

A patient with acute heart failure and renal impairment

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INTRODUCTION

- Cardiac and renal diseases are common and frequently coexist to significantly increase mortality, morbidity, and the complexity and cost of care.
- Primary disorders of 1 of these 2 organs often result in secondary dysfunction or injury to the other. Such interactions represent the pathophysiological basis for a clinical entity called cardiorenal syndrome (CRS) .

DEFINITION OF CRS

- CRS can be generally defined as a patho physiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of one organ may induce acute or chronic dysfunction of the other.

- *European Heart Journal* (2010) 31, 703–711,

CLASSIFICATION

World congress of nephrology classified cardiorenal syndromes into 5 subtypes based on patho-physiology:

- **CRS type 1** : acute **cardio**-renal syndrome
- **CRS type 2** : chronic cardio-renal syndrome
- **CRS type 3** : acute **reno**-cardiac syndrome
- **CRS type 4** : chronic reno-cardiac syndrome
- **CRS type 5** : **secondary** cardio-renal syndrome

ACUTE CRS

CRS type 1 (acute CRS)-- is characterized by a rapid worsening of cardiac function, leading to acute kidney injury (AKI).

- Acute heart failure (HF) may be divided into 4 subtypes:
 - Hypertensive pulmonary edema with preserved left ventricular (LV) systolic function,
 - Acutely decompensated chronic HF,
 - Cardiogenic shock, and
 - Predominant right ventricular failure

EPIDEMIOLOGY OF CRS1

- In the Acute Decompensated Heart Failure National Registry (ADHERE) of 1,05,000 individuals admitted for acute decompensated HF, 30% had a history of renal insufficiency, 21% had serum creatinine concentrations >2.0 mg/dL, and 9% had creatinine concentrations >3.0 mg/dL.

IMPACT OF RENAL DISEASE ON CLINICAL OUTCOMES IN PATIENTS WITH HF

- Renal dysfunction is one of the most important independent risk factors for poor outcomes and all-cause mortality in patients with HF.
- Baseline glomerular filtration rate (GFR) appears to be a stronger predictor of mortality in patients with HF than left ventricular ejection fraction or NYHA functional class.
- Both elevated serum creatinine on admission and worsening creatinine during hospitalization predict prolonged hospitalization, rehospitalization, and death.

PREDICTORS OF WORSENING RENAL FUNCTION IN HF PATIENTS :

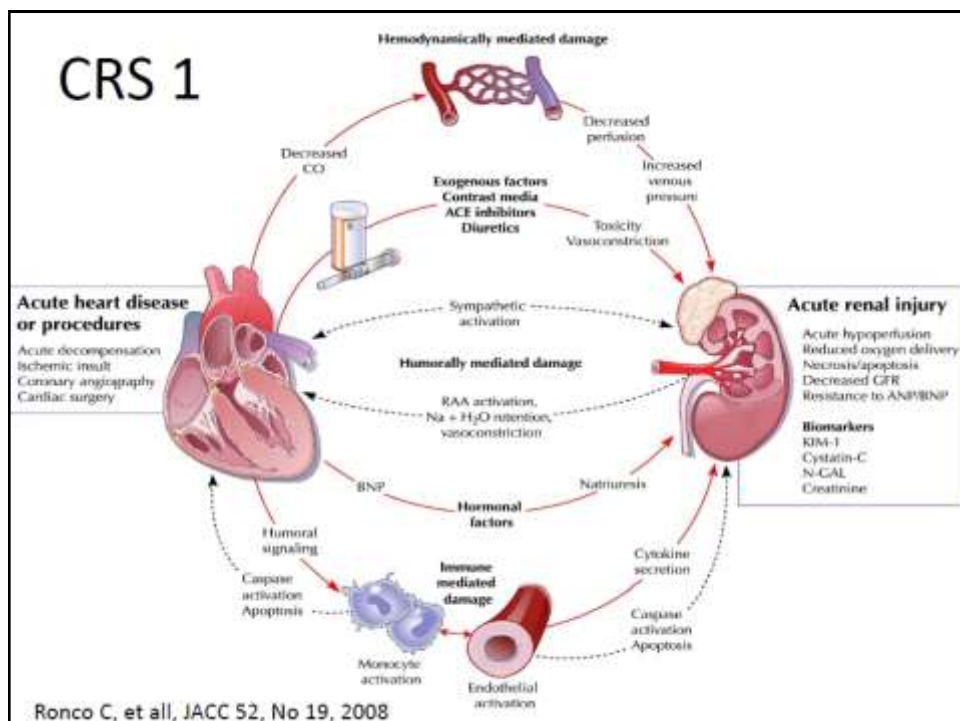
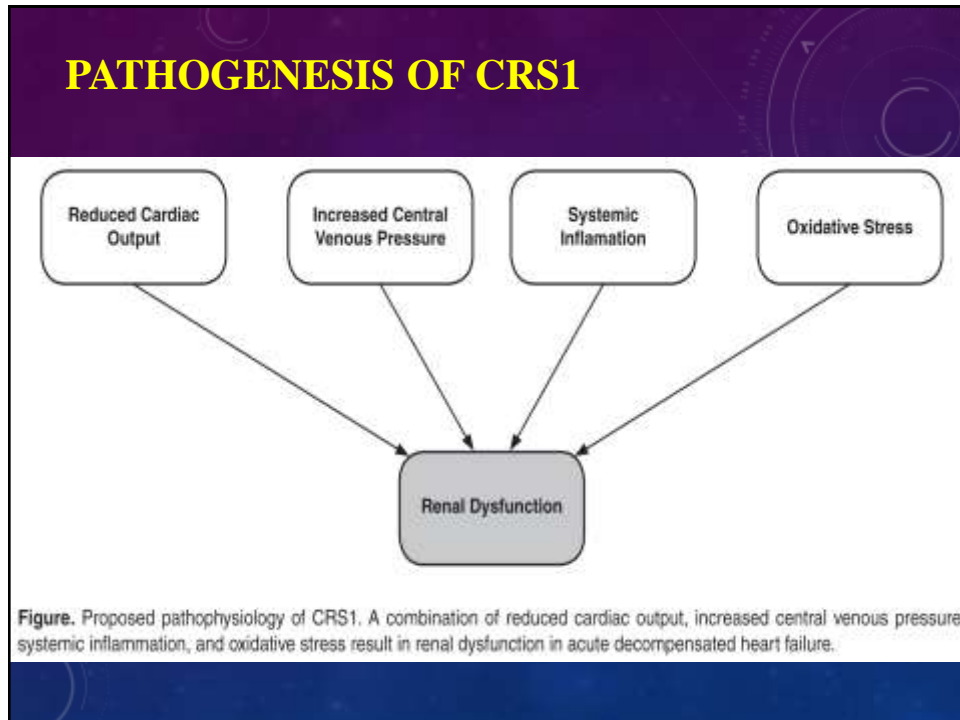
In the Studies of Left Ventricular Dysfunction (SOLVD), factors that correlated with worsening renal function (defined as a rise in serum creatinine of 0.3 mg/dL) were:

- Old age
- Low ejection fraction
- Elevated baseline creatinine level
- Low systolic blood pressure
- Diabetes mellitus
- Hypertension
- Use of antiplatelet therapy, diuretics, or beta-blockers

PATHOGENESIS OF CRS1

- The mechanisms by which the onset of acute HF or acutely decompensated chronic HF leads to AKI are multiple and complex.
- The clinical importance of each mechanism is likely to vary from patient to patient (e.g., acute cardiogenic shock vs. hypertensive pulmonary edema) and situation to situation (acute HF secondary to perforation of a mitral valve leaflet from endocarditis vs. worsening right HF secondary to noncompliance with diuretic therapy).

- In acute HF, AKI appears to be more severe in patients with impaired LV ejection fraction compared with those with preserved LV function, achieving an incidence 70% in patients with cardiogenic shock.
- Furthermore, impaired renal function is consistently found as an independent risk factor for 1-year mortality in acute HF patients, including patients with ST-segment elevation myocardial infarction .



WHAT TESTS TO PERFORM?

Table 1. Classification of Acute Kidney Injury Using RIFLE [68], AKIN [69], and KDIGO [70] Guidelines Based on Creatinine or eGFR Changes

Classification	Stage	Definition Based on sCr
RIFLE	Risk	≥ 1.5 -fold increase in baseline sCr or decrease in eGFR $\geq 25\%$
	Injury	≥ 2.0 -fold increase in baseline sCr or a decrease in eGFR $\geq 50\%$
	Failure	≥ 3.0 -fold increase in baseline sCr or decrease in eGFR $\geq 75\%$. If baseline sCr ≥ 4.0 mg/dL, then an increase in sCr of 0.5 mg/dL
AKIN	1	Increase in sCr ≥ 0.3 mg/dL or 1.5- to 1.9-fold increase in baseline sCr within 48 hours
	2	2.0- to 2.9-fold increase in baseline sCr
	3	≥ 3.0 -fold increase in baseline sCr or if baseline sCr ≥ 4 mg/dL, then an increase of ≥ 0.5 mg/dL
KDIGO	1	≥ 1.5 -fold increase in baseline sCr within 7 days or ≥ 0.3 mg/dL increase within 48 hours
	2	≥ 2.0 -fold increase in baseline sCr
	3	≥ 3.0 -fold increase in baseline sCr or an increase to ≥ 4.0 mg/dL

AKIN = acute kidney injury network; KDIGO = kidney disease improving global outcomes; RIFLE = risk, injury, failure, loss of kidney function and end-stage kidney disease; sCr = serum creatinine.

BIOMARKERS OF AKI

In CRS type 1, the early diagnosis of AKI remains a challenge, classic markers such as creatinine increase when AKI is already established and very little can be done to prevent it or to protect the kidney

- **Neutrophil gelatinase-associated lipocalin (NGAL)**

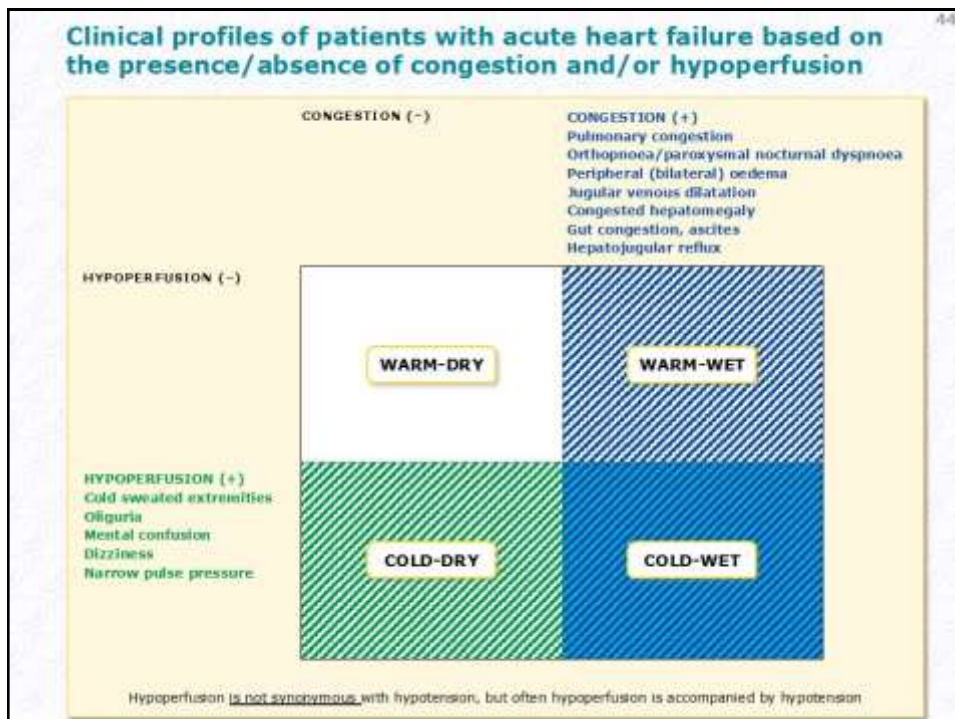
appears to be one of the earliest markers detected in the blood and urine of humans with AKI .

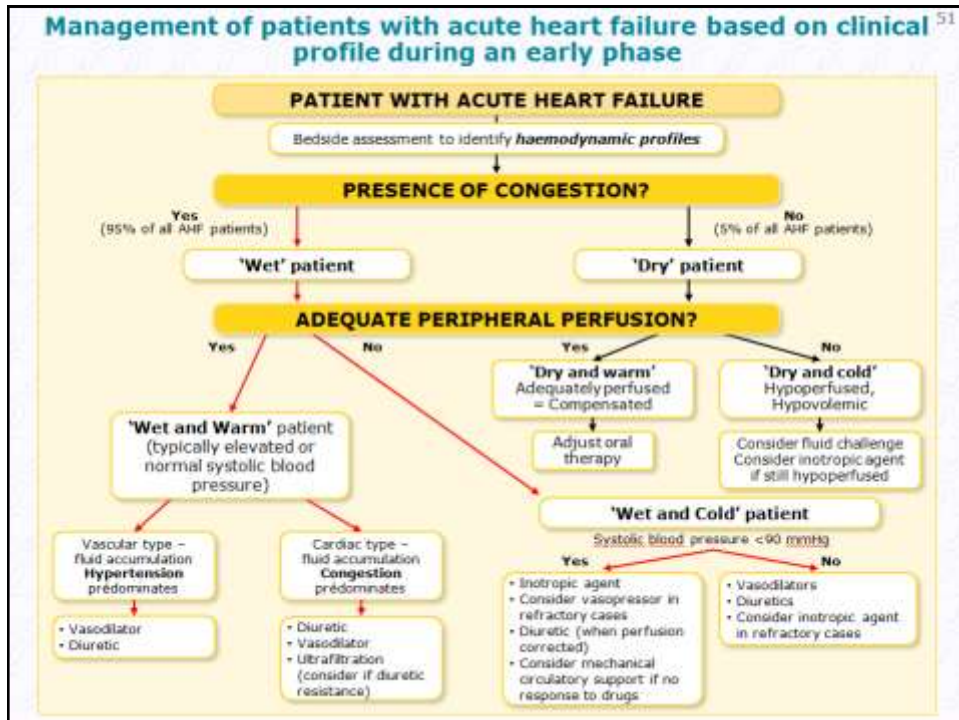
- **Kidney injury molecule 1** is a protein detectable in the urine after ischemic or nephrotoxic insults to proximal tubular cells and seems to be highly specific for ischemic AKI.

- **Cystatin C** predicts AKI and the requirement for renal replacement therapy earlier than creatinine.

TREATMENT OF THE CRS 5 IMPORTANT QUESTIONS...

- What is the **fluid status**?
- Is the **BP** adequate for renal perfusion?
- What is the **cardiac output**?
- Is there evidence of high **CVP** ?
- Is there **intrinsic renal** disease?





CLINICAL PROFILES OF CRS

Profile	Fluid status	CO	SVR	Treatment
To dry	Dry	Low	N or High	Fluids Stop diuretics
Too wet	Wet	N	N	Diuretics, aquaretics Ultrafiltration
Too clamped	Wet or N	Low	High	ACEI, Nitroprusside Nesiritide, seralaxin
Vasodilated	N or Wet	N or High	Low	Stop VD, Vasopressin, inotropes
No pump	Wet	Low	N	Inotropes, vasopressors, LVAD

- The first clinical principle is that the onset of AKI in this setting implies **inadequate renal perfusion** until proven otherwise, which should prompt one to consider the diagnosis of a low cardiac output state and/or marked increase in venous pressure leading to renal congestion.
- The second important consequence of type 1 CRS is **decreased diuretic responsiveness**. In a congestive state, decreased response to diuretics may result from the physiological phenomena of diuretic braking (diminished diuretic effectiveness secondary to postdiuretic sodium retention) .

- In addition, concerns of aggravating AKI by the administration of diuretics at greater doses or in combination also can act as an additional, iatrogenic mechanism.
- Diuretics are best provided to HF patients with evidence of systemic fluid overload with the goal of achieving a gradual diuresis.
- Loop diuretics may be titrated according to **renal function, systolic blood pressure, and history of chronic diuretic use**.
- High doses may cause tinnitus, and a **continuous low-dose diuretic infusion** might be more efficient

- Measurement of cardiac output (arterial pressure monitoring combined with pulse contour analysis or by Doppler ultrasound) and venous pressure may help ensure adequate and targeted diuretic therapy and allow safer navigation through the precarious situation of combined HF and AKI.
- If **diuretic-resistant** fluid overload exists despite an optimized cardiac output, removal of isotonic fluid can be achieved by the use of **extracorporeal ultrafiltration**.

- The presence of AKI with or without concomitant **Hyperkalemia** may also affect patient outcome by inhibiting the prescription of ACE inhibitors, angiotensin receptor blockers (ARBs), and aldosterone antagonists (drugs that have been shown in large randomized controlled trials to increase survival in the setting of heart failure and myocardial infarction).
- However, provided there is close monitoring of renal function and potassium levels, the potential benefits of these interventions often outweigh their risks, even in these patients.

- The acute administration of beta-blockers in the setting of type 1 CRS generally is not advised. Such therapy should wait until the patient has stabilized physiologically and until concerns about a low output syndrome have been resolved.
- Particular concern applies to beta-blockers excreted by the kidney, such as **atenolol** or **sotalol**, alone or in combination with **calcium antagonists**.
- This should not inhibit the slow, careful, titrated administration of betablockers later on, once patients are hemodynamically stable.

Table 3. Summary of Treatment Approaches for CRS1 Including Pathophysiology Targeted, Benefits, and Drawbacks

Treatment Strategy	Pathophysiology Targeted	Benefits	Drawbacks	Level of Evidence*
Diuretics	Volume overload and elevated CVP	Effective for volume removal	Metabolic derangements	1b
Inotropes	Reduced cardiac output	May improve renal perfusion in low output state	Increased risk of arrhythmias	5
Dopamine	Altered renal perfusion	No clear benefits	Increased risk of arrhythmias (tachycardia)	1b
Nesiritide	Volume overload	No clear benefits	Cost and hypotension	1b
Adenosine antagonists	Adenosine-mediated renal vasoconstriction	May potentiate diuresis	Not FDA-approved, seizures	1b
ADH antagonists	Volume overload and hyponatremia	May potentiate diuresis and improve hyponatremia	Costs, no improvements in hard outcomes	1b
Corticosteroids	Unknown: Possibly renal perfusion and anti-inflammatory effects	Increased urine output, improved renal function and survival	Hyperglycemia, hypertension, and delirium	1b
Serelaxin	Unknown: Possibly renal perfusion	Reduced incidence of renal impairment	Not FDA-approved	2b
Ultrafiltration	Volume overload and elevated CVP	Increased fluid removal as compared to diuretic management	Costs and risks of complications associated with access placement and anticoagulation	1a
Continuous renal replacement therapy	Volume overload and elevated CVP	No clear benefits	Costs and risks of complications associated with access placement and	2b

TAKE HOME MESSAGES

- The Acute Cardio-Renal Syndrome is a worst case scenario for the CHF patient.
 - Mortality is clearly worsened.
 - Management is difficult.
- Early diagnosis and use of novel biomarker may improve response to therapy.
- Management requires careful balance between volume status, renal perfusion, and intra-renal hemodynamics.

TAKE HOME MESSAGES

- Thoughtful approach to volume management
 - Diuretics high dose and combinations
 - Use ultrafiltration if massive or refractory volume overload
- Many other therapeutic options are tested but its effect on the outcome is lacking
- Many studies are underway testing many therapeutic modalities searching for effective therapy that may improve the gloomy outcome of acute CRS.

