Diuretic resistant CHF on top of chronic renal impairment

Khaled Elnady, M.D.,FESC.,FSCAI.
Military medical academy

Introduction

- cardiovascular morbidity and mortality is significantly increased in CHF patients with mild chronic renal insufficiency. The mechanisms by which decreased renal function correlated with cardiovascular disease are still not fully understood.
- It is unclear if cardiac pump failure secondarily leads to diminished renal function or if mild renal dysfunction leads to progression of functional cardiac deterioration.

Introduction

- What is clear is that these interactions between the heart and kidney can lead to poor outcomes in patients with CHF.
- When kidney function is compromised, the kidney loses its ability to maintain extracellular fluid (ECF) volume within normal limits.

Introduction

- Although diuretic-induced natriuresis may decrease ECF volume and provide symptomatic relief, loop diuretics may worsen renal function in some patients and become ineffective in others who develop diuretic resistance.
- Diuretics can also decrease cardiac pre-load, diminishing cardiac index, and increasing blood urea nitrogen and serum creatinine to levels that may necessitate discontinuation of the diuretic

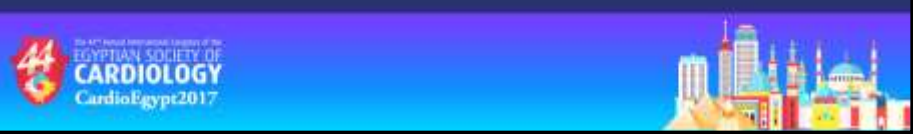
Diuretic resistance in CHF

Definition

Clinical state in which diuretic response is diminished or lost before the therapeutic goal of relief from edema has been reached.

Causes

- Hyponatremia
- Diuretic pharmacokinetics
- Sodium retention
- Renal impairment



Association between CHF and renal impairment

Study	Data source	Number of HF patients	Mean age	Women (%)	African American (%)	Method to define CKD	Advanced CKD excluded	Prevalence of CKD
Heywood JT et al., 2007	ADHERE	118465	72	52	21	MDRD	No	64%
Masoudi FA et al., 2005 [	NHCP	62376	79	58	10	MDRD	No	67%
Ahmed A*	AHFP, 1994	1091	79	60	18	MDRD	No	68%
Ahmed A*	AHFP, 2001	8555	76	58	24	MDRD	No	65%
Ahmed A et al., 2007	DIG	7788	64	25	15	MDRD	Yes	45%
Ahmed A*	CHS	262	75	52	20	MDRD	No	53%
Ahmed A*	FHS	70	74	70	0	MDRD	No	74%
Ahmed A et al. 2008	REGARDS	357	65	65	59	MDRD	No	55%
McAlister FA et al., 2004	University Clinic	754	67	34	-		No	56%
Ezekowitz J et al., 2004	APPROACH	6427	69	35	-	C-G equation	No	39%
Bibbins-Domingo K et al., 2004	HERS	702	68	100	12	C-G equation	No	58%
Berger AK et al., 2007	Minnesota Heart Survey	2169	69	47	-	C-G equation	No	53%

Association between CHF and renal impairment

Prevalence of Worsening Renal Function During Hospitalization According to Categories of Admission CVP, CI, SBP, and PCWP Mullens, W. et al. J Am Coll Cardiol 2009;53:589-596

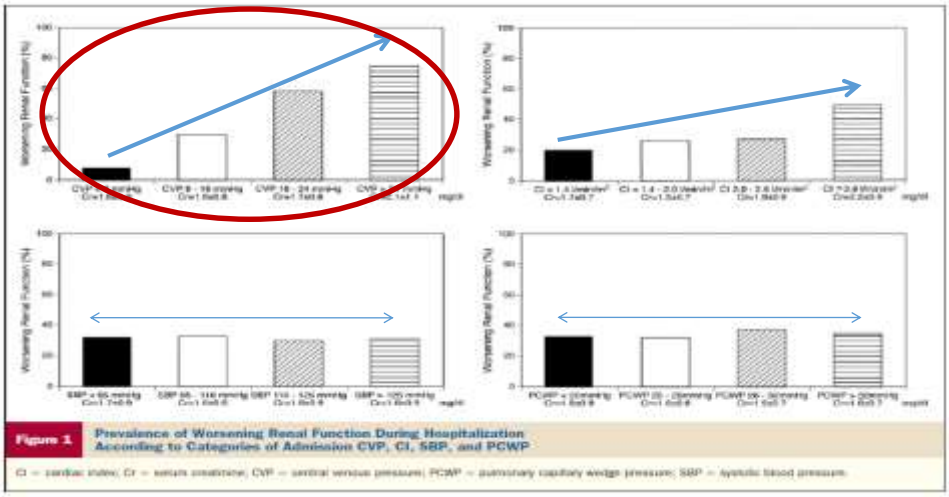


Figure 1 Prevalence of Worsening Renal Function During Hospitalization According to Categories of Admission CVP, CI, SBP, and PCWP

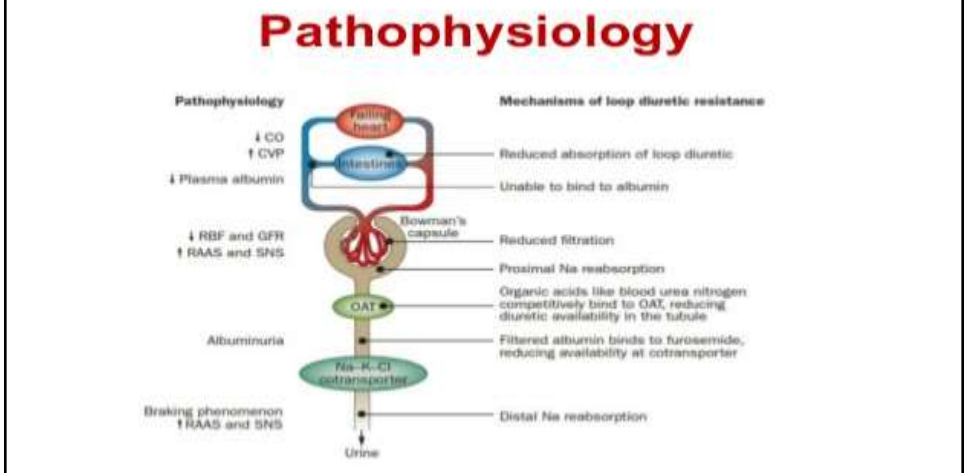
CI = cardiac index; Cr = serum creatinine; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure.

Diuretic used in CHF with renal impraiment

Classes of Diuretic Agents Used in CKD

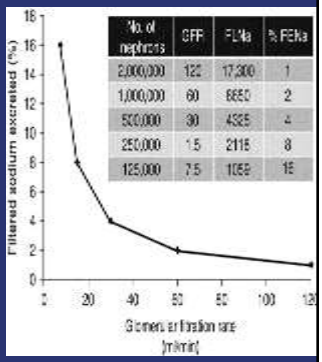
	Thiazide	Loop	Potassium-Sparing
Pharmacodynamic Effects	Increases excretion of sodium, potassium and magnesium. Decreases excretion of calcium	Increases excretion of sodium, potassium, hydrogen ion, calcium and magnesium	Increases excretion of sodium. Decreases excretion of potassium, hydrogen ion, calcium and magnesium
Site of action	Distal tubule	Thick ascending limb	Collecting tubule
Delivery to site of action	Organic anion transporter – proximal tubule	Organic anion transporter – proximal tubule	Organic cation transporter – proximal tubule
Transporters affected	Apical Na^+-Cl^- cotransport system	Na^+-K^+-$2Cl^-$ cotransporter	Epithelial sodium channels (triamterene, amiloride) or mineralocorticoid receptors (aldosterone antagonists)
Percent of filtrate reabsorbed at site of action	6%-11%	20%-30%	Less than 5%
Bioavailability	40%-90%	50%-100%	30%-90%
Route of elimination	Liver/kidney	Liver/kidney	Liver/kidney
Elimination half-life	2.5-60 hours	1-5 hours	2-26 hours
Dose schedule	Usually once daily	Usually twice daily	Once or twice daily

Mechanisms of Diuretic Resistanance
in CHF with Renal Impairment

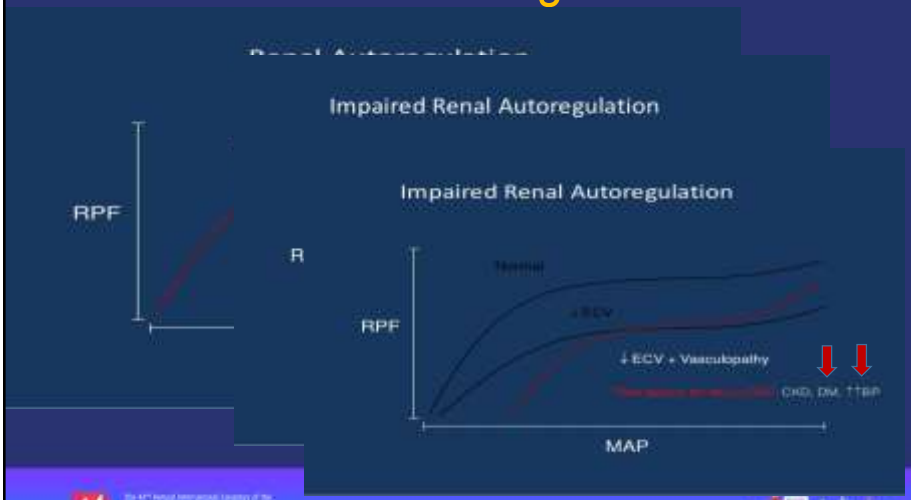


Mechanisms of Diuretic Resistanance
in CHF with Renal Impairment

- *Decreased GFR*
  - *I. Abrupt lowering of preload with decreasing of CO*
  - *II. Overdosing of ARBS /ACEI*
  - *III. Using of nephrotoxic drugs eg: NSAIDs*
  - *IV. Aggressive afterload reduction in sitting of impaired renal autoregulation*



Renal autoregulation



Mechanisms of Diuretic Resistanance
in CHF with Renal Impairment

- *Inadequate diuretic delivery to kidney*
  - *I. Unpredictable gut absorption (often irregular and reduced)*
  - *II. Reduced delivery of the drug due to decrease CO*
- *Decreased ECV with increased solute reabsorption in Proximal nehron*

Management of Diuretic Resistance

The fractional excretion of sodium (FENa) is the percentage of the sodium filtered by the *kidney* .

Management of Diuretic Resistance

Oral Diuretic → IV Diuretics → Diuretic resistance

Renal impairment

Stepped Pharmacological approach

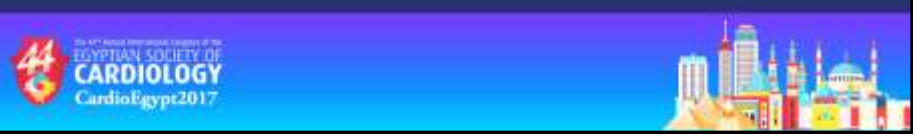
?

Ultrafiltration

Others

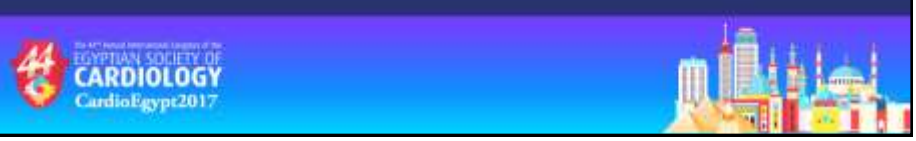
Management of Diuretic Resistance

- Insure dietary and drug compliance
- Restriction of daily fluid intake
- Restriction of daily salt intake
- Institution of ACE inhibition
- Avoid aggressive vasodilator therpy
- Oral adminstartion of loop diuretic in several divided and increasing doses



Management of Diuretic Resistance

- Recumbency after diuretic dosing
- Maximize GFR by reducing or withdrwal of offending medication
  I. NSAIDs
  II. RAAS blockers
  III. Drugs produce aggressive afterload reduction
  IV. High dose of BB.



Management of Diuretic Resistance

Stepwise pharmacological approach

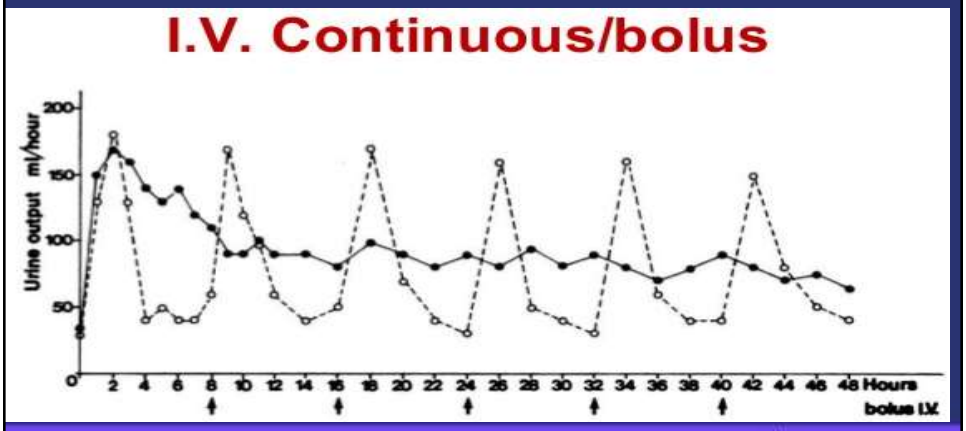
Loop diuretics

- Bolus loop diuretic with sufficient dose to achieve serum threshold.
- Increase dose to effective response
- Increase dosing frequency
- Continuous infusion of loop diuretics

Maximal response with severe CKD occurs with

I. Furosemide 160-200 mg
II. Torsemide 150-200 mg
III. Bumetanide 6-8 mg

Management of Diuretic Resistance



Management of Diuretic Rresistance

Stepwise pharmacological approach

Thiazide diuretics

- Adding thiazide diuretic to loop diuteric
  I. Higher doses may be needed with severe CKD
  II. Increase risk of hyponatremia, hyokalemia and may worsen renal function

Management of Diuretic Rresistance

Stepwise pharmacological approach

Potssium sparing diuretic

Adding small dose with ACE inhibition or larger dose in absence of ACE inhibition

Acetazolamide

Consider short-term acetazolamide in selected cases

Manegement of diuretic resistance

Limitations of Stepwise pharmacological approach

1. Efficacy: high percentage of admitted patients were discharged with symptoms of congestion after receiving diuretic therapy
2. Worsening of renal function during hospital admission.
3. Uncertainties about optimal dose, mode of administration and stepped approach in resistant cases. “Diuretic secretion is impaired in CKD”
4. Electrolyte abnormalities: (hypokalemia, etc.,,,)
5. Hypersensitivity and ototoxicity.

Manegement of diuretic resistance

Ultrafiltration

Manegement of diuretic resistance

Current guidelines on use of Ultrafiltration in CHF with or without renal impairment

Table 3 Current guidelines for the use of ultrafiltration for ADHF

AHA/ACC practice guideline (2009)	UF is reasonable for patients with refractory congestion, not responding to medical therapy	Class IIa	Level of evidence: B
European Society of Cardiology (2008)	UF should be considered to reduce fluid overload in select patients and to correct hyponatremia in symptomatic patients, refractory to diuretics	Class IIa	Level of evidence: B
Heart Failure Society of America (2010)	UF may be considered when congestion fails to improve in response to diuretics	Class IIa	Level of evidence: C
Canadian Cardiovascular Society (2012) (58)	Venovenous ultrafiltration may be of benefit in relieving congestion particularly in diuretic-resistant patients Patients with persistent congestion despite diuretic therapy, with or without impaired renal function, may, under experienced supervision, receive continuous venovenous ultrafiltration		

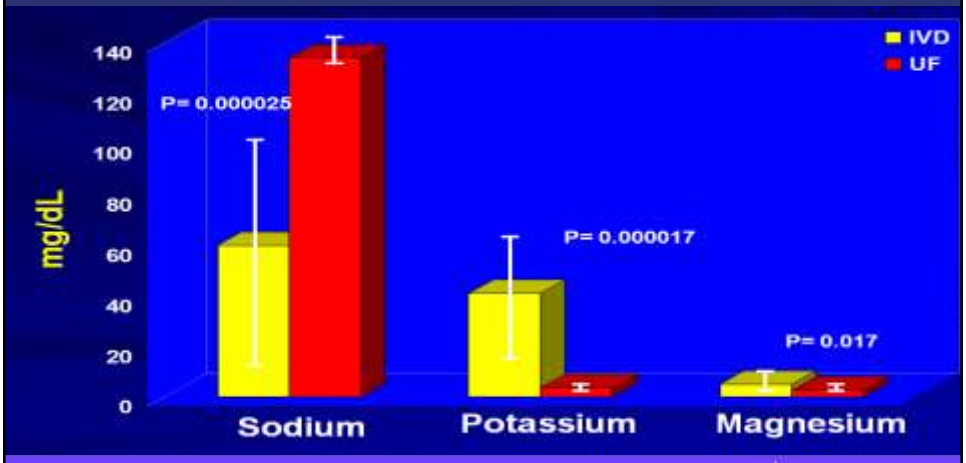
Manegement of diuretic resistance

Theoretical advantages of ultrafiltration UF

1. Higher mass clearance of sodium for similar volumes of fluid removal.
2. Rapid controlled fluid removal.
3. Decreased renal venous congestion.
4. Lack of neurohormonal activation.
5. No resistance to its action.
6. Low risk of electrolyte abnormalities.
7. Sustained clinical benefits.
8. Decreased hospital length of stay and rehospitalization for HF.
9. Ability to restore diuretic sensitivity.

Manegement of diuretic resistance

Urine electrolytes after IV diuretic Vs UF



EGYPTIAN SOCIETY OF CARDIOLOGY
CardioEgypt2017

Other treatment modalities

Adenosine type I receptor antagonists

Heart Failure

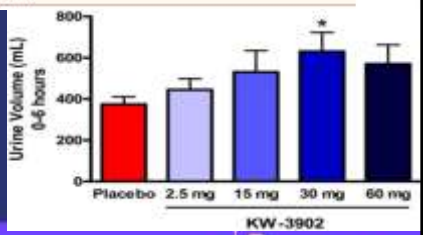
The Effects of KW-3902, an Adenosine A1-Receptor Antagonist, on Diuresis and Renal Function in Patients With Acute Decompensated Heart Failure and Renal Impairment or Diuretic Resistance

Michael M. Givertz, MD, FACC,* Barry M. Massie, MD, FACC,† Tara K. Fields, BA,† Lesanne L. Pearson, RN, BS,‡ Howard C. Dittrich, MD, FACC,‡§ on behalf of the CKI-201 and CKI-202 Investigators

Boston, Massachusetts; and San Francisco and San Diego, California

Conclusions

In patients with ADHF and volume overload, KW-3902 (rolofylline) an adenosine A1-receptor antagonist, enhances the response to loop diuretics and may have a renal protective effect.



EGYPTIAN SOCIETY OF CARDIOLOGY
CardioEgypt2017

Other treatment modalities

Vasopressin Antagonists

ORIGINAL CONTRIBUTION

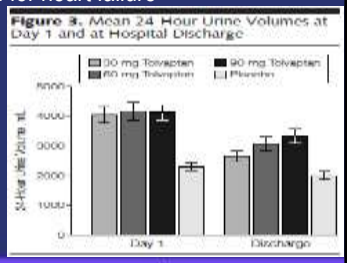
Effects of Tolvaptan, a Vasopressin Antagonist, in Patients Hospitalized With Worsening Heart Failure

A Randomized Controlled Trial

Conclusion Tolvaptan administered in addition to standard therapy may hold promise for management of systemic congestion in patients hospitalized for heart failure

Vaptans(conivaptan, tolvaptan, lixivaptan)

- Allows free water loss without natriuresis
- Predominantly used to treat eu/hypervolemic hyponatremia



Other treatment modalities

glucocorticoids

Potent diuretic effects of prednisone in heart failure patients with refractory diuretic resistance

Canadian Journal of Cardiology Volume 23, Issue 11, September 2007, Pages 865–868

Conclusions

- That study demonstrated that prednisone can rapidly eliminate volume overload and improve clinical status and renal function in CHF patients with diuretic resistance. Further prospective randomized clinical studies are warranted to confirm its clinical efficacy.

Others

- Hypertonic saline
- Mannitol
- Positive inotropic drugs eg: dopamine , levosimendan

كَم ذا يُكابِدُ عاشِقٌ وَيُلاقي
في حُبِّ مِصرَ كَثيرَةِ العُشّاقِ
إِنّي لَأَحمِلُ في هَواكِ صَبابَةً
يا مِصرُ قَد خَرَجَت عَنِ الأَطواق

Thank you

Thank you

EGYPTIAN SOCIETY OF CARDIOLOGY
CardioEgypt2017