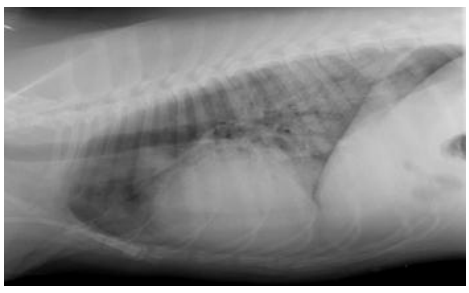
cpdsolutions
transferring knowledge through excellence in training

Current Concepts in Cardiology for Advanced Practitioners Mini Series

Session 3: Mechanisms and Management of Diuretic Resistance

Nuala Summerfield BSc BVM&S DipACVIM(Cardiology) DipECVIM-CA (Cardiology) MRCVS
RCVS & European Recognised Specialist in Veterinary Cardiology



Diuretic Usage in Veterinary Cardiology and the Problem of Diuretic Resistance

Part 1

Pathophysiology of volume overload in CHF

- In patients with acute heart failure, a decrease in cardiac function causes reduced cardiac output and arterial under-filling.
- This leads to decreased activation of arterial stretch receptors, which causes compensatory systemic and intra renal vasoconstriction.
- Decreased stretch of the glomerular afferent arteriole stimulates renin release, which leads to angiotensin II production.
- Angiotensin II release leads to afferent and efferent vasoconstriction, stimulation of sodium retention in the proximal tubule and release of aldosterone.
- Heart failure also results in baroreceptor-mediated sympathetic nervous system activation that promotes vasoconstriction and contributes to further RAAS activation and renal sodium and water retention.
- The release of antidiuretic hormone exacerbates these effects.
- Furthermore, the protective effect of natriuretic peptides is diminished in patients with acute heart failure.

Role of diuretics in CHF management

- Congestion (defined as elevated cardiac filling pressures) is a major component of the clinical syndrome of heart failure.
- Diuretics do not directly treat the pathologic changes that occur with CHF.
- However they remain the cornerstone of congestion management in both humans and veterinary patients.

Accurate assessment of volume status is of fundamental importance when treating CHF

- Congestion / oedema in CHF is usually due to increase in circulating blood volume.
- Blood volume can be increased by as much as 30 % in severe CHF.
- Diuretics are not indicated unless patient is in CHF – unnecessary stimulation of RAAS may cause more rapid progression of disease.

- But, it is important to remember that congestion is not always just a result of volume overload.

- Volume shifts from the splanchnic circulation towards the systemic circulation can either cause or exacerbate cardiac decompensation.
    - Under SNS activation, a decrease in capacitance of the venous reservoir corresponds to an almost instantaneous increased preload.
    - In patients with cardiac dysfunction, this sympathetically stimulated reduction in venous capacitance would serve to shift volume out of the splanchnic vessels and increase effective circulating blood volume, leading to increases in preload in the absence of any changes in total circulating blood volume or total body (intracellular plus extracellular) volume.

- This explains why, in some CHF patients, early symptoms of congestion occur without significant weight gain.
- These patients may be particularly prone to intravascular underfilling and arterial hypotension, due to the fact that a volume shift rather than true volume overload had lead to the congestion.
- Important to rely on unambiguous signs of volume overload such as oedema and weight gain to help to differentiate between volume shift and true volume overload.
- This will help guide diuretic therapy.

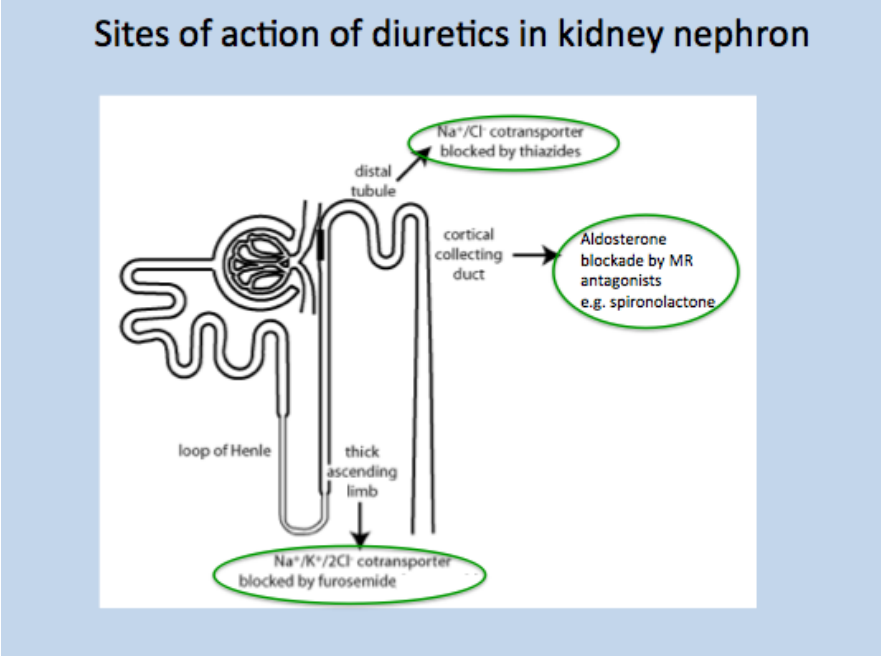
Renal nephron physiology

- In patients with normal renal function, 99% of the filtered sodium is reabsorbed.
- Approximately 60% of sodium is reabsorbed in the proximal tubule of the nephron, with an additional 30% being reabsorbed in the thick ascending limb of the loop of Henle.
- Nephron segments past the thick ascending limb of Loop of Henle do not maintain a prominent reabsorptive capacity (7-9% in distal convoluted tubule, 1-3% in collecting duct).

Diuretic classification

- Regulation of renal sodium excretion involves several sequential transport mechanisms in the renal tubule.
- Diuretics act on specific sodium transport mechanisms, and are classified based on their tubular site of action.
- Classes of diuretics used to treat congestive heart failure (CHF):

Loop diuretics
Thiazides
Aldosterone antagonists.



Level of evidence

- Level of evidence cited by current human and veterinary clinical practice guidelines is primarily based on expert opinion (Level C).
- Diuretics (with exception of aldosterone antagonists) have not been scrutinized as carefully as the other cardiac drugs.
- Several reasons for this:

Placebo-controlled studies are difficult to perform due to need to manage clinical symptoms of congestion.

Studies of diuretics as monotherapy are unethical due to published evidence of mortality benefits of other drugs that inhibit RAAS.

Safety of diuretic therapy

- Little information exists regarding the efficacy and safety of diuretic therapy in human and veterinary patients with CHF.
- Diuretics (with the exception of aldosterone antagonists) have not been shown to decrease heart failure progression or improve mortality.
- Safety studies are confounded by the association of higher diuretic doses with greater severity of illness and comorbidity.
- Can activate RAAS and sympathetic nervous system (SNS).
- May be associated with:
    - Potentially dangerous electrolyte imbalances
    - Worsening renal function (WRF)
        - Receiving a lot of attention in human medicine.
- Conventional diuretic therapy may lead to diuretic resistance.

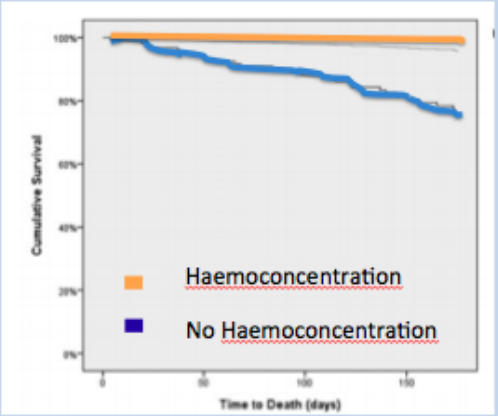
Cardio-renal interactions in CHF

- A major symptom of heart failure is decreased organ perfusion.
- The kidney can compensate for a drop in renal blood flow by increasing the filtration fraction via angiotensin II-mediated efferent vasoconstriction and thereby preserve GFR.
- The combination of pump failure, neurohormonal activation and therapies for heart failure, particularly angiotensin-converting- enzyme inhibitors and angiotensin-receptor blockers, can eventually overcome the kidney's capacity to compensate for reduced perfusion.
- In humans, renal dysfunction occurs frequently in patients with both acute and chronic HF.
- WRF is associated with higher mortality and morbidity.
- Cause of renal dysfunction in HF is multifactorial, but major contributing factors are:
- Decreased perfusion of kidney
- Venous congestion of kidney.
- Important to balance the negative effect of diuretic actions on arterial renal perfusion vs. the positive effect on venous congestion.
- Complex interplay between renal and cardiovascular systems.
- "Cardiorenal syndrome (CRS)" in humans is defined as "disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other" (Ronco et al 2010).
- In vet medicine, CRS has been named "cardiovascular-renal disorders (CvRD)" (Cardiovascular–renal axis disorders in the domestic dog and cat: a veterinary consensus statement Pouchelon et al JSAP 2015).
- $CvRD_H$ refers to kidney injury or dysfunction emanating from a primary disease process involving the cardiovascular system.
- In dogs and cats the existence of $CvRD_H$ is indirectly supported by observation that kidney dysfunction increases with severity of heart disease (Nicolle et al 2007, Gouni et al 2008)
    - further studies are warranted.

Importance of complete decongestion in acute CHF and potential impact on renal function

DOSE Trial Felker et al NEJM 2011

- Higher doses of diuretics are likely to be more efficacious in relieving congestion than a low-dose strategy.
- The small worsening of renal function does not appear to have long-term consequences in terms of outcomes.



- Haemoconcentration is significantly associated with measures of aggressive fluid removal and deterioration in renal function.
- However, despite this, haemoconcentration is associated with substantially improved survival.

(Testani et al Circulation 2010)

The concept of “dry weight”

- Very important goal for both short and long term care of patients suffering from fluid overload.
- ACC and the AHA recommendations:

“In general, patients should not be discharged from the hospital until a stable and effective diuretic regimen is established, and ideally, not until euvolaemia (dry weight) is achieved.

Patients who are sent home before these goals are reached are at high risk of recurrence of fluid retention and early readmission, because unresolved oedema may itself attenuate the response to diuretics.”

The potential role of dietary sodium restriction

- Common recommendation for human CHF patients (ACC/AHA 2013 guidelines):
  - “Sodium restriction is reasonable for patients with symptomatic CHF to reduce congestive symptoms (Level of Evidence: C)”.
- Several studies have looked at the potential role of sodium restriction in dogs with CHF.
- Results suggested some benefit
  - But studies were small and there was concern about owner compliance.
- No clinical studies published on sodium restriction in cats with CHF, but underlying pathology would support this approach.

Loop diuretics

- The loop diuretics used in veterinary cardiology:
  Furosemide
  Torasemide.
- Loop diuretics act on the Na^{+}-K^{+}-$2Cl^{-}$ co transporter in the thick ascending limb of the loop of Henle to inhibit sodium, chloride and potassium reabsorption.
- Require active secretion across proximal renal tubular cells in order to reach the lumen and its site of action.
- IV loop diuretics cause transient rapid venodilation (via prostaglandins or nitric oxide) resulting in a fall in cardiac filling pressures and decreased pulmonary congestion prior to the onset of diuresis.

Furosemide

- First line drug for treatment of acute CHF (IV boluses or CRI).
- Oral furosemide has variable absorption and bioavailability.
- Very short acting drug.
- Significant natriuresis for 6-hour period following drug dosing.
- Once daily dosing leads to “rebound” sodium retention

Sodium excretion falls to very low levels during the rest of the day because the resulting volume depletion leads to activation of RAAS and SNS.
Dosing frequency is an important consideration in cats (compliance vs. efficacy)
Especially if dietary sodium intake is not restricted
Role of sodium restriction in veterinary CHF patients?

- More effective when given in several divided doses per day
- N.B. Diuretics in diastolic heart failure

CO and BP are dependent on high filling pressures.
Patients with diastolic HF are more prone to the adverse consequences of hypovolaemia from overdiuresis.

Diuretics should be used judiciously in this situation (together with vasodilators?).
Pertinent to cats with HCM, RCM.

- The importance of achieving a “Minimal Effective Dose”

The reduction in intracardiac pressures induced by diuretics lowers intravascular pressure, which mobilises oedema fluid from interstitium into blood vessels (plasma refill rate).
Once extracellular oedema has resolved, this defence against intravascular volume depletion is not available.
Chronic over-diuresis can lead to a decline in cardiac output and activation of the RAAS (potential cause of WRF).

- Sleeping/resting respiratory rate (counted and recorded by owner) is a very effective method for home monitoring of CHF, to help guide diuretic dose reductions / increases.

Torasemide

- Second generation loop diuretic.
- Oral torasemide has higher bioavailability than oral furosemide due to its relatively consistent absorption and longer half-life (SID dosing).
- Recently licensed for dogs but has been studied as a treatment for CHF in both dogs and cats (Uechi et al J Vet Med Sci 2003).
- TORIC (Torasemide in Chronic Heart Failure) study results showed significantly less total and cardiac mortality in the group of patients treated with torasemide vs. furosemide/other diuretics (Cosin et al Eur J Heart Fail 2002).
- Due to greater bioavailability of torasemide or anti-fibrotic effects?

Does not act as MRA as previously proposed (Gravez et al 2013)

Torasemide reduces aldosterone synthase mediated pro-fibrotic signalling (Adam et al J Mol Cell Cardiol 2015).

Factors effecting loop diuretic efficacy

- Gastrointestinal oedema or gut hypoperfusion will result in impaired absorption of oral diuretics.
- Absorption might differ substantially between diuretics e.g. absorption of oral torasemide is likely to be better than that of oral furosemide under these conditions.
- SC or IM (or IV) administration of furosemide can overcome the impaired absorption of oral diuretics.
- Exacerbated by decreased renal perfusion or renal venous congestion resulting in decreased delivery of loop diuretics to kidney.
- May explain the frequent clinical observation that patients experience progressively diminishing diuretic efficacy of outpatient diuretics in the days leading up to a clinical decompensation.

Sequential nephron blockade

- Combination of other diuretic types (thiazides and/or aldosterone antagonists) with loop diuretics can improve efficacy of CHF management.

Thiazide diuretics

- Like loop diuretics, require active secretion across renal tubular cells to reach site of action, so efficacy falls with renal impairment.
- Inhibit reabsorption of sodium and chloride from the distal convoluted tubules by blocking the thiazide-sensitive Na^+ Cl^- co transporter.
- Used alone, they are relatively “mild” diuretics.
- Prevent “post-diuretic sodium retention” after the effect of loop diuretic wears off, as thiazides have longer half-life.
- The addition of a thiazide as a strategy of sequential nephron blockade is a common approach in human CHF patients who require high doses of loop diuretic (ACCF/AHA 2013 Guidelines Yancy et al JACC 2013).
- Important to monitor for volume depletion or electrolyte disturbances when combine thiazide with loop diuretic.

Aldosterone antagonists – (e.g. Spironolactone)

- Inadequate ACE inhibition by ACE-I (aldosterone escape)

Aldosterone escape occurs in dogs even with high dose ACE-I (Ames et al Am J Vet Res 2015).

- Aldosterone antagonists competitively antagonize the MR and reduce sodium reabsorption in collecting duct (conserve potassium).
- In humans with CHF, the benefits of spironolactone are believed to be largely due to its antagonism of aldosterone rather than to a diuretic effect
  RALES: 30% reduction in risk of death when compared with placebo (Pitt et al NEJM 1999).
- Survival benefits are reported in veterinary patients with CHF:

Dogs with CHF due to MMVD (Bernay et al JVIM 2010)
2 – 2.7 mg/kg/day

Cats with CHF due to cardiomyopathy (SEISICAT study. James R. Research communication. 25th Annual ECVIM-CA Congress, Lisbon, 2015)
1.7 – 3.3 mg/kg/day.

Low dose spironolactone (0.5 – 0.8 mg/kg/day) had no effect on survival in dogs with CHF due to MMVD or DCM (Schuller et al J vet Pharmacol Therap 2010).

- Concurrent use with ACE-I seems safe with regard to hyperkalaemia in cats and dogs.
- Ulcerative facial dermatitis appears to be an uncommon complication in cats.
- In humans with acute CHF, high-dose spironolactone has been used to increase the diuretic response (Ferreira et al Clin Res Cardiol 2013).

Home monitoring for chronic CHF

- Structured telephone monitoring
    - Potential to positively affect outcomes during vulnerable period after discharge.
    - Increased patient contact time to reinforce the importance of compliance with medication and diet regimens.
    - *Applicable to veterinary medicine.*

- Wearable technology
    - Promising for continuous noninvasive surveillance.
    - Wearable external device on a constant basis – compliance issues.
    - Role for a defined period post discharge.
    - *PetPACE collar, VoycePro system – new veterinary developments, but not yet validated in clinical practice to assess their true utility for CHF monitoring in dogs and cats.*

- Implantable technology
    - CardioMEMS® (direct pulmonary artery (PA) pressure measurements from wireless sensor implanted in PA) is the first and only FDA approved remote CHF monitoring device for humans (FDA approved in 2014).

Part 1 Summary

- Diuretics remain the cornerstone of congestion management in both humans and veterinary patients.
- Accurate assessment of volume status is of fundamental importance when treating CHF.
- Patients with diastolic heart failure are more prone to the adverse effects of hypovolaemia from over-diuresis than patients with systolic heart failure.
- In all patients the aim should be to use the lowest effective diuretic dose to ensure complete decongestion, whilst minimizing adverse effects, especially on renal function.
- Further studies into optimal use of diuretics, home monitoring of CHF and cardiorenal interactions are warranted.

Part 2

Diuretic resistance

- The administration of loop diuretics to achieve decongestion is the cornerstone of therapy for CHF.

- Unfortunately, impaired response to diuretics can develop in CHF patients and is associated with adverse outcomes.

- Definitions vary:
    - Persistent oedema despite adequate and escalating diuretic doses.
    - Diminished natriuretic response to repeated doses.
    - Failure to respond to IV loop diuretics.
    - Decreased efficacy of diuretics with prolonged treatment.

- CHF represents the most common clinical situation in which diuretic resistance is observed.
- In mild CHF, diuretic resistance is not commonly encountered, as long as renal function is preserved.
- However, in moderate and severe CHF patients, diuretic resistance occurs more frequently and often becomes a clinical problem.
- Although difficult to quantify, diuretic resistance is thought to occur in as many as 1 in 3 human patients with CHF.

Evaluating diuretic response

- Diuretic response should be determined objectively based on the effect of the diuretic dose administered:

Weight loss per unit of furosemide
Net fluid loss per milligram of loop diuretic during hospitalization
Natriuretic response to furosemide as the ratio of urinary sodium to urinary furosemide.

- Haemoconcentration has also been suggested as a practical and readily applicable strategy to assess diuretic response.
- Ultimately, the use of such measures of diuretic response could be used to help to identify patients who might benefit from alternative decongestive therapies and to guide treatment selection.

- Diuretic resistance is important because studies have shown that in humans, the patients that require the highest doses of loop diuretics to control their CHF have the poorest survival, but more studies are needed to confirm that the relationship is causative.

Mechanisms of diuretic resistance

- What causes diuretic resistance?
    - Diminished effect in heart failure and renal failure

Decreased absorption, binding, delivery +/- secretion.
Venous congestion impairs renal tubular function
Recognised in acute CHF, uncertain role in <u>chronic</u> CHF.

- Stimulation of NH axes (braking phenomenon).
- Hypertrophy of distal tubules impairs natriuretic response.
- Post-diuretic (“rebound”) NaCl retention.
- N.B. Also consider:
    - Drug interactions e.g. NSAIDS /BUN.
    - Owner compliance.
    - Dietary sodium intake.

The role of hypoalbuminaemia in diuretic resistance

- Most loop diuretics and thiazide diuretics are bound to plasma albumin.
- These diuretics act on their molecular target from the luminal side.
- Consequently, these drugs must be filtered by the glomerulus and actively secreted into the tubular lumen by the proximal tubule's organic anion transporter (OAT) in order to function.
- Hypoalbuminaemia, which is common in human patients with heart failure, impairs the uptake and secretion of active furosemide and enhances conversion to its inactive form.
- Additionally, albumin lost into the tubule might bind furosemide and prevent it from acting on the sodium–chloride–potassium co-transporter.
- Coadministration of albumin and furosemide improves diuretic response in human patients with cirrhosis, nephrotic syndrome, or chronic kidney disease, but no data are available in individuals with heart failure.

The role of the "braking phenomenon" in diuretic resistance

- At the onset of diuretic treatment, the natriuretic effect results in the intended negative sodium balance.
- The resulting decrease in extracellular volume triggers a homeostatic response, mediated by activation of the RAAS and SNS, leading to increased sodium retention at tubular sites not targeted by the specific diuretic.
- However, in patients with pre-existent secondary hyperaldosteronism, such as those with heart failure, this phenomenon can be pronounced, causing rapid and abundant sodium reabsorption and contributing to diuretic resistance.

The role of distal tubular hypertrophy in diuretic resistance

- Persistent delivery of sodium or diuretics to the distal tubule leads to hypertrophy of the distal tubular cells.
- Bypasses the proximal effect of the loop diuretic and results in enhanced sodium retention.

The role of NSAIDs in diuretic resistance

- NSAIDs potentially lead to diuretic resistance by interfering with prostaglandin synthesis (vasodilator PGs are responsible for vasodilation of afferent renal arteriole).
- Reduced GFR (from vasoconstriction of afferent renal arteriole) results in decreased delivery of furosemide to kidney.
- NSAIDs also inhibit OAT- mediated secretion of furosemide into lumen of PCT
    - furosemide needs to be actively secreted into lumen of PCT in order to reach site of action in ascending loop of Henle.

The role of blood urea nitrogen (BUN) in diuretic resistance

- Patients with heart failure and chronic renal dysfunction have elevated levels of circulating organic acids such as blood urea nitrogen (BUN).
- BUN can competitively inhibit the organic anion transporter (OAT) and further reduces diuretic availability at the site of action.

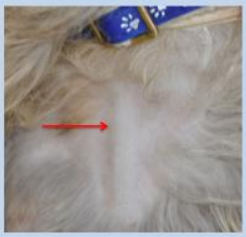
Some important considerations when assessing a patient with diuretic resistance (apparent decreased response to loop diuretics and worsening renal function)

- What is the patients' volume status?

congested or hypovolaemic

- Is the patient vasoconstricted?
- Is the cardiac pump function adequate to maintain renal perfusion?

High central venous pressure



Patient is too wet!

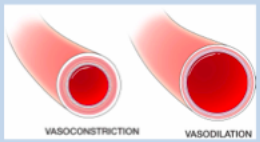
- Poor renal perfusion due to high central venous pressure.
- Diuretics often withheld because of worsening renal function and misguided idea of " intravascular volume depletion".
- Continue diuretics to reduce central venous pressure.
- Drain ascites if present.

Hypovolaemic

Patient is too dry!

- Overdiuresed or intercurrent illness results in volume loss and renal dysfunction.
- Give fluids, stop diuretics and IV vasodilators.
- Often a reluctance to give fluids to HF patients but it may be critical in this situation and time is of the essence to avoid irreversible renal damage.

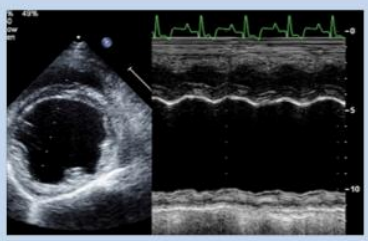
Vasoconstriction



Patient is clamped down!

- Low CO and hence renal hypoperfusion due to HF mediated vasoconstriction (Ang II, endothelin induced increased afterload).
- ACEI and vasodilators can be very useful since CO can increase significantly if afterload normalized
  - Vasodilator drugs to consider: pimobendan, nitroprusside, amlodipine, hydralazine.
- Actual improvement in renal function may be seen.
- May need temporary inotropic support if systolic BP <80 as vasodilators are added (pimo would have this added benefit).

Myocardial systolic failure



No pump!

- Inadequate renal perfusion because of low cardiac ouput and/or BP.
- Needs inotropes, pressors (pimobendan or dobutamine).

Treatment options for diuretic resistance

- Chronic CHF:

Change loop diuretic.
Combination of loop diuretic plus thiazide
Sequential Nephron Blockade.
Switch from PO to SC home dosing.
More frequent daily dosing of loop diuretic (TID or QID).
Acute CHF (In hospital):
CRI vs. IV bolus dosing.
Combination hypertonic saline + loop diuretic??

Change loop diuretic

- Oral torasemide has higher bioavailability than oral furosemide due to its relatively consistent absorption and longer half-life.

Suitable for once daily dosing.

- Remember, torasemide is much more potent than furosemide!

A single dose of torasemide had approximately 20 times the diuretic effect of a single dose of furosemide

Sequential nephron blockade

- Combine loop diuretic with a thiazide

Inhibition of Na+ reabsorption in DCT.
Prevent post-diuretic sodium retention after effect of loop diuretic wears off; thiazides have longer half-life.
Synergism.

- Add aldosterone antagonist (spironolactone)

To block Na+ reabsorption in CD caused by hyperaldosteronism.
Conserve K+.

Potential benefit of giving furosemide as a continuous rate infusion (CRI) vs. bolus

- In dogs:

The same total dose of CRI furosemide resulted in more diuresis, natriuresis and calciuresis and less kaliuresis than intermittent bolus furosemide in healthy Greyhound dogs over an 8 hour period.

- N.B. these were healthy research dogs, not in CHF.
- (Adin et al JVIM 2003)

- In humans:

Bolus vs. continuous infusion: DOSE-AHF study (Felker NEJM 2011).
No difference in symptom relief or survival.

Investigational treatment options for diuretic resistance:

- Given the limitations of traditional diuretics in heart failure, there has been substantial interest in developing alternative strategies to manage congestion and volume retention in heart failure patients.
- Various intravenous agents have been investigated in acute heart failure in humans.
- Although none has shown convincing survival benefits in CHF to date, several have mechanisms of action that might be helpful in overcoming diuretic resistance in CHF.

Combination of hypertonic saline solution (HSS) + loop diuretic.
Vasopressin antagonists
Synthetic natriuretic peptides
Adenosine receptor antagonists
Serelaxin
Ultrafiltration

Current challenges faced in veterinary cardiology

- We need to validate methods to measure diuretic efficacy in our patients.
- Studies are needed of new diuretic strategies as rescue agents in acute CHF.
- Studies are needed of diuretic combinations in chronic CHF, for example:

Torasemide vs. furosemide
Optimal methods of sequential nephron blockade.

Part 2 summary

- The administration of loop diuretics to achieve decongestion is the cornerstone of therapy for acute heart failure.
- Impaired diuretic response is a common complication in human patients with heart failure and is associated with increased rehospitalization and mortality compared with patients who have normal diuretic response.
- Likely to also be the case for our veterinary CHF patients.
- Impaired absorption, decreased renal blood flow, inadequate decongestion, braking phenomenon and DCT hypertrophy diminish diuretic effectiveness.
- Several treatment strategies, including changing loop diuretic, sequential nephron blockade, SC home dosing and increasing frequency of home dosing of loop diuretic, can all help to improve diuretic responsiveness.