The Renin-Angiotensin-Aldosterone System: Pathologic Implications and Strategies to Break the Cycle

Presentation Notes

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Heart failure (HF)

- Heart failure defined as clinical symptoms associated with the heart's inability to provide sufficient cardiac output to meet the body's metabolic demands
- Congestive heart failure defined as the clinical signs associated with fluid accumulation secondary to cardiac decompensation
- Systolic dysfunction – myocardial infarction, DCM, ARVC
- Diastolic dysfunction – systemic hypertension, HCM, RCM, UCM
- Combination

Neurohormonal response to HF

- Decreased cardiac output → decreased renal perfusion → stimulates renin and ADH release
- Decreased cardiac output → increased sympathetic tone → stimulates renin release
- Decreased cardiac output and stimulation of RAAS → natriuretic peptide (NP) release

RAAS

- Role of RAAS is to replenish vascular volume via Na and water retention
- Stimulators of RAAS
    - Hypovolemia
    - Hypotension
    - Hyponatremia
    - Sympathetic tone
    - Iatrogenic – furosemide, amlodipine
- RAAS pathway
    - Renin released by juxtaglomerular cells of the renal afferent arterioles
    - Renin converts angiotensinogen (from the liver) to angiotensin I
    - Angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II in plasma and tissues
        - ACE is produced in endothelial cells; most concentrated in the lungs
    - Angiotensin II stimulates:
        - Aldosterone release
        - ADH release
        - Vasoconstriction (one of the most potent)
        - Fibrosis – myocardium and kidneys most affected
        - Na reabsorption
        - Negative myocardial energy balance
        - Thirst
    - Aldosterone then leads to:
        - Na reabsorption
        - Fibrosis

Plasma vs. tissue RAAS

- 10% of all ACE activity is in the plasma
- Remaining 90% of ACE activity is in tissues – mainly in the myocardium and kidneys
    - Non-ACE pathways responsible for converting angiotensin I to angiotensin II
        - Chymase, cathepsin G

Aldosterone breakthrough

- Definition
    - Increased aldosterone concentrations despite ACE-inhibitor or angiotensin receptor blocker (ARB) therapy
        - Increased a certain % from baseline
        - Increased above a specific cutoff value
- Incidence
    - Aldosterone concentrations increase within 7 days of treatment with furosemide and ACE-inhibitors in healthy dogs
    - ~ 30% incidence in dogs treated for CHF

What can we do to try and stop this process?

- ACE-inhibitors
    - Classically, these have been used to prevent conversion of AT-I to AT-II
    - Strong benefit shown in humans in the past few decades
    - Debatable benefit in dogs, but overall most likely beneficial
    - Aldosterone breakthrough still occurs in humans and dogs despite their use
- Angiotensin receptor blockers (ARBs)
    - Used in place of ACE-inhibitors in humans if ACE-inhibitors are not well-tolerated
    - May not be superior to ACE-inhibitors in humans
    - Not evaluated extensively in clinical veterinary patients
    - Aldosterone breakthrough still occurs
- Spironolactone
    - Improved morbidity and mortality in humans and dogs
    - Shows the impact aldosterone can have on prognosis

What can the heart do to stop this process?

- Natriuretic peptides (NP)
    - Peptides released from the atrial and ventricles
    - Body’s own anti-RAAS hormonal system
        - Inhibits renin release
        - Inhibits sympathetic tone
        - Inhibits angiotensin II release and production
        - Inhibits aldosterone release
        - Reduces hypertrophy
        - Improves myocyte metabolism
        - Increased GFR
        - Angiogenesis
        - Vasodilation
    - Production
        - Atrial NP (ANP) mostly from the atrial

        - Brain NP (BNP) mostly from the ventricles
    - Release
        - Released during stretch and increased wall tension of the cardiac chambers
    - Clearance
        - Removed via clearance receptors and neprilysin (enzyme)
        - Inhibiting neprilysin prevents NP degradation → increases NP concentrations

Using natriuretic peptides to mitigate RAAS

- Administering exogenous NPs
    - Lowers BP
    - Enhances GFR
    - Mediates natriuresis and diuresis
    - Suppresses RAAS + inhibits aldosterone
    - Anti-fibrotic effects
- Inhibiting neprilysin
    - Lowered BP
    - Not superior to ACE-inhibitors
    - Neprilysin degrades angiotensin II
        - **Simultaneous RAAS suppression is necessary with neprilysin inhibition therapy or angiotensin II levels increased drastically → increased morbidity**

- Entresto (Novartis) was developed
    - Combination of sacubitril (neprilysin inhibitor) + valsartan (angiotensin receptor blocker)
    - Reduced morbidity and mortality in humans by 20% compared to enalapril
    - Less renal adverse effects vs. enalapril
    - Improved quality of life vs. enalapril
    - Became standard of care for HF in humans in place of ACE-inhibitors

- Proof of mechanism study with Entresto performed in dogs (Dr. Mochel et al.)
    - Healthy dogs with experimentally-induced RAAS activation
    - Compared Entresto to:
        - Placebo
        - Benazepril
        - Valsartan
    - Entresto caused a significantly greater reduction in plasma aldosterone concentrations compared to all other medications
    - Renin and angiotensin II levels increased to a greater extent in the Entresto group, showing its efficacy at interrupting the RAAS
    - cGMP increased to a greater extent in the Entresto group
        - cGMP is a secondary messenger in the NP cascade
    - No adverse effects

- Entresto in dogs with naturally occurring myxomatous mitral valve disease
    - Clinical trial performed at the AUVTH
    - Inclusion criteria – small-breed dogs with stage B2 MMVD
        - All patients enrolled were on pimobendan as standard of care
        - Minimum database performed in all patients to rule out systemic disease
    - Methods

        - Two groups – placebo group (PO BID) and Entresto group (20 mg/kg PO BID)
        - Sampling occurred on day 0 (initial screening day), day 7, and day 30
            - Serum renal profile and electrolytes – days 0, 7, and 30
            - Thoracic radiographs – days 0 and day 30
            - Systolic blood pressure (Doppler) – days 0, 7, and 30
            - Echocardiography – days 0 and day 30
            - Plasma NT-proBNP concentrations – days 0, 7, and 30
            - Urine aldosterone:creatinine concentrations – days 0, 7, 30
    - Results
        - Urinary aldosterone:creatinine concentrations significantly lower in the Entresto group
        - No change in NT-proBNP concentration between groups
        - No changes to renal values or electrolyte concentrations
        - No adverse effects noted at home
    - Conclusion
        - Entresto appears to be effective at lowering/preventing an increase in aldosterone concentrations in dogs with naturally occurring MMVD
    - Future directions
        - Comparing Entresto to ACE-inhibitors in stage B2 dogs
        - Comparing morbidity and mortality between Entresto and ACE-inhibitors in stage C dogs

Summary

- The RAAS is detrimental to our patients, increasing morbidity and mortality
- Current standard of care medications may not be mitigating the detrimental effects of RAAS as well as we would like
- Entresto or drugs with similar mechanisms of action may be beneficial for medical therapy of congestive heart failure in veterinary patients.