may restore responsiveness to conventional doses of loop diuretics.
CCVS [2] Updated based upon UNLOAD data	In highly selected patients and under experienced supervision, intermittent slow continuous venovenous ultrafiltration may be considered.
ESC [3] Updated based upon UNLOAD data	Ultrafiltration should be considered to reduce fluid overload (pulmonary and/or peripheral oedema) in selected patients and correct hyponatremia in symptomatic patients refractory to diuretics. (Class of recommendation IIa, level of evidence: B)

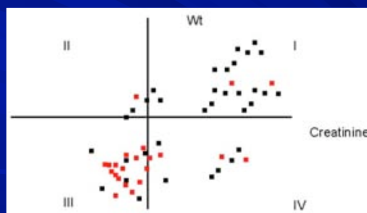
1. Jessup M. et al. J Am Coll Cardiol, 2009; 53(15):e1-e90
2. Howlett JG. et al. Can J Cardiol 2009;25(2):85-105.
3. Dickstein K. et al. Eur Heart J 2008; 29: 2388-2442

*CAR*diorenal *RES*cue Study in Acute Decompensated *H*eart *F*ailure (CARESS-HF)

- NIH Heart Failure Network trial
- Prospective, randomized trial
- 100 patients each arm
- Patient Population:
  - Patients hospitalized with ADHF will be eligible for enrollment if they develop cardiorenal syndrome (defined as an increase in sCr of ≥ 0.3 mg/dl from baseline) while demonstrating signs and symptoms of persistent congestion
- Primary endpoint
  - Change in sCr and weight together as a “bivariate” endpoint assessed at 96 hrs post enrollment
- Secondary Endpoint
  - PE assessed at days 1-3 and 7 days
  - Treatment failure, weight and fluid loss, clinical decongestion, peak sCr, change in electrolytes, LOS, biomarkers, change in diuretic doses all at various time points

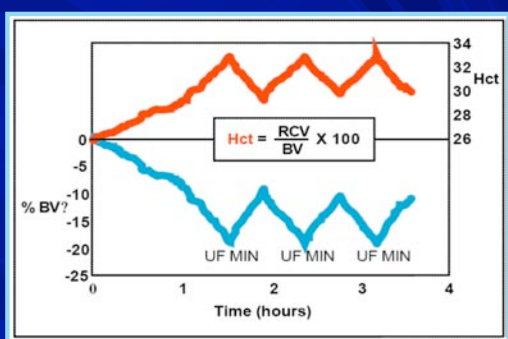
CARESS-HF Clinical Trial

- **Primary endpoint**
  - Change in sCr and weight together as a "bivariate" endpoint assessed at 96 hrs post enrollment

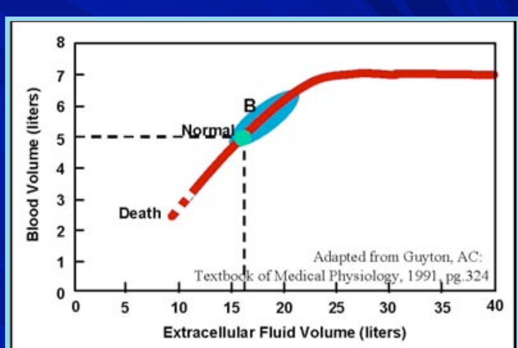


Red= Ultrafiltration
Black= Stepped Pharmacologic Care

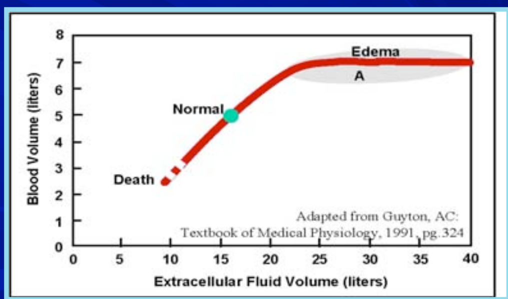
Hct Relative to BV



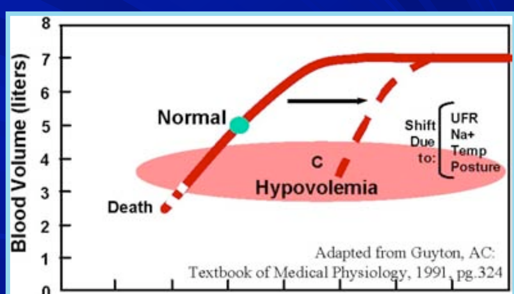
Intravascular Volume



Extracellular volume



Hypovolemia



Changes in Plasma Volume and Refilling Rate During UF

$\Delta PV = 100/(100 - Hct_{pre}) \times [100(Hct_{pre} - Hct_{post})]/Hct_{post}$

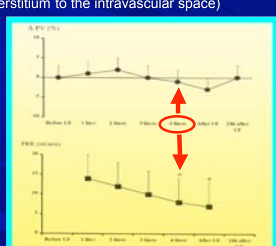
Where: ΔPV = Change in plasma volume

Hct_{pre} = Hematocrit before ultrafiltration

Hct_{post} = Hematocrit after ultrafiltration

PRR (ml/min) =Ultrafiltrate volume/Ultrafiltration time

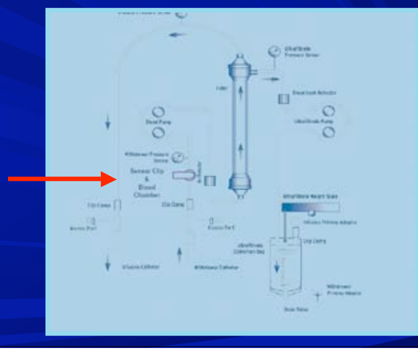
Where PRR= Plasma refilling rate (measurement of the fluid volume transported from the interstitium to the intravascular space)



Marenzi GC et al.

JACC 2001; 38: 963-968

Aquadex Circuit
Built in Blood Chamber



Crit-Sat Cable Connection with the Aquadex Device

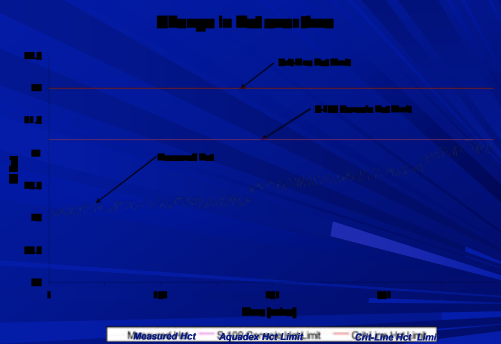
Aquadex/Crit-Sat

- Crit-Sat:
  - Attaches to the same cart as the Aquadex
  - Communicates with the Aquadex via a cable
- Aquadex:
  - Must have the revised software to recognize Crit-Sat input
  - Must use the A2000 circuit
    - Has in-line blood chamber

Aquadex with Crit-Sat

- ✓ Aquadex communicates with Crit-Sat
- ✓ Hct limits are set on both Aquadex and Crit-Sat
- ✓ Aquadex will stop UF pump if Hct limit is exceeded (Aquadex limit)-No alarm will sound
- ✓ Alarm will sound if Hct limit is exceeded on Crit-Sat (Fail safe mechanism)
- ✓ The safest method is to set the Aquadex limit lower than the Crit-Sat limit

Hct Settings



Remaining Questions

- Optimal ultrafiltration rates and duration
- Effects on cardiac remodeling
- Effects on Mortality
- Outpatient use

Cardiorenal Syndrome (CRS) General Definition:
A pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ

CRS Type I (Acute Cardiorenal Syndrome)
Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury

CRS Type II (Chronic Cardiorenal Syndrome)
Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease

CRS Type III (Acute Renocardiac Syndrome)
Abrupt worsening of renal function (e.g. acute kidney ischaemia or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia)

CRS Type IV (Chronic Renocardiac Syndrome)
Chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events

CRS Type V (Secondary Cardiorenal Syndrome)
Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

Ronco C et al. J Am Coll Cardiol 2008; 52: 1527-39

Managing Volume Overload in Acute Decompensated Heart Failure - *Conclusions* -

- Optimal volume management in ADHF requires in depth knowledge of the mechanisms leading to salt and water retention *despite* hypervolemia.
- Apart from intrinsic renal insufficiency, *venous congestion*, rather than reduced CO, may be the primary hemodynamic factor driving WRF in ADHF pts.
- Loop diuretics reduce congestion, but their *effectiveness is reduced* by excess salt intake, underlying CKD, renal adaptation to diuretics and neurohormonal activation
- Compared with removal of hypotonic fluid with diuretics, withdrawal of *isotonic fluid* with ultrafiltration may result in enhanced sodium extraction, lesser neurohormonal activation, and improved outcomes
- A consensus definition of the *cardiorenal syndrome* may help to design RCTs aimed at identifying pathophysiologically sound interventions targeting specific patient populations