Management Strategies in Cardio-Renal Syndromes

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Cardio-Renal Syndromes

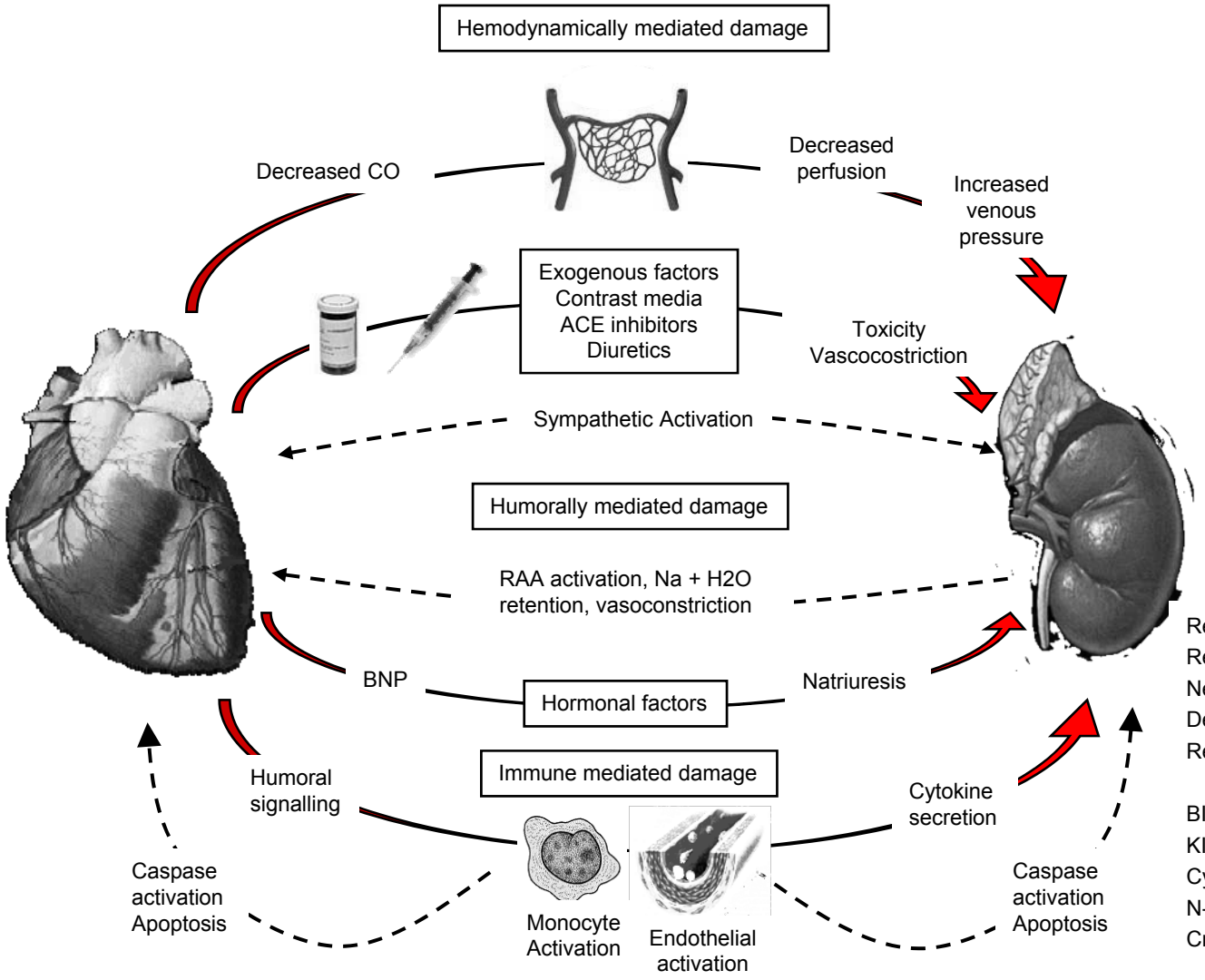
- Recently, ADQI Consensus conference defined 5 subtypes of Cardio-Renal Syndromes

Cardio-Renal Syndromes (CRS) General Definition: Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other
Acute Cardio-Renal Syndrome (Type 1) Acute worsening of cardiac function leading to renal dysfunction
Chronic Cardio-Renal Syndrome (Type 2) Chronic abnormalities in cardiac function leading to renal dysfunction
Acute Reno-Cardiac Syndrome (Type 3) Acute worsening of renal function causing cardiac dysfunction
Chronic Reno-Cardiac Syndrome (Type 4) Chronic abnormalities in renal function leading to cardiac disease
Secondary Cardio-Renal Syndromes (Type 5) Systemic conditions causing simultaneous dysfunction of the heart and kidney

Acute CRS (Type I)

- This presentation will focus on prevention and management of Acute CRS
- Arguably one of the most clinically vexing and challenging to manage
- Worsening renal failure (WRF, defined as an acute rise of >0.3 mg/dL of serum creatinine) during the management of acute decompensated heart failure (ADHF) portends a worse prognosis
- Higher risk of mortality and readmission for CHF

CARDIORENAL SYNDROME: TYPE 1



Acute Heart Disease or Procedures

Acute decompensation
Ischemic insult
Coronary angiography
Cardiac surgery

Acute Kidney Injury

Renal hypoperfusion
Reduced oxygen delivery
Necrosis / apoptosis
Decreased GFR
Resistance to ANP/BNP

BIOMARKERS
KIM-1
Cystatin-C
N-GAL
Creatinine

Adapted from Ronco C, Haapio M, House AA et al, J Am Coll Cardiol. 2008; 52(19):1527-39

Overview on Management of CRS Type I (Acute CRS)

- General management (empiric)
- Preventative novel drug therapies
- Extracorporeal strategies
- Devices (electrophysiologic, augmentative)
- Transplant

Who are the patients with Acute CRS?

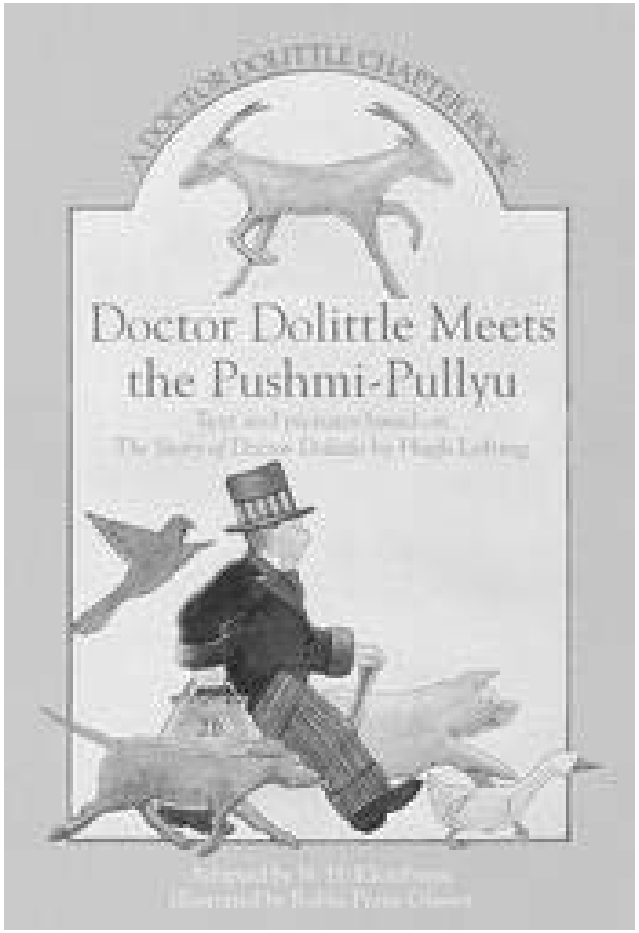
- The patient admitted with worsening symptoms of congestive heart failure where treatment is limited by diuretic resistance or complicated by WRF
- The patient with myocardial infarction and cardiogenic shock who develops oliguria
- The CHF patient who develops a volume-contracting illness while on RAAS blockade and subsequent AKI
- The patient with preserved LV systolic function presents with hypertension, pulmonary edema and while in hospital develops WRF
- The patient with isolated right heart failure presents with no respiratory symptoms, but poor forward output and significant hepatic and venous congestion, WRF

Appearance of WRF

- During management of ADHF, one may see oliguria and/or WRF for a variety of potentially “fixable” causes:
  - Due to decreased cardiac output or rapidly decreasing effective circulating volume
  - Increased venous pressure leading to renal venous congestion
  - Increased intra-abdominal pressure
  - Persistent renal vasoconstriction from tubuloglomerular feedback, vasoactive substances (adenosine, endothelin)
  - Decreased renal responsiveness to natriuretic peptides
  - Impaired autoregulation of GFR (RAAS blockade)
- Diuretic resistance is multifactorial
  - Decreased delivery to tubules due to decreased renal blood flow, decreased GFR, hypoalbuminemia
  - Diuretic “braking” due to enhanced sodium reabsorption, distal tubular hypertrophy

General management

- Accurate volume assessment
  - Assess for signs of increased venous pressure, decreased cardiac output or both
  - Studies are suggesting that increased venous pressure is more predictive than baseline hemodynamics
- Coordinated efforts between cardiology and nephrology to avoid the “Pushmi-Pullyu” strategy of volume management
- Appropriate oxygenation +/- PPV
- Pain/distress relieved with morphine
- Specific management for ACS, arrhythmia, tamponade, dissection, pulmonary embolus, thyrotoxicosis, etc.



Other General Measures

- Angiotensin blockade interferes with the autoregulation of GFR and may need to be withheld if renal function continues to deteriorate
- Avoidance of other agents which interfere with renal sodium handling (e.g. NSAIDs, Coxibs, Thiazolidinediones) or potentially nephrotoxic (e.g. contrast)
- Serum potassium may also limit continued use of RAAS blockade or K-sparing diuretics

PA catheter guided therapy

- Mullens W (JACC 2009) used a protocol driven approach using PA catheters in 145 subjects with ADHF
  - Targeted PCWP≤18, CVP ≤8, CI≥2.4L/min/m^2 and MAP >65-70 mmHg using IV diuretics, vasodilators, inotropes
  - added ACE/ARB, beta blockers, aldosterone antagonists where tolerated
  - Mean EF 20%, and WRF in 40%
  - Predictors were higher baseline creatinine and high baseline CVP
  - 75% with CVP>24 developed WRF
  - Baseline cardiac index was *higher*, not lower, in those developing WRF
- Nohria A (JACC 2008) presented a post hoc analysis of ESCAPE trial (RCT of PAC vs clinical in 433 subjects)
  - No clinical or mortality advantage to use of PAC
  - Right atrial pressure correlated more with renal function than did baseline CI, PCWP
  - PAC guided management had less adverse effect on delta creatinine, but proportion with pre-defined WRF similar (26 vs 33%, p=0.18)

Diuretics – the double-edged sword

- Effective at reducing pulmonary congestive symptoms and decreasing venous congestion; in many instances renal function improves
- Goal should be to deplete ECF at a rate that allows extravascular refilling
- Potentially aggravate electrolyte imbalances, contract effective circulating volume, may contribute to neurohormonal responses

Diuretics – largely unstudied

- No trials in acute heart failure
- Faris RF (Cochrane 2006) examined diuretics (excluding RALES & EPHESUS) for stable CHF
  - Decreased mortality, decreased admission for CHF, increased exercise capacity
- Salvador DR (Cochrane 2004) examined in-hospital use of bolus versus continuous infusion
  - Greater urine output with continuous infusion
  - Less problems with hearing loss or tinnitus
  - ?Better survival and improved length of stay
- DOSE-AHF to examine optimal furosemide use in ADHF
  - Enrolling 300 patients in 2X2 factorial design
  - High dose versus low dose, infusion versus bolus
  - Evaluating change in creatinine and patient symptoms

Vasodilators

- Intravenous nitrates (venodilation) or nitroprusside (preload and afterload reduction) are used when SBP >110, with caution if 90-110
  - Nitroprusside avoided with renal dysfunction due to thiocyanate toxicity
  - Extreme caution in patients with aortic stenosis
- Nesiritide (recombinant BNP) has an unclear role due to potential worsening of AKI
  - Increases stroke volume and cardiac output
  - At low doses increases diuretic responsiveness
  - Higher doses leads to significant hypotension and possibly worsen AKI

Nesiritide

- Aaronson KD and Sackner-Bernstein J (JAMA 2006) analyzed 3 pivotal studies of nesiritide for ADHF in 862 randomized subjects
  - Crude 30-day mortality 7.6% for nesiritide vs 4.0% for control
  - Adjusted hazard ratio 1.93 (95% CI 1.06-3.52, p=0.03)
- These authors (Circulation 2005) and others have suggested that nesiritide may also worsen kidney function
  - Hazard ratio for WRF 1.54 (95% CI 1.19-1.98; P=0.001).
- Subsequent meta-analyses with greater numbers of trials have been conflicting
- Studies in cardiac surgery with lower doses seem to be better tolerated
- ASCEND-HF is a 7000-patient multi-center study designed to answer these questions in patients with ADHF

Inotropes

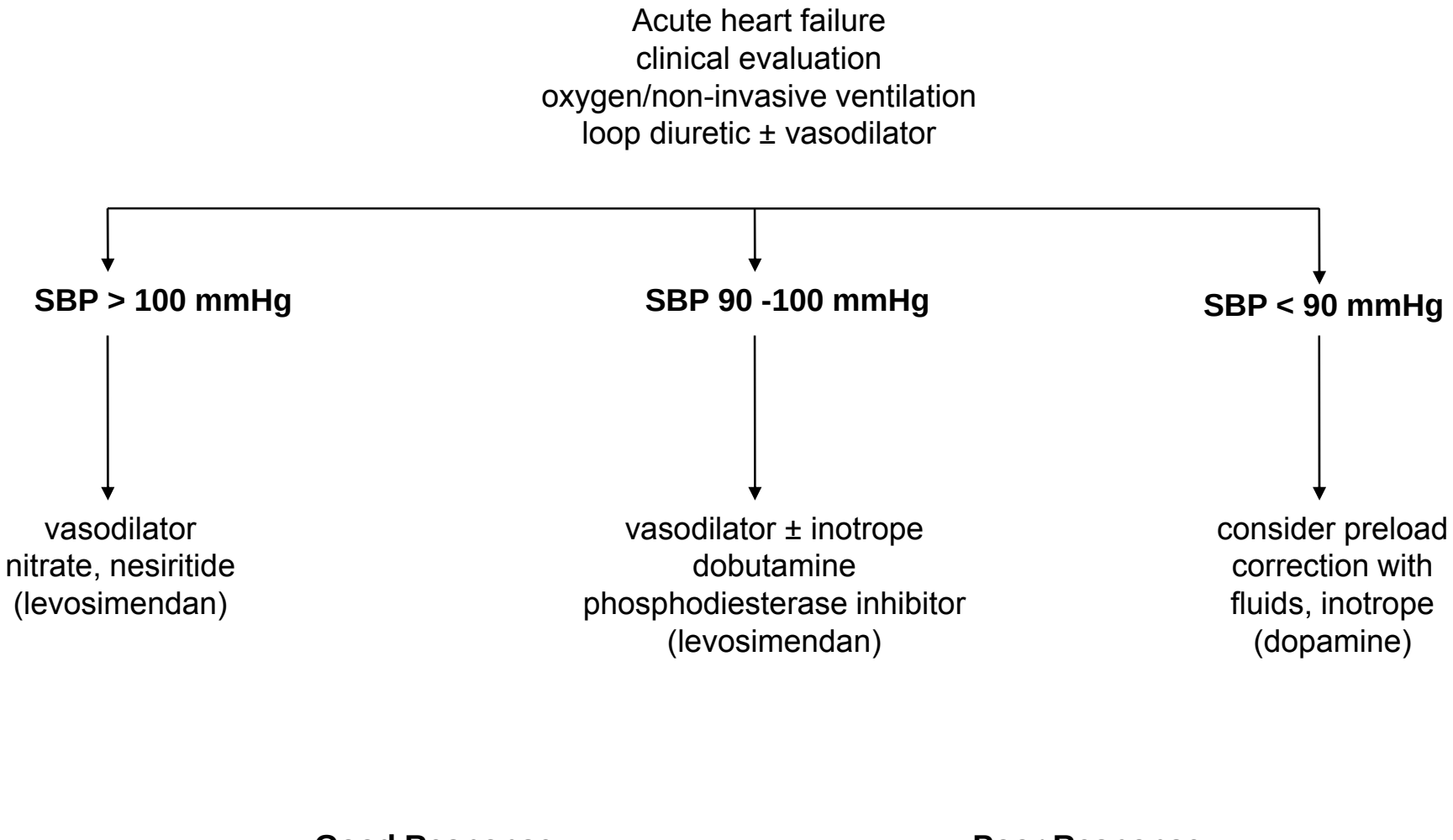
- Patients with low BP or CI, ongoing organ hypoperfusion or congestion
- Inotropes may improve hemodynamics in the short-term, stabilize patient, serve as bridge to mechanical support or transplant
- May accelerate some pathophysiologic mechanisms, increase myocardial injury, arrhythmias, potentially worsen outcomes
- Dobutamine causes dose-dependent hypotension
- Dopamine at low doses is inotropic and diuretic, at higher doses may be arrhythmogenic, increase SVR

Phosphodiesterase Inhibitors

- Examples are milrinone, enoximone
- inhibit the breakdown of cyclic AMP and have inotropic and peripheral vasodilating effects
- increase CO and SV, decrease PCWP, SVR
- Milrinone is renally excreted, requires dose reduction or avoidance in more advance renal insufficiency
- Cuffe MS (JAMA 2002) reported on randomized OPTIME CHF trial of milrinone, found more hypotension, more arrhythmias, no benefit on mortality or hospitalization
- In post hoc analysis of OPTIME, milrinone may increase mortality in patients with coronary artery disease
- Effects on AKI or WRF not reported

Levosimendan

- Phosphodiesterase inhibitor with lusitropic activity (calcium sensitizer) available in >40 countries worldwide
- Improves hemodynamics, renal vasodilator, reverse angiotensin-mediated mesangial contraction, anti-inflammatory
- Yilmaz MB (Cardiovasc Drugs Ther 2007) randomized 88 patients 2:1 to levosimendan vs dobutamine
  - Both drugs improve EF from 20 to 25%
  - Urine output increased in both
  - eGFR at 72h increased 45.5% vs. 0.1% ($p<0.001$)
- Mebazaa A (JAMA 2007) found no benefit on survival, other outcomes in SURVIVE trial (same drugs) and no difference in the AE “Renal Failure”, but did not report on creatinine, eGFR or WRF



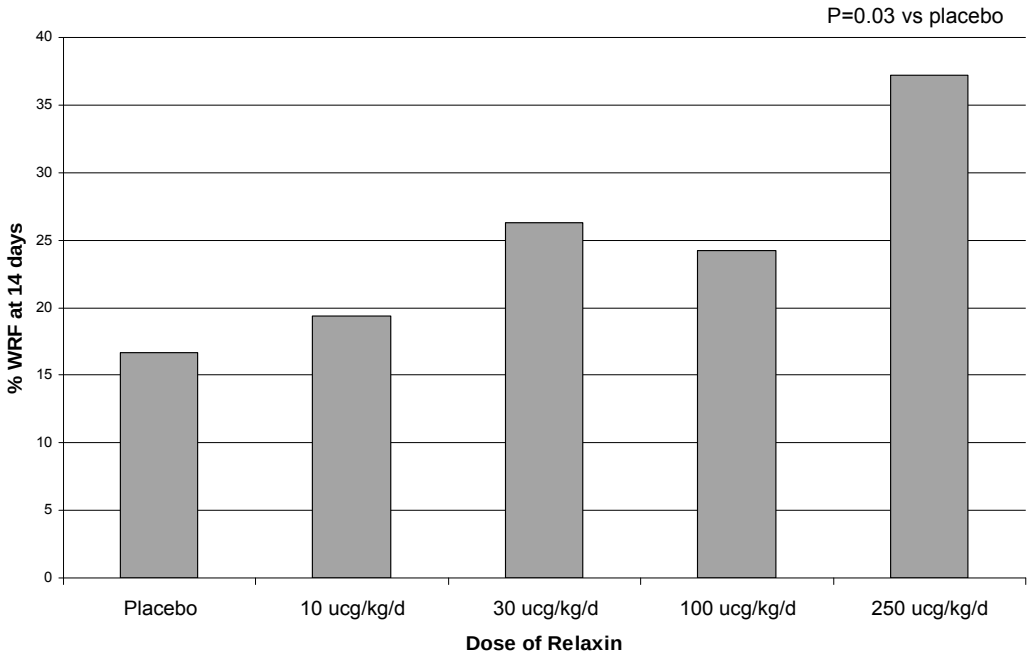
Adapted from Dickstein K, ESC Heart Failure Guidelines 2008 (Eur J Heart Fail 2008)

Preventative Novel Drug Strategies

- Relaxin
- Vasopressin antagonists (“Vaptans”)
- Endothelin antagonists
- Adenosine antagonists
- Other natriuretic peptides
  - CD-NP (designer molecule)
  - Ularitide (synthetic urodilatin)

Relaxin

- Natural peptide modulating vasodilation and renal function in pregnancy
- Increases CO, decreases SVR, PCWP, BNP
- Teerlink JR (Lancet 2009) reported the Pre-RELAX-AHF trial
- 234 patients with acute HF and preserved SBP, eGFR 30-75 mL/min
- Placebo or one of four doses given for 48h
- 30 ucg/kg/d dose associated with better dyspnea, more weight loss, less diuretic use, lower CV death or readmission, no difference all-cause mortality
- No significant difference in renal function between intermediate dose and placebo



Adapted from Teerlink JR, Lancet 2009

Vaptans

- Examples are Tolvaptan, Conivaptan, Lixivaptan
- Tolvaptan is an oral V_2 receptor antagonist which leads to aquaresis (hypotonic fluid)
- EVEREST Study results published by Konstam MA and Gheorghiade M, both in JAMA 2007
  - Over 4000 patients with hospitalized ADHF randomized to 30 mg Tolvaptan per day or placebo
  - Tolvaptan group had more weight loss, improved dyspnea, better serum Na
  - No differences in mortality
  - No significant differences in renal outcomes, but greater rise in serum creatinine in Tolvaptan group (0.08 vs 0.02 mg/dL, $p<0.001$)

Endothelin Antagonists

- Class includes bosentan, darusentan, tezosentan
- In an early study of tezosentan examining dose, Torre-Amione G (JACC 2003) found increased CI, decreased dyspnea and PCWP, however “Renal Failure” as an AE found in 0% of placebo, 2.2% of 50 mg/h dose and 5.0% of 100 mg/h dose
- Numerous larger clinical trials
  - ENABLE 1-2 – bosentan
  - HEAT-CHF, EARTH – darusentan
  - RITZ 1-4, VERITAS 1-2 – tezosentan
- Trials mostly neutral or hint at early worsening of CHF
- Significant adverse events, including worsening renal function in RITZ-1
- HEAT-CHF showed higher mortality at higher doses studied

Adenosine

- Adenosine is a complex vasoactive substance
- In general it is a vasodilator, but in kidney tends to be vasoconstrictor, can decrease GFR significantly, role in TG feedback
- Renal effects through 3 G-protein receptors
  - A1 vasoconstriction, decr. GFR, incr. Na reabs
  - $A2_{A,B}$ vasodilation, preserve RBF
  - A3 ?effects on GFR
- In CHF adenosine is elevated, has significant effects on GFR, systemic vasodilation may be blunted
- By blocking afferent vasoconstriction and TGF while preserving A2 activity, A1 receptor blockers could be potentially useful in CRS

Potential harm?

- Decreased GFR and TG feedback may be a response to metabolic stress and injury to the tubular cells and could be a protective response
- Hence falling GFR may be termed “acute renal success” (credit to Thurau and Boylan, *Am J Med* 1976)
- Blocking adenosine might preserve GFR, but provide added stress to the already hypoxic medulla
- In animals, A1 blockade modifies the seizure threshold, and there are uncertain effects in humans on the myocardium and conducting system

Adenosine Antagonists

- Several A1 receptor blockers under investigation for CRS
  - KW3902 (rolofylline) - PROTECT
  - BG 9719 (CVT 124)
  - BG 9928 (Adentri) – TRIDENT-1, POSEIDON
  - SLV 320

Rolofylline

- Dittrich HC (J Card Fail 2007)
  - 32 patients with stable CHF
  - Crossover design vs placebo
  - Incr. GFR by 32%, incr. diuresis by 500 mL
- Givertz MM (JACC 2007)
  - 146 patients with ADHF, CrCl 20-80 mL/min
  - Placebo or 1 of 3 doses IV for 3 days
  - All doses increased urine output and decreased serum creatinine versus placebo
  - Also studied patients with diuretic resistance and mean CrCl 34 mL/min and found increased urine output and decreased serum creatinine

PROTECT (Rolofylline)

- Recently presented at ESC Sept 2009 by Metra and colleagues
- 2033 patients with ADHF, CrCl 20-80mL/min randomized 2:1 rolofylline:placebo
- 30 mg/day up to 3 days
- Complex combined outcome of “success” or “failure” based on dyspnea, death, worse CHF, rehospitalization, WRF, need for ultrafiltration
- No difference in primary combined outcome
- No differences in death, hospitalization or persistent renal impairment
- More rolofylline patients with seizures and CVA (small numbers)

Other Adenosine Antagonists

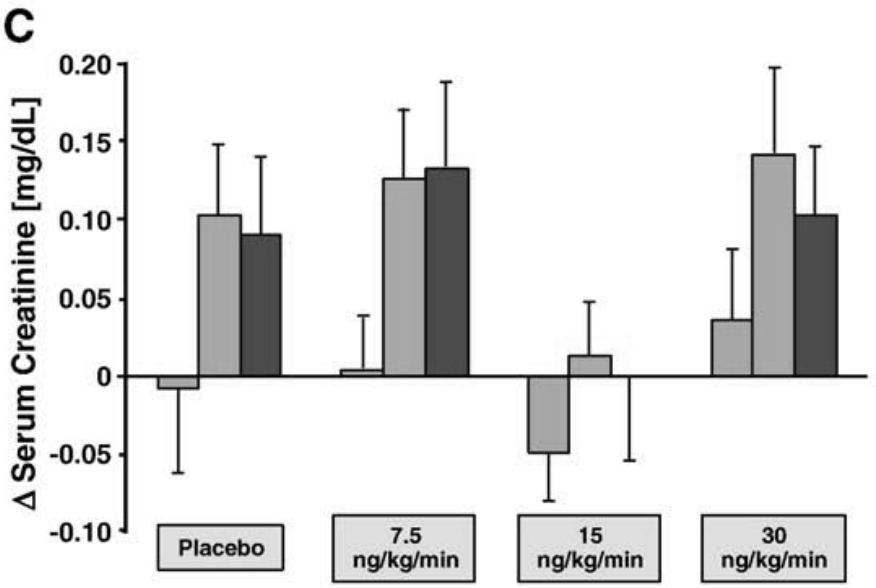
- BG9719 - Gottlieb SS (Circ 2002)
  - 63 pts. with and without furosemide
  - Alone, it increased urine output and GFR
  - With furosemide, it increased urine output by 2L and prevented the fall in GFR seen by furosemide alone
- BG9928 - Greenberg B (JACC 2007)
  - 50 pts. with mild-moderate CHF
  - Increased natriuresis and diuresis
  - Ongoing TRIDENT-1 and POSEIDON trials for CRS in 1200 pts
- SLV 320 – Mitrovic V (HFSA Meeting 2008)
  - 111 pts. With CHF, randomized to SLV320 or placebo for 3 days
  - Favorable trends in hemodynamics
  - Significant increase in urine output, Na and K excretion, decrease in Cystatin C
  - Ongoing trial in 450 patients

CD-NP

- Novel chimeric natriuretic peptide for acute CRS
- Combines the venodilating properties of CNP with renal-enhancing, aldosterone-suppressing actions of DNP
- Designed to work on the kidneys like nesiritide, without causing significant hypotension
- In phase I and II trials in 22 subjects
  - Incr. urine output, incr. natriuresis
  - Decr. Aldosterone
  - Slight decr. BP
  - Preserved GFR
- Lieu H (HFSA meeting Sep 2009)
  - open label study in 18 HF patients vs. furosemide
  - Incr. urine output by ~500 mL/day
  - Incr.CrCl, decr. serum Cr, decr. Cystatin C

Ularitide

- Ularitide is synthetic urodilatin
- Natriuretic peptide secreted within the kidney
- Lüss H (Am Heart J 2008) SIRIUS-2 trial
  - 221 ADHF pts randomized to placebo or 1 of 3 doses of ularitide infused over 24 hours
  - Intermediate dose (15 ng/kg/min) improved CHF symptoms, improved hemodynamics, preserved GFR
  - Lower dose had a decline in GFR
  - Higher dose had more hypotension, and decline in GFR

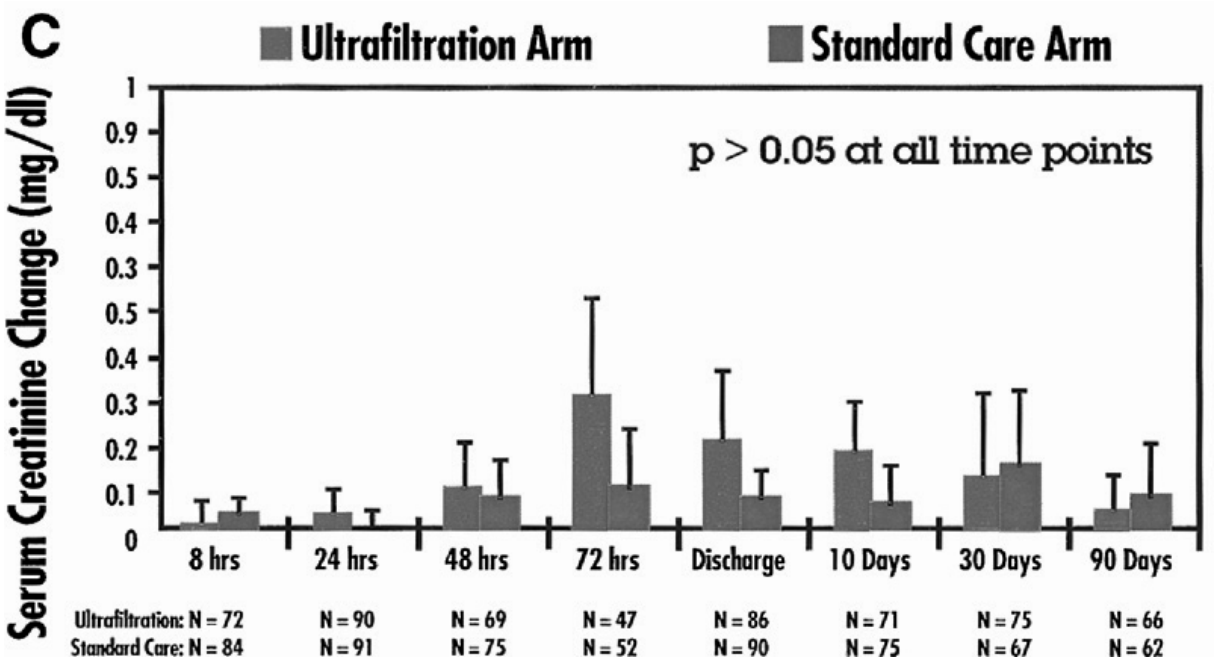


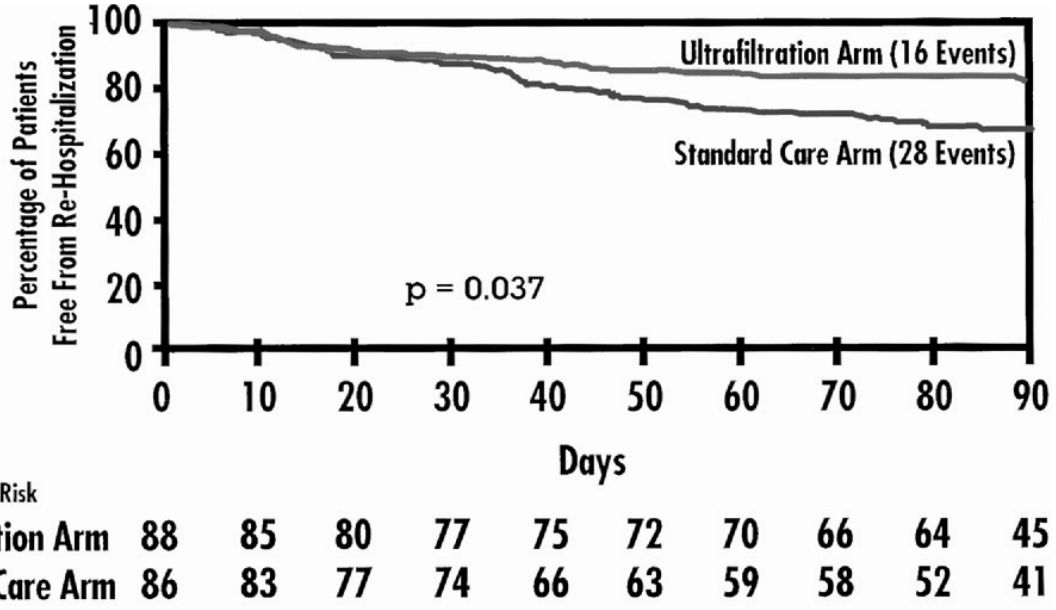
Extracorporeal strategies

- Bart BA (JACC 2005) RAPID-CHF
  - 20 pts received usual care, 20 UF
  - UF was a max of 500 cc/h X 8h
  - 70% in each group on ACEI/ARB
  - 4.65 vs 2.84 L negative balance first 24h (p=0.001)
  - Delta creat 0.1 mg/dL at 48h in both groups
  - No change in BP
  - 81.3 vs 43.8% had mod-marked improvement in symptoms at 48h (p-0.023)

UNLOAD Trial

- Costanzo MR (JACC 2007)
  - 200 *in-patients* with hypervolemic CHF randomized to UF or diuretic strategy (100 in each group)
  - Mean Cr 1.5 mg/dL, mean BNP~1300 pg/mL
  - In first 48h UF group receive no diuretics, max UF 500 mL/h (duration as per MD)
  - Weight loss 5.0 vs 3.1 kg (p=0.001)
  - Less need for vasoactive drugs 3.1 vs 12.0% (p=0.015)
  - WRF in 26.5 vs 20.3% at 48h (p=0.43)
  - Fewer rehospitalizations and ER visits in UF group
  - No difference in mortality
  - CARRESS-HF trial underway to test this therapy in patients with ADHF and acute CRS / WRF





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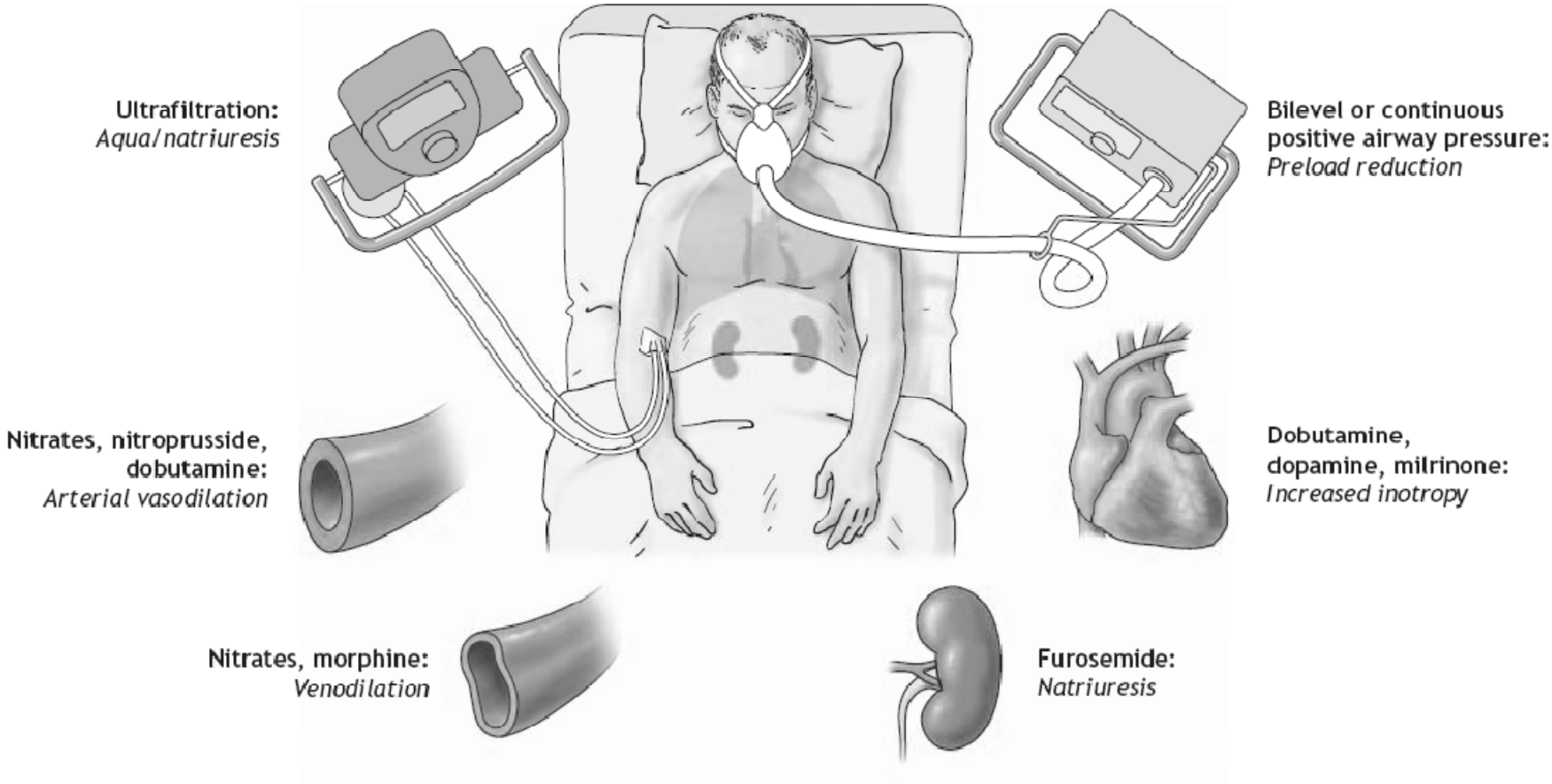

From Allen and O'Connor, CMAJ 2007

Devices

- Cardiac resynchronization therapy (CRT)
- Boerrigter G (J Card Fail 2008) MIRACLE study
  - Class 3-4 CHF
  - 225 control (device OFF), 228 CRT (device ON)
  - Compared eGFR at 0 and 6 months
  - All combined delta GFR was no different between groups
  - In stage 3 CKD (30-60 mL/min) creatinine increased by 0.16 mg/dL in control versus decrease of 0.04 mg/dL in CRT (p=0.001)
  - Fewer CRT patients developed WRF
- No studies in Acute CRS; seems promising in Chronic CRS (type 2)
- Mechanisms may go beyond simple hemodynamics, as CRT has been shown to decrease TNFα and apoptotic pathways in endomyocardial biopsies (D'Ascia C, EHJ 2006)

Mechanical Augmentation Intra-aortic Balloon Pump

- Norkiene I (Interact Cardiovasc Thorac Surg 2007) examined IABP in 11 pts awaiting VAD or OHT
  - MAP, CVP, PAP and PCWP all improved
  - EF from 14.7 to 21%
  - Creat fell from 1.8 to 1.26 mg/dL at 48h
  - 3 pts successfully weaned (no VAD, no OHT)
  - Consistent with earlier dog studies showing dampened renal sympathetic nerve activity and improved renal blood flow with IABP

Mechanical Augmentation Ventricular Assist Device

- Butler J (Ann Thorac Surg 2006) reported on 220 pts with advanced decompensated HF treated with LVAD
  - Overall 38% mortality
  - Relative risk of death 1.95 (1.14-3.63, p=0.03) in lowest versus highest quartile of CrCl
  - Renal function improved dramatically with LVAD
  - CrCl from 77 to 92.1 mL/min ($p<0.01$) from pre-op to week 1
  - Those with worst function improved from 36.7 to 60.1 mL/min ($p<0.01$) at week 1
  - Even those on IABP saw improvement in renal function with LVAD
- Authors concluded that LVAD improves renal function, and cautioned *against* using failure of kidneys to improve on IABP as a contraindication to transplant

Mechanical Augmentation Artificial Heart

- Roussel JC (Ann Thorac Surg 2009) reported on outcomes of 42 pts implanted with artificial heart
  - Serum Cr 175 umol/L pre-implant
  - 30 survived to transplant, and 89% of those survived to hospital discharge
  - 64% required renal replacement therapy post-operatively
  - Only 1 had persistent dialysis dependence at 1 year
  - No data on renal function in recovered patients

Heart Transplant

- In 1969, Dr. Christiaan Barnard published extensive follow up on the first 3 human cardiac transplants (CMAJ 1969)
- 2 patients had significant renal dysfunction at the time of transplant which quickly resolved
  - “In our second patient, Dr. P. Blaiberg, the immediate postoperative period was uneventful and again one was impressed by the rapid disappearance of symptoms and signs of heart failure. Renal function soon improved and jaundice disappeared.”

Key messages

- Acute CRS is an important determinant of poor outcome in patients with cardiac disease
- Cause of acute CRS is multi-factorial, but emerging data implicate venous congestion rather than poor forward flow as a significant contributor
- Strategies to reduce congestion without stimulating adverse neurohormonal signals are being studied (diuretics, ultrafiltration, vasodilators)
- Natriuretic peptides and promising vasoactive drugs continue to be studied to determine their utility in CRS
- Mechanical augmentation of cardiac performance through IABP or VAD can serve as a bridge to transplantation or recovery with stabilization or improvement of CRS