#326 NephMadness 2022: Cardiorenal Syndrome

Lose your heart to NephMadness 2022! Dr. Joel Topf (@kidney_boy) and Dr. Sadiya Khan (@HeartDocSadiya) tackle the NephMadness 2022 Cardiorenal Syndrome region, leading us through the pathophysiology of cardiorenal syndrome, how to approach the creatinine "bump" with diuresis, managing patients with diuretic resistance, and more.

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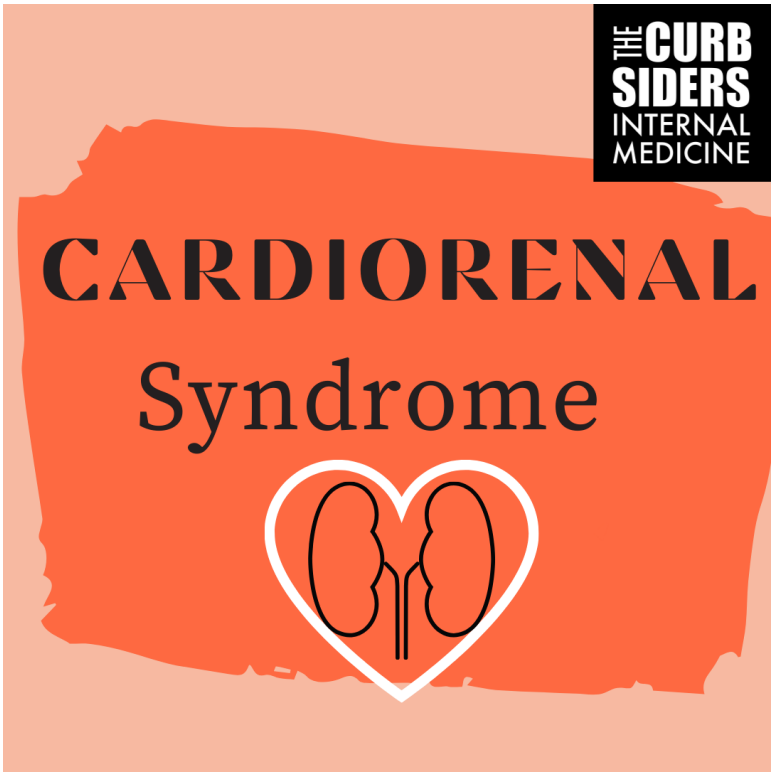

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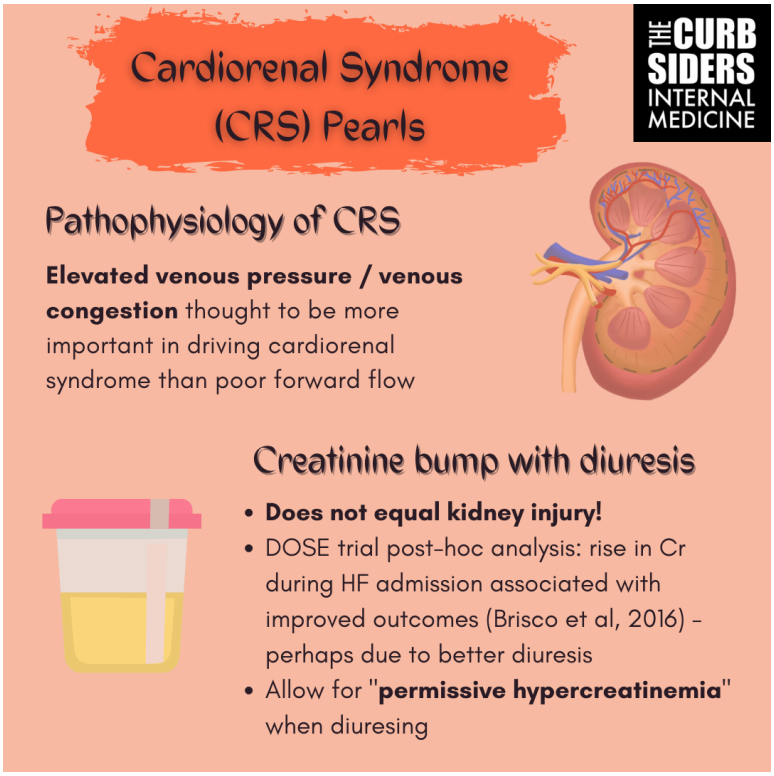
Show Segments

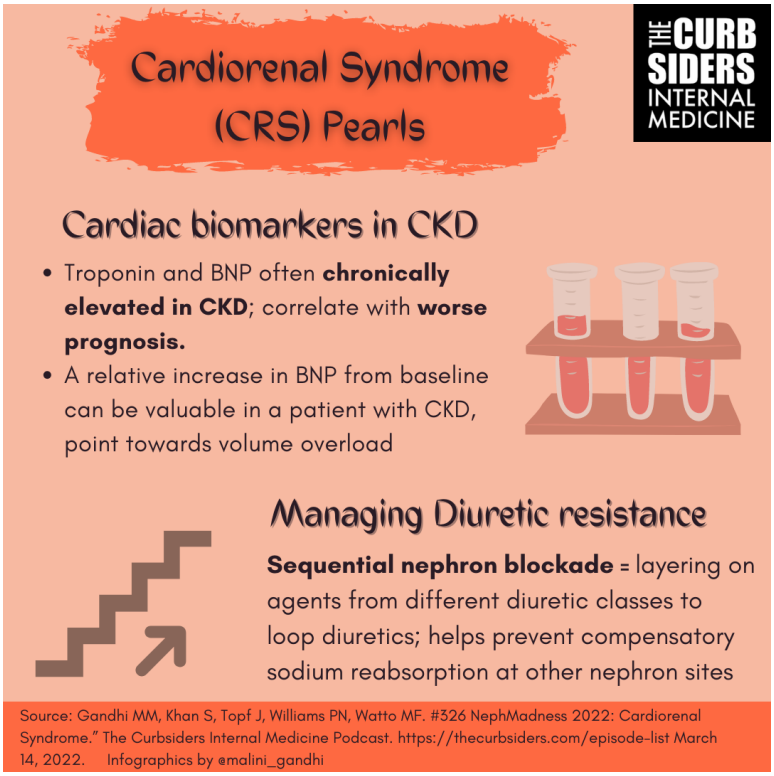
- Intro, disclaimer, guest bios
- Guest one-liners, Introduction to Nephmadness 2022
- Case #1 from Kashlak: acute decompensated heart failure with elevated creatinine
- Definition and pathophysiology of cardiorenal syndrome
- Use of home ACE-is/ARBs and SGLT-2 inhibitors in cardiorenal syndrome
- Case #2 from Kashlak: the creatinine bump with diuresis
- Approach to the creatinine bump with diuresis
- Tips for the volume exam
- Interpreting cardiac biomarkers in patients with chronic kidney disease
- Case #3 from Kashlak: diuretic resistance
- Maximizing loop diuretic efficacy
- Sequential nephron blockade
- Use of hypertonic saline

- Outro

Cardiorenal Syndrome Pearls

1. Elevated venous pressure/venous congestion, rather than reduced cardiac index/poor forward flow, is thought to be the major contributor to the pathophysiology of cardiorenal syndrome.
2. Home ACE-is/ARBs and SGLT-2 inhibitors do not necessarily need to be stopped in patients with acute decompensated heart failure with an increase in creatinine, as long as the patient is not hypotensive or hyperkalemic. If these medications are stopped during hospitalization, be sure to restart them prior to discharge.
3. A creatinine "bump" with diuresis does not necessarily signify kidney injury. Allow for "permissive hypercreatinemia" while diuresing. Avoid stopping diuresis prematurely with residual congestion on board simply because of a rise in creatinine.
4. Invasive measures like right heart catheterizations and non-invasive measures like POCUS can help clarify volume status.
5. Cardiac biomarkers such as troponin and BNP are often chronically elevated in patients with CKD, and correlate with worse prognosis. A relative change in BNP from baseline can be informative in patients in CKD.
6. Sequential nephron blockade (i.e. layering on additional diuretics that act at different sites in the nephron) can help with management of patients with diuretic resistance.





Cardiorenal Syndrome - Show Notes

Definition and pathophysiology of cardiorenal syndrome

Definition of cardiorenal syndrome: Cardiorenal syndrome describes the bi-directional interactions between the heart and the kidneys. It encompasses both the effects that impaired heart function can have on renal function, as well as the impact of renal injury or chronic kidney disease on cardiac function (Rangaswami 2019).

Cardiorenal syndrome classification schemes: The five categories of cardiorenal syndrome first introduced by Ronco 2010 are:

- Type 1 - Acute worsening of heart function leading to kidney dysfunction
- Type 2 - Chronic heart failure leading to kidney dysfunction
- Type 3 - Acute worsening of kidney function (AKI) leading to heart dysfunction
- Type 4 - Chronic kidney disease leading to heart dysfunction
- Type 5 - Systemic factor causing dysfunction of both the heart and kidney (i.e. "something else knocking out both of them")

These classification schemes can be a helpful framework for thinking about what is happening. However, according to Dr. Topf, the vast majority of cases seen in the hospital will fall into the bucket of type 1 cardiorenal syndrome.

Pathophysiology of cardiorenal syndrome: Classically, the pathophysiology of cardiorenal syndrome was thought of as decreasing cardiac index leading to poor forward flow and subsequent reduced kidney perfusion/kidney dysfunction. However, in recent years, it has become apparent that reduced cardiac index/forward flow is not the primary driver of kidney dysfunction (Hanberg 2016). In fact, most patients coming in with decompensated heart failure, even those with reduced ejection fraction, have preserved cardiac indices.

Instead, it has become increasingly recognized that elevated venous pressure/ venous congestion plays a critical role in the pathophysiology of cardiorenal syndrome (Rangaswami 2019; Mullens 2020). Perfusion of any organ depends on the difference in pressure between the arterial and venous sides. While for many years it was thought that decreased arterial pressure was the culprit in causing kidney dysfunction in acute decompensated heart failure, it turns out that increased back pressure on the venous side leading to impaired kidney perfusion appears to be much more important (Mullens 2009; Damman, 2009). According to Dr. Topf, this pathophysiology directly

points to the therapeutic solution: If venous congestion is the problem, then drugs to reverse this congestion are the answer. Thus, we should not shy away from using diuretics in patients with acute decompensated heart failure presenting with an elevated creatinine - in fact, decongestion will likely directly address the underlying pathophysiology of their renal dysfunction.

Of course, if a patient is frankly hypotensive, the story is different, and poor forward flow may also contribute to renal dysfunction (Mullens 2020). In this case, use of inotropes and other measures will come into play, according to our guests.

Use of home ACE-is/ARBs and SGLT-2 inhibitors in patients presenting with acute heart failure and elevated Cr: In a patient presenting with acute decompensated heart failure and an elevated creatinine, there is a knee-jerk reaction to stop their home ACE-is/ARBs and SGLT-2 inhibitors. However, Dr. Topf argues that if they are not hypotensive or hyperkalemic, then there may not be any need to stop their ACE-is/ARBs and SGLT-2 inhibitors. If these medications are stopped during the hospitalization, our guests stressed that it is critically important to make sure that they are re-started prior to discharge, so that these important medications don't fall off following a hospital stay as too often happens in practice.

Approaching the creatinine "bump" with diuresis

Very commonly, a bump in creatinine will be observed with diuresis for acute decompensated heart failure, which can prompt fear of continuing to diurese, even if a patient still appears volume up. However, Dr. Topf and Dr. Khan both stress that a creatinine increase with diuresis does not necessarily signify kidney injury (Ahmad 2018; NephMadness blog post). In fact, our guests note that increased blood volume in the setting of volume overload can often dilute the creatinine to a certain degree, and thus decreasing the blood volume with diuresis will concentrate the creatinine and result in an increased creatinine lab value (akin to hemoconcentration, i.e. concentration of red blood cells, that is also seen with volume contraction). Thus, hemodynamic changes in creatinine with diuresis most often don't actually represent intrinsic, permanent damage to the kidney.

Indeed, in a post-hoc analysis of the DOSE trial, a rise in creatinine during admission for decongestion for acute decompensated heart failure was actually associated with improved outcomes (primary endpoint of death or rehospitalization / ER visit within 60 days) (Brisco 2016). According to Dr. Khan, this is likely because these patients were better diuresed. Dr. Khan notes that one of the most important markers of how well a patient admitted for decompensated heart failure will do when they leave the hospital is how dry they were when they left (Rubio-Gracia 2018). Thus, our guests emphasized that if a patient is still volume overloaded, it is important to continue to diurese even if their creatinine starts to rise - a concept known as "permissive hypercreatininemia" (NephMadness blog post).

Of course, the frequent ambiguity of the volume exam is one of the major challenges in deciding whether to push forward with diuresis and one of the reasons for the temptation to use a creatinine bump as an indication to stop diuresing. Dr. Khan notes that the volume exam can be especially tricky given that many patients don't have significant right-sided heart failure, so they won't present with marked lower extremity edema or a significantly elevated JVP. She says that it may be beneficial to turn more often to invasive hemodynamics (i.e. a right heart cath) to directly measure pulmonary artery pressure. The growing use of implantable pulmonary artery pressure monitoring devices will be very useful in this regard. Additionally, the use of POCUS to non-invasively evaluate the JVP or lungs can also help with clarifying volume status in combination with the history and exam (Beaubien-Souligny 2020).

Interpreting cardiac biomarkers in patients with CKD

Cardiac biomarkers such as troponin and BNP are difficult to interpret in patients with chronic kidney disease, as they are often chronically elevated in this population (NephMadness blog post; Bansal 2022). Yet these biomarkers are not completely uninformative in the setting of CKD. First of all, Dr. Khan stresses that while the absolute BNP may be difficult to interpret, the relative change in BNP from baseline in an individual with CKD is still valuable, as it can help point towards development of volume overload. Additionally, chronic elevation of cardiac biomarkers in many patients with CKD is not simply due to reduced clearance of these markers by the kidney. It turns out that prognostically, patients with CKD and elevated cardiac biomarkers have worse outcomes than those with normal cardiac biomarker levels (Michos 2014; Bansal 2019; Lamprea-Montealegre 2019; Wang 2020). Our guests emphasized that while a chronically elevated troponin in patients with CKD is usually not indicative of epicardial coronary disease (i.e. atherosclerotic coronary blockage), it does indicate that the patient has cardiac disease resulting in loss of cardiac muscle, most likely due to microvascular disease/endothelial dysfunction, which can lead poor cardiac outcomes down the road.

Managing diuretic resistance

Definition of diuretic resistance: Inability to achieve euvolemia despite being on a maximally tolerated dose of a diuretic (NephMadness blog post).

Maximizing Loop Diuretic Efficacy: Dr. Topf and Dr. Khan shared several tricks to optimizing use of loop diuretics in the setting of diuretic resistance:

- **Continuous IV loops diuretics vs bolus loop dosing:** The DOSE trial did not see a difference in efficacy between continuous IV dosing versus bolus dosing of loop diuretics (Felker 2011), though Dr. Topf notes that this trial evaluated continuous vs. bolus dosing as initial therapy, rather than in cases of diuretic resistance where bolus dosing has already failed. Additionally, according to Dr. Topf, an advantage of continuous IV dosing is that it

allows you to achieve a higher total dose of diuretic over a 24 hour period while avoiding large swings in diuretic levels/high peak levels, thus minimizing the risk of ototoxicity.

- **Choice of loop diuretic:** Bumetanide has several advantages over furosemide. Unlike furosemide, bumetanide levels are not as affected by GFR, so large dose adjustments do not need to be made to bumetanide dosing in kidney failure (Felker 2020). Additionally, in terms of oral use, bumetanide has better bioavailability than furosemide in the setting of gut edema (Felker 2020) (particularly important in HFpEF patients that tend to hide significant volume in their abdomen, according to Dr. Khan).

Sequential nephron blockade - layering on other diuretics: One of the major drivers of diuretic resistance is compensatory sodium reabsorption at sites distal to where loop diuretics act (NephMadness blog post; Rao 2017). A key strategy in managing patients with diuretic resistance is sequential nephron blockade, or blocking other "ports of re-entry" through which the kidney can try to reabsorb sodium. This can be done by layering on agents from different diuretic classes (NephMadness blog post.)

- **Thiazides / thiazide-like diuretics** - Combination therapy with a loop diuretic and a thiazide is often employed to treat diuretic resistance. According to Dr. Khan, she will usually start metolazone 2.5 mg three times per week (i.e. Monday/ Wednesday/Friday.) Metolazone has a long half life, and Dr. Khan stresses that some patients can have profound hypokalemic responses to even one dose (which can be dangerous in patients with low ejection fractions/susceptibility to ventricular arrhythmias.) Thus, closely monitoring the potassium is key.
- **Mineralocorticoid receptor antagonists** (ex. eplerenone, spironolactone) - According to our guests, MRAs can also be useful add-on therapies, particularly to address hypokalemic in patients being treated with loop diuretics +/- thiazides (See Curbsiders #308: Metabolic Alkalosis and Hypokalemia)
- **Acetazolamide, SGLT-2 inhibitors**: Both block sodium reabsorption at the proximal tubule.

Hyperdiuresis: Hyperdiuresis refers to the seemingly paradoxical strategy that has emerged in recent years of giving patients a small bolus of hypertonic saline with a loop diuretic (NephMadness blog post; Paterna 2011; Griffin 2020). According to Dr. Topf, this strategy may work by several possible mechanisms, including suppressing RAAS signaling to prevent sodium retention and drawing in interstitial fluid to the vascular compartment by osmosis (NephMadness blog post). This strategy should be used with caution and typically as a last resort. (Call to MedTwitter - has anyone used this strategy?)

Links

1. AJKD NephMadness 2022 Blog
2. NephMadness 2022 Sign-up

Goal

Listeners will develop an approach to evaluating and managing patients with cardiorenal syndrome, treating patients with diuretic resistance, and interpreting cardiac biomarkers in CKD.

Learning objectives

After listening to this episode listeners will…

1. Define cardiorenal syndrome (CRS)
2. Explain the hypothesized pathophysiology underlying cardiorenal syndrome
3. Approach a patient undergoing diuresis who experiences a bump in creatinine
4. Describe the role of cardiac biomarkers in a patient with CKD
5. Approach the work-up and management of a patient with diuretic resistance

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Disclosures

Dr. Topf has commercial interests with Bayer and AstraZeneca. Dr. Khan reports no relevant disclosures. The Curbsiders report no relevant financial disclosures.

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