

Overcoming the Cardiorenal Syndrome

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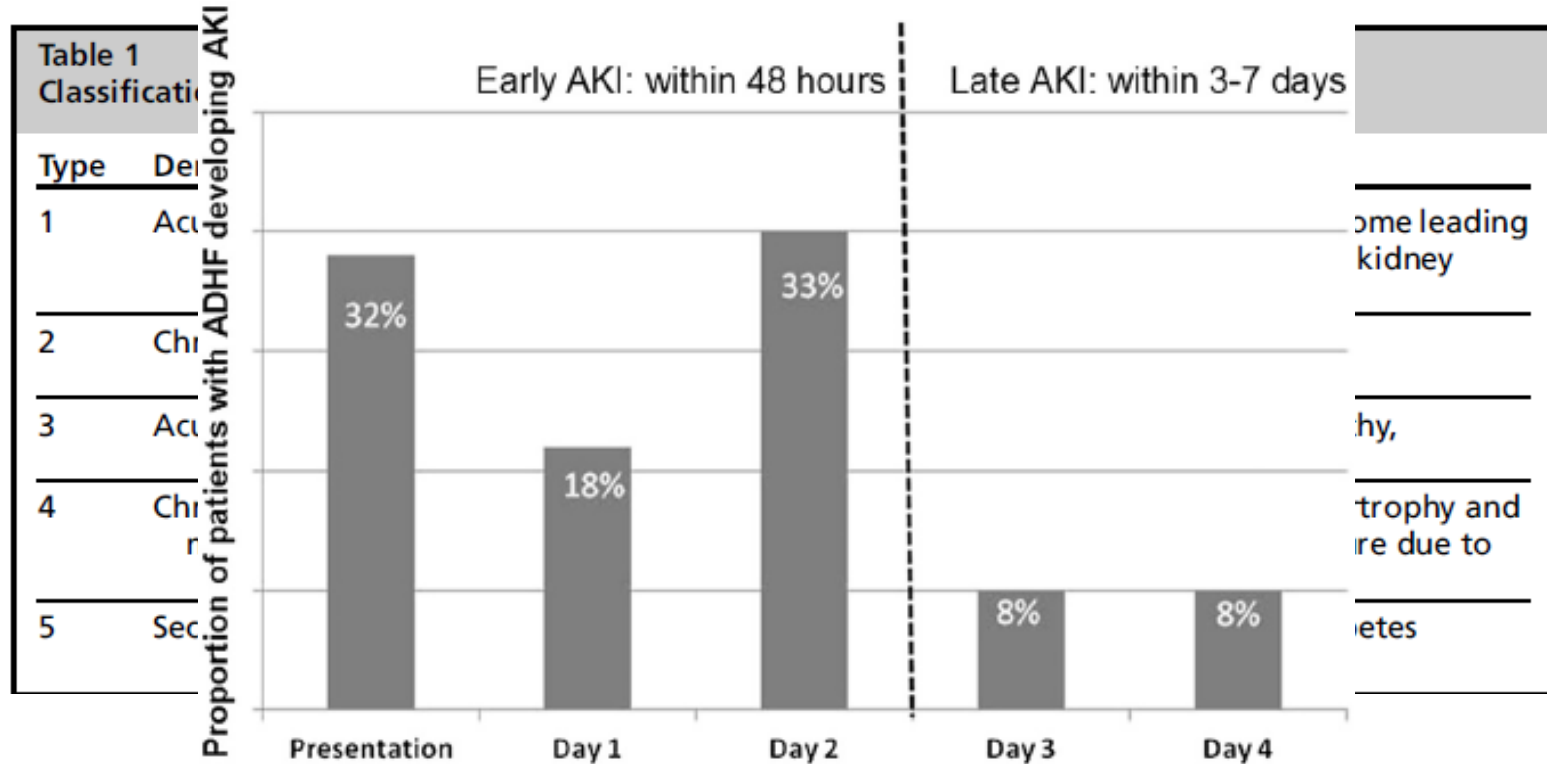
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Overcoming the Cardiorenal Syndrome

- Definitions
- Pathophysiology
- Tactics to manage



Classification of Cardio-Renal Syndrome



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



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Ronco C et al. J ACC 2008;52;1527-1539

Cardio-Renal Syndrome

from a cardiology perspective

- CRS Type 1
 - Acute heart failure leading to AKI/WRF
 - Acute MI, cardiogenic shock, ADHF
- CRS Type 2
 - Chronic heart failure leading to CKD
- CRS Type 5
 - Systemic disease (diabetes, hypertension, atherosclerosis) leading to heart and renal failure

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



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Cardio-Renal Syndrome Type 4

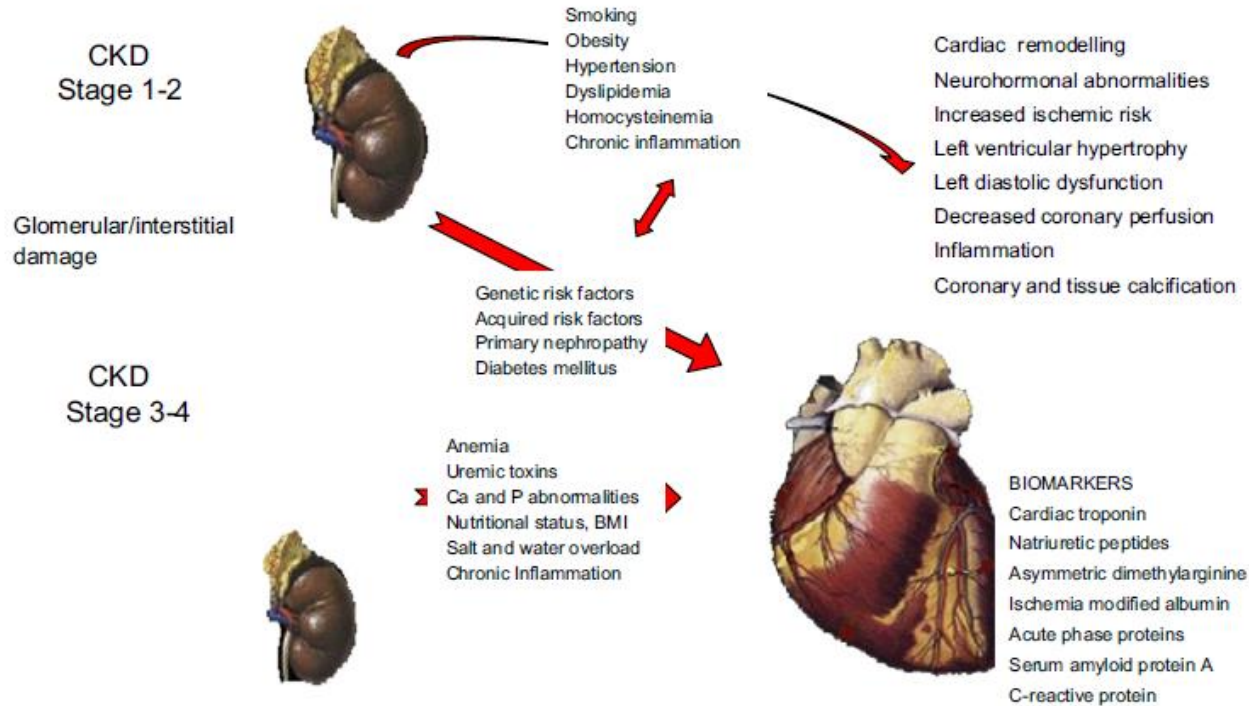


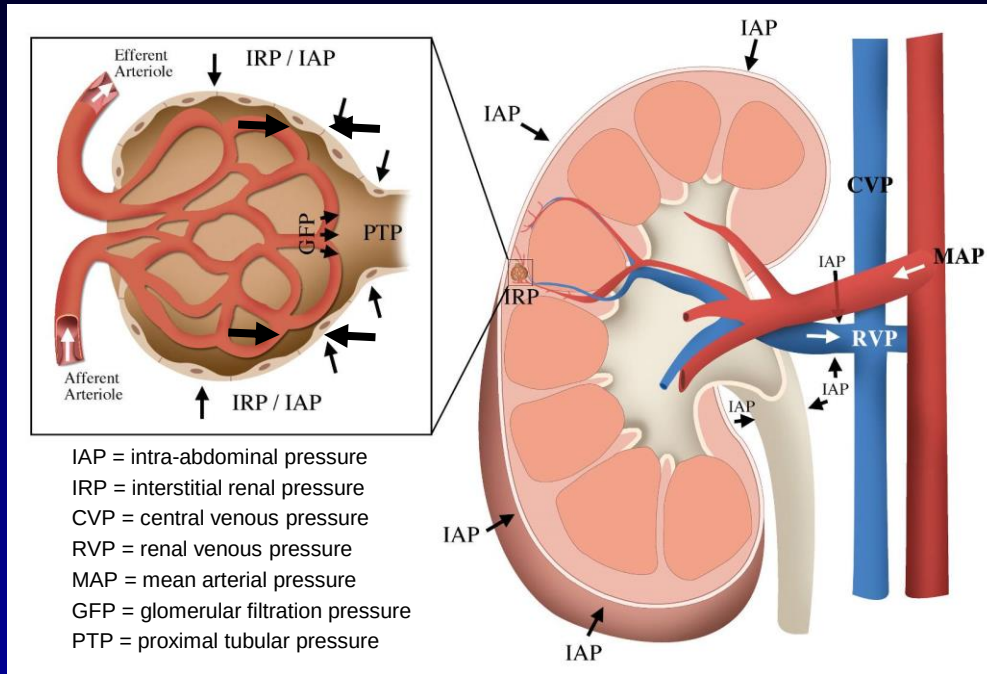
Fig. 6. Pathophysiology of CRS type 4. BMI, body mass index.

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

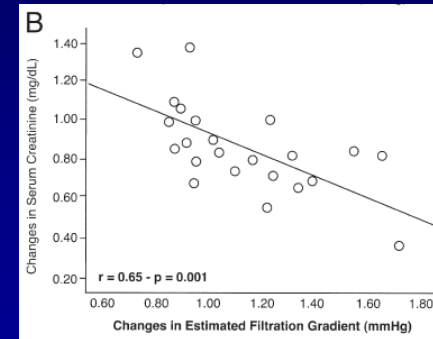


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Multi-Factorial Impact of Venous Congestion and Arteriolar Resistance on Renal Function



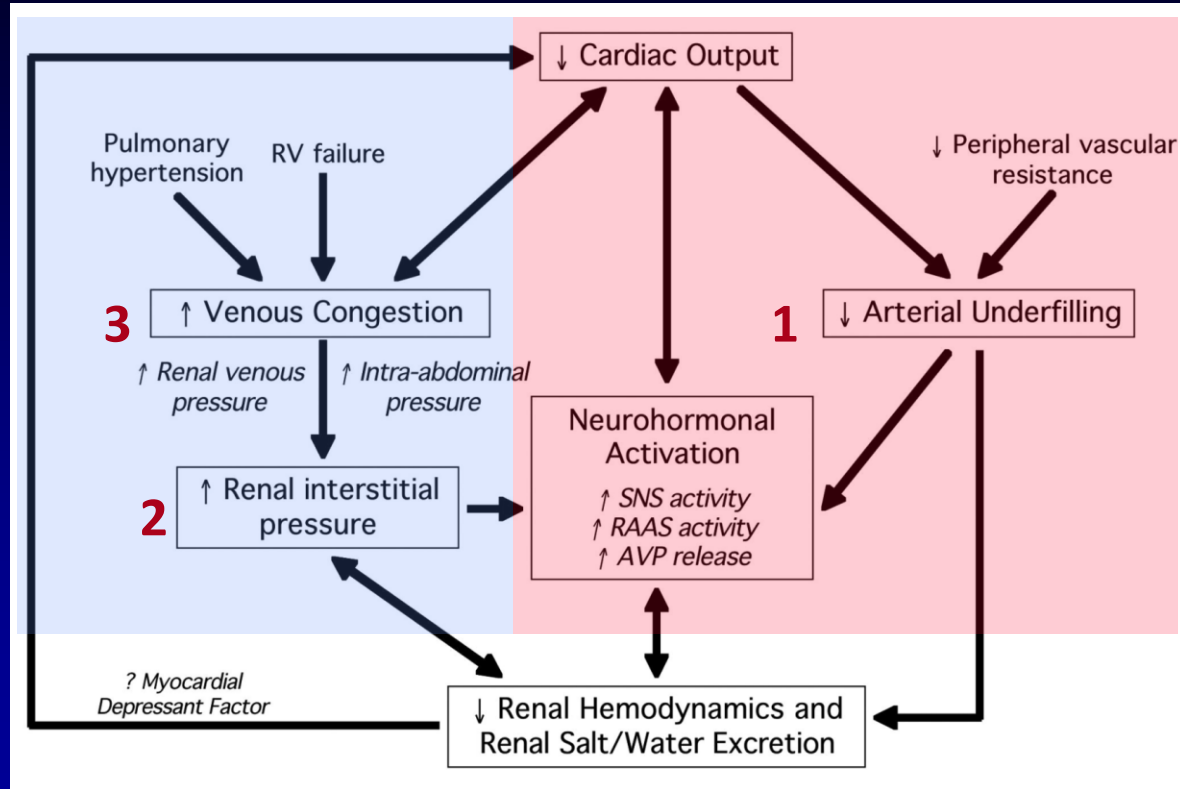
Renal
Filtration
Gradient:
 $GFP - PTP$



Dupont et al, *Curr Heart Fail Rep* 2011

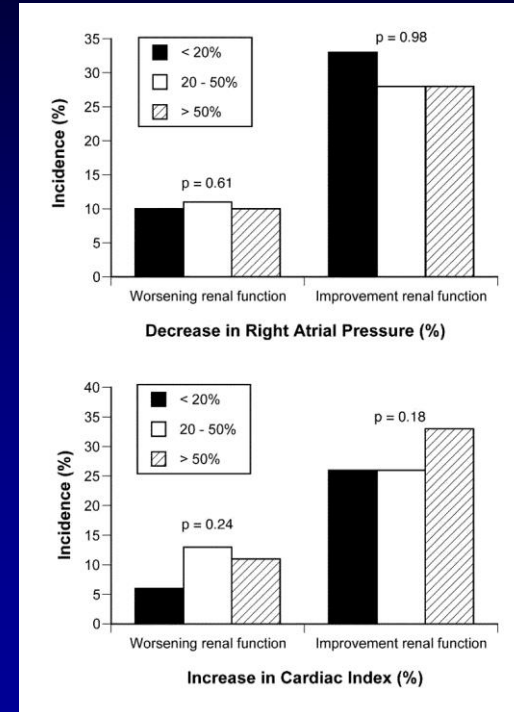
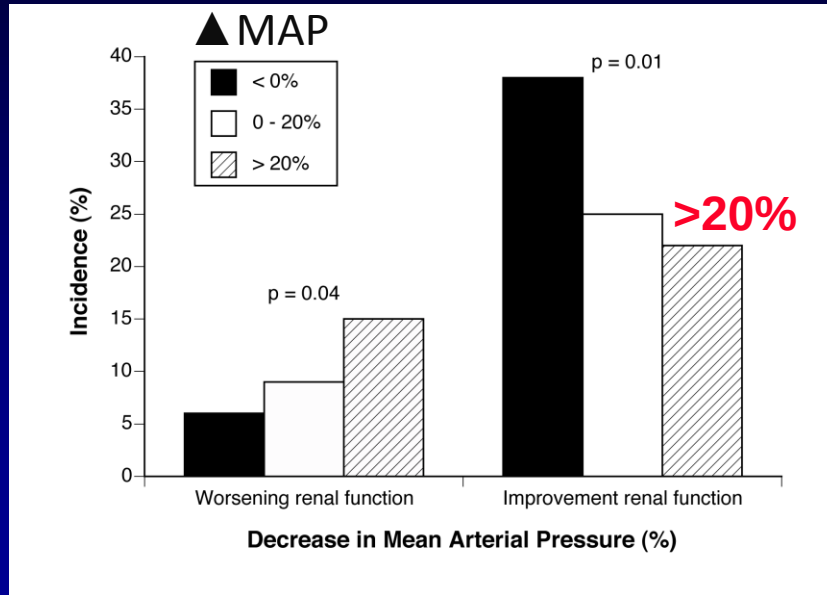
Mullens W et al *JACC* 2008;51:300-6.

Complex Interplay Cardiorenal Syndrome



Decreases in Mean Arterial Pressure rather than Changes in Central Hemodynamics Portend Cardiorenal Syndrome

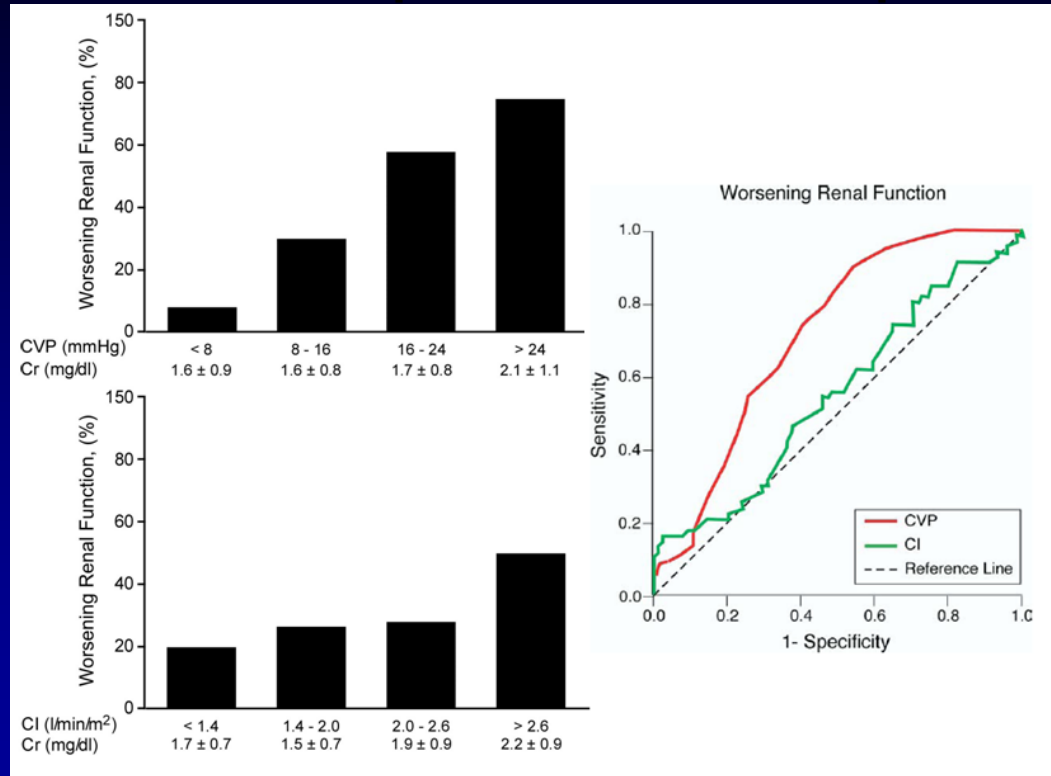
dynamics in hospital



Venous Congestion and Renal Function in Acute Systolic HF: measured on presentation to hospital

CVP but NOT
Cardiac Index
Predictive of
WRF

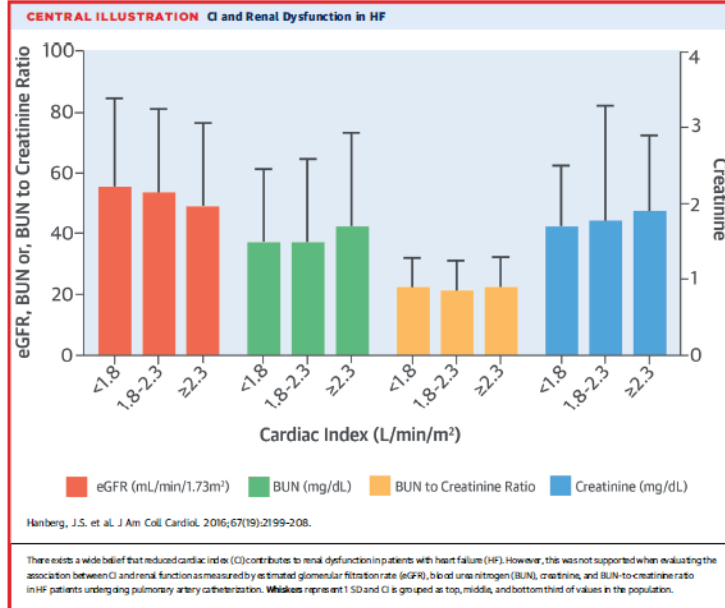
CVP 18.7 WRF vs 12.6
 $p < 0.001$



Reduced Cardiac Index Is Not the Dominant Driver of Renal Dysfunction in Heart Failure



Jennifer S. Hanberg, BA,^a Krishna Sury, MD,^b F. Perry Wilson, MD, MSCE,^{a,b,c} Meredith A. Brisco, MD, MSCE,^d Tariq Ahmad, MD, MPH,^b Joeline M. ter Maaten, MD,^e J. Samuel Broughton, BS,^a Mahlet Assefa, BS,^a W.H. Wilson Tang, MD,^f Chirag R. Parikh, MD, PhD,^{a,b,c} Jeffrey M. Testani, MD, MTR^{a,b}



PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The severity of renal dysfunction in hospitalized patients with heart failure does not correlate with reduced cardiac index.

TRANSLATIONAL OUTLOOK: Additional research is necessary to elucidate the factors responsible for the renal impairment that commonly occurs in patients with heart failure.

J Am Coll Cardiol 2016;67:2199-208.



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Failed Trials to Preserve Renal Function and Improve Diuresis

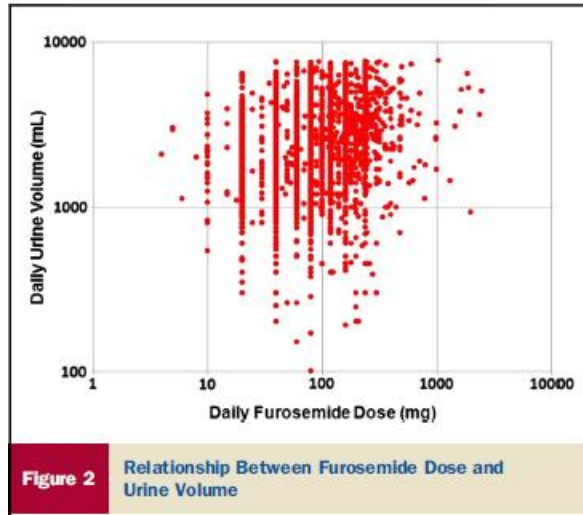
- Nesiritide ASCEND HF
- Ultrafiltration CARRESS
- Dopamine ROSE, DAD HF II
- Rolofylline PROTECT
- Serelaxin RELAX AHF
- Tolvaptan TACTICS- HF



Effects of Nesiritide and Predictors of Urine Output in Acute Decompensated Heart Failure

Results From ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure)

Stephen S. Gottlieb, MD,* Amanda Stebbins, MS,† Adriaan A. Voors, MD, PhD,‡
Vic Hasselblad, PhD,† Justin A. Ezekowitz, MBCh, MSc,§ Robert M. Califf, MD,||
Christopher M. O'Connor, MD,† Randall C. Starling, MD, MPH,¶ Adrian F. Hernandez, MD, MHS†
*Baltimore, Maryland; Durham, North Carolina; Groningen, the Netherlands; Edmonton, Alberta, Canada;
and Cleveland, Ohio*
(J Am Coll Cardiol 2013;62:1177-83)



Spearman correlation 0.154 ($p < 0.0001$)

Nesiritide did NOT lead to increased urine output

Factors Affecting ability to diurese

- Dose of diuretic
- Sicker patients more refractory
- BUN more predictive than cr
- Lower diastolic BP impairs

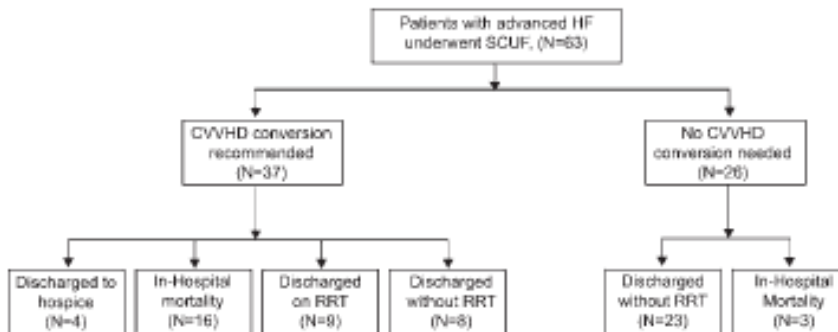


Cardiorenal Outcomes After Slow Continuous Ultrafiltration Therapy in Refractory Patients With Advanced Decompensated Heart Failure

Maria Patarroyo, MD,* Edgard Wehbe, MD,† Mazen Hanna, MD,* David O. Taylor, MD,* Randall C. Starling, MD, MPH,* Sevag Demirjian, MD,† W. H. Wilson Tang, MD*

Cleveland, Ohio

J Am Coll Cardiol. 2012 Nov 6;60(19):1906-12.



**59% in hosp RRT
14% home RRT
30% mortality**

EDITORIAL COMMENT

Ultrafiltration in End-Stage Heart Failure

Too Little, Too Late?*

Larry A. Weinrauch, MD,††
Akshay S. Desai, MD, MPH,‡
Eldrin F. Lewis, MD, MPH,‡
John A. D'Elia, MD†

Boston, Massachusetts

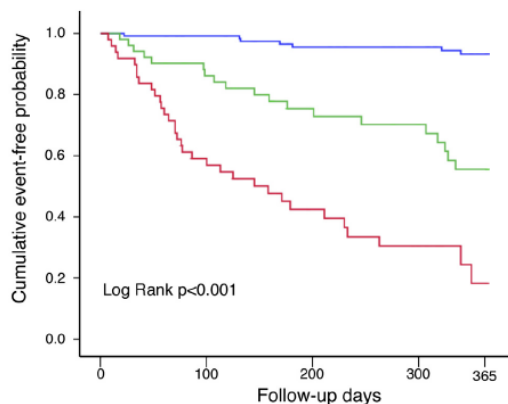


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Clinical Implications of Intrarenal Hemodynamic Evaluation by Doppler Ultrasonography in Heart Failure

FIGURE 2 Kaplan-Meier Estimate Curves According to IRVF



Number at risk

Continuous flow	117	115	109	104	93
Biphasic flow	51	42	28	23	16
Monophasic flow	49	28	18	11	5

Kaplan-Meier curves at 1-year follow-up for the probability of freedom from death from cardiac causes and unplanned hospitalizations for heart failure of 3 classifications of intrarenal venous flow. IRVF = intrarenal venous flow.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Intrarenal Doppler ultrasonography is a useful method for assessing intrarenal hemodynamics in patients with heart failure. In particular, intrarenal venous flow may be associated with exacerbating factors of HF including renal congestion.

TRANSLATIONAL OUTLOOK: The pathophysiological determinants of IRD profiles should be investigated through clinical and basic research to make IRD a guide for HF therapy.

J Am Coll Cardiol HF 2016;4:674-82.



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Strategies to Overcome Cardiorenal Syndrome

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



Summary

- Current approach with diuretics associated with WRF, neurohormonal activation, increased mortality and readmission rate
- Lack of response to diuretics independently predicts adverse outcomes
- Better methods to assess “diuretic efficiency” needed
- Diuretic resistance is multifactorial, related to intrinsic renal substrate, physiology, age and comorbidities
- Mechanical strategies not superior to diuretics; UF may be harmful
- Methods to improve diuresis and avoid diuretic resistance and overcome CRS remain an unmet need



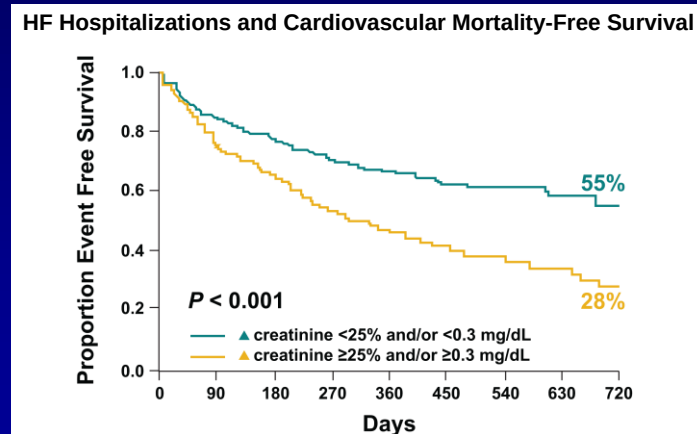
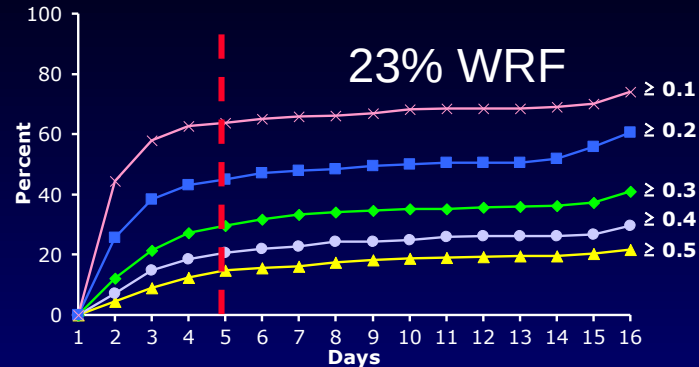
Back Up Slides



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“Worsening Renal Function”

- Serum creatinine $\uparrow \geq 0.3$ mg/dL:
- In-hospital mortality:
 - Sensitivity of 65%
 - Specificity of 81%
- 2.3 days $\uparrow$ length of stay
- 67% $\uparrow$ risk of death within 6 months after discharge
- 33% $\uparrow$ risk for readmission
- **Risk factors:**
 - Co-morbidities (diabetes)
 - Age
 - CKD (admit Cr >2.5 mg/dL)
 - Nephrotoxic drugs



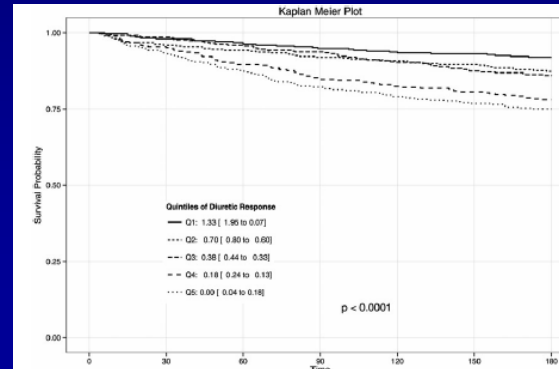
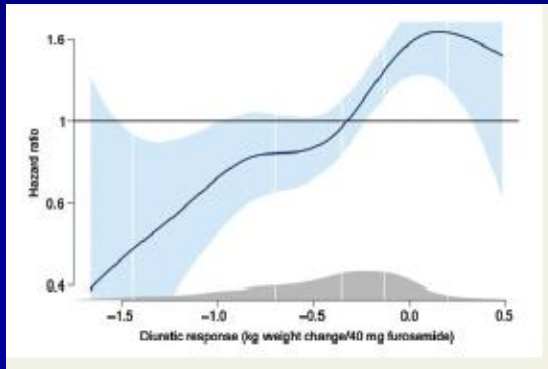
Krumholz et al, *Am J Cardiol* 2000; Smith et al, *J Card Fail* 2003; Gottlieb et al, *J Card Fail* 2002; Metra et al, *Eur J Heart Fail* 2007
 Damman K et al, *Eur Heart J* (2014) 35 (7): 455-469.

Diuretic response in acute heart failure: clinical characteristics and prognostic significance

Mattia A. E. Valente¹, Adriaan A. Voors^{1*}, Kevin Damman¹, Dirk J. Van Veldhuisen¹, Barrie M. Massie², Christopher M. O'Connor³, Marco Metra⁴, Piotr Ponikowski⁵, John R. Teerlink², Gad Cotter⁶, Beth Davison⁶, John G.F. Cleland⁷, Michael M. Givertz⁸, Daniel M. Bloomfield⁹, Mona Fiuzat³, Howard C. Dittrich¹⁰, and Hans L. Hillege^{1,11}

Am Heart J 2015;170(2):313-21.

- Diuretic response: ▲ weight kg/ 40 mg furosemide
- Median response -0.38 kg/40 mg furosemide
- Poor response: diabetes, low SBP, ↑ Bun, ASCVD
- Worse response predicted mortality and morbidity

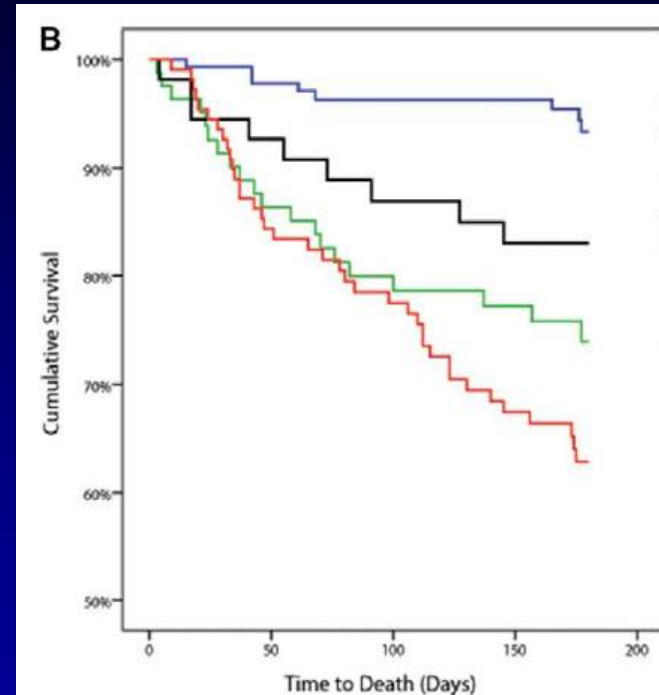


Loop Diuretic Efficiency

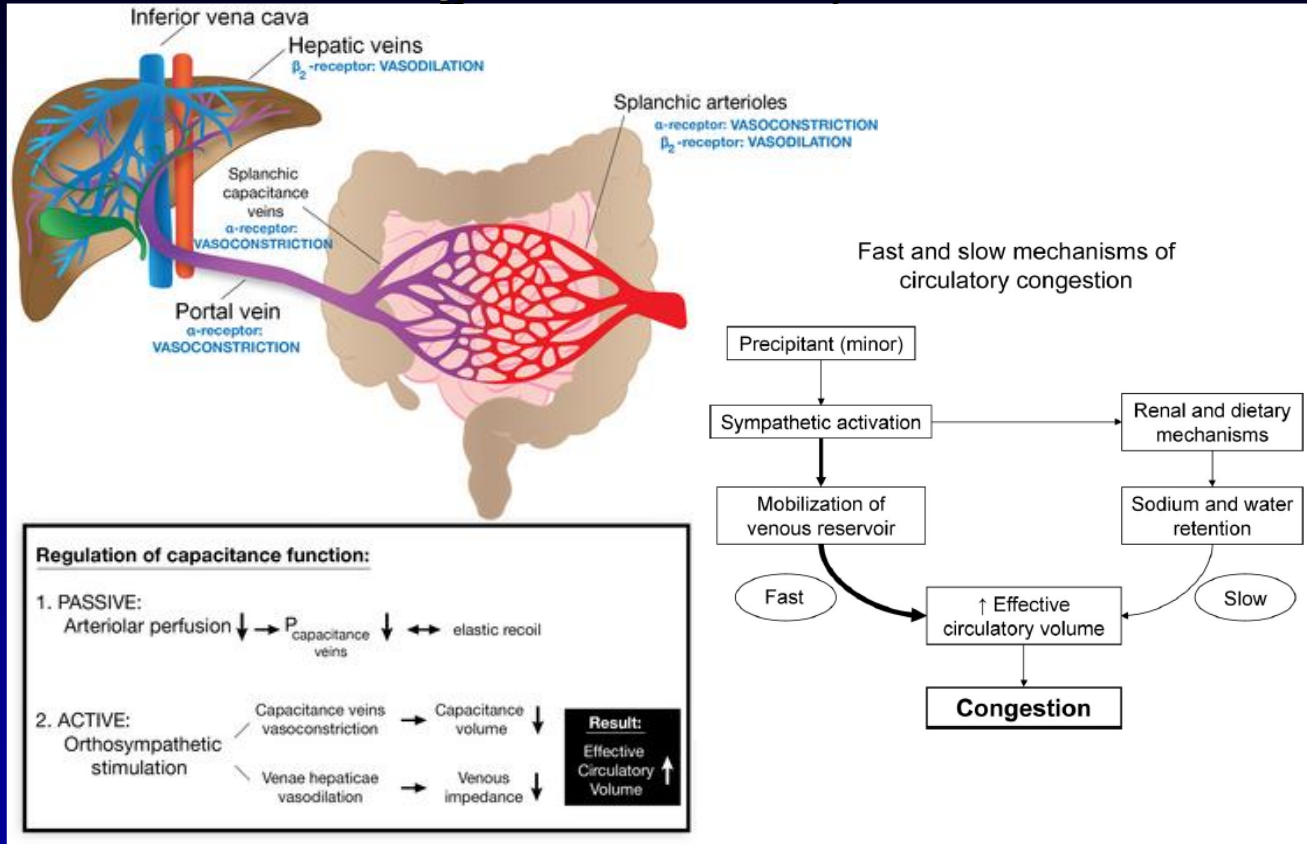
A Metric of Diuretic Responsiveness With Prognostic Importance in Acute Decompensated Heart Failure

Jeffrey M. Testani, MD, MTR; Meredith A. Brisco, MD, MSCE; Jeffrey M. Turner, MD;
Erica S. Spatz, MD, MHS; Lavanya Bellumkonda, MD; Chirag R. Parikh, MD, PhD;
W.H. Wilson Tang, MD

- Diuretic efficiency (DE) was estimated as the net fluid output produced per 40 mg of furosemide equivalents
- moderate correlation between DE and both intravenous diuretic dose and net fluid output ($r^2 \leq 0.26$)
- low DE during decongestive therapy portends poorer long-term outcomes in patients hospitalized with decompensated heart failure



Abdominal Contribution to Cardio-Renal Dysfunction: right heart failure, TR



Diuretic Resistance....mechanisms?

- Decreased GFR
- Increased activation of RAAS
- Hypertrophy of distal tubule epithelial cells
- Decreased intestinal absorption of drug
- Altered pharmacokinetics;
 - impaired concentration of drug in renal tubule



Hypertonic saline with furosemide for the treatment of acute congestive heart failure: A systematic review and meta-analysis[☆]

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^b Sunnybrook Health Sciences Centre, Division of Cardiology, University of Toronto, ON, Canada

^c Trinity College, Dublin, Ireland

International Journal of Cardiology 173 (2014) 139–145

Conclusion: The results of this meta-analysis demonstrate that in patients with advanced CHF concomitant hypertonic saline administration improved weight loss, preserved renal function, and decreased length of hospitalization, mortality and heart failure rehospitalization. A future adequately powered, multi-centre, placebo controlled, randomized, double dummy, blinded trial is needed to assess the benefit of hypertonic saline in patients with renal dysfunction, in diverse patient populations, as well using a patient population on optimal current heart failure treatment. Pending further validation, there is promise for hypertonic saline as an advanced therapy for the management of acute advanced CHF.

- Potential benefit
- Need for a future adequately designed clinical trial

