



BEYOND FUROSEMIDE: THE ROLE OF DIURETICS IN CONGESTIVE HEART FAILURE *Part 2: Spironolactone*

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This article reviews information from the session, **Cardiology Without Intimidation**, presented at the NAVC Institute 2014. The NAVC Institute 2016 takes place in Orlando, Florida, May 15 to 20; visit navc.com/institute for further information.



Diuretics are a critical component of the pharmacotherapy of congestive heart failure (CHF). In humans with heart failure, 90% receive at least one diuretic.¹ Of these, loop diuretics—furosemide, bumetanide, and torsemide—are the most potent and commonly used diuretics. When a single drug is administered in humans, furosemide is given 87% of the time.¹

Furosemide has been, and remains, the diuretic of choice for acute and chronic management of CHF in both humans and animals since its release in 1966. However, other interesting options are now available, including:

- Torsemide, a loop diuretic that can be used as an adjunct or alternative to furosemide
- Spironolactone, a weak, potassium-sparing diuretic and mineralocorticoid receptor (MR) blocker that is used primarily for additional blockade of the renin-angiotensin-aldosterone system (RAAS). In heart failure, it typically accompanies a more potent diuretic, such as furosemide.

This article, the second in a 2-part series, discusses spironolactone. Read **Part 1: Torsemide** (January/February 2016) at tvjournal.com.

ACTIVITY & ADMINISTRATION

Spironolactone is a synthetic 17-lactone drug and competitive aldosterone receptor (mineralocorticoid

receptor) blocker (MRB). This antagonism of the MR in distal renal tubule cells results in an *increase* in urinary sodium and water excretion and *decrease* in potassium excretion.

In the dog, spironolactone is relatively quickly absorbed through the gastrointestinal tract into the plasma; then converted to several active metabolites.^{2,3} The bioavailability of spironolactone in dogs is highest when it is administered with food, reaching 80% to 90%.⁴

Using an experimental model of hyperaldosteronism, mimicking that in heart failure (see **Heart Failure: Effects of Hyperaldosteronism**), Guyonnet and colleagues found that the spironolactone

Heart Failure: Effects of Hyperaldosteronism

In animals with heart failure, chronic exposure to high concentrations of aldosterone:

- Results in excessive sodium retention, with expansion of extracellular volume
- Favors potassium and magnesium wasting
- Inhibits myocardial norepinephrine reuptake
- Diminishes heart rate variability (a sign of cardiac health)
- Produces cardiac arrhythmias
- Decreases baroreceptor sensitivity
- Contributes to endothelial dysfunction and vascular inflammation.

High concentrations of aldosterone are also independently associated with renal, vascular, and cardiac remodeling and heart failure.

dosage of 2 mg/kg PO Q 24 H restored the urinary sodium:potassium ratio to near normal via increased urinary sodium excretion and decreased urinary potassium excretion.⁴ On the basis of this result, and analysis of pharmacokinetic and pharmacodynamic data, the optimal dosage of spironolactone in dogs appears to be 2 mg/kg PO Q 24 H. The dosage established by this preclinical trial has been used in subsequent clinical trials.^{4,5} Of note, in this study, spironolactone was administered with food.

An earlier study found that spironolactone had no effect on urinary sodium and water excretion in normal dogs when it was administered at dosages of 1, 2, 4, and 8 mg/kg PO Q 24 H for 8 days.⁶ Urinary potassium excretion, however, did decrease significantly at dosages of 1 and 2 mg/kg. These results—when compared to the results of the study by Guyonnet and colleagues—may be explained by the lack of hyperaldosteronism and administration of spironolactone to fasted dogs. While differences in timing of blood sampling for one of spironolactone's active metabolites (canrenone) does not allow for direct comparison between studies, blood canrenone concentrations were apparently higher in dogs that received spironolactone *with* food.

RATIONALE FOR USE

Spironolactone was initially used to provide sequential nephron blockade and combat hypokalemia that resulted from the use of loop and thiazide diuretics. In the past 3 decades, the understanding of the consequences of excessive and prolonged aldosterone secretion in the progression and perpetuation of chronic cardiovascular and renal disease has grown significantly.^{7,8}

Specifically, aldosterone has been implicated in the pathologic remodeling—inflammation, hypertrophy, fibrosis—of cardiovascular and renal tissues. Therefore, the primary rationale for adding spironolactone as adjunctive therapy for heart failure is now MR (specifically, aldosterone) blockade.

RAAS BLOCKADE

In Humans

Spironolactone and another synthetic MRB, eplerenone, have recently been evaluated in humans with mild to severe heart failure and low ejection fraction.⁹⁻¹¹ The positive results of these studies showed that the addition of spironolactone or eplerenone to standard heart failure therapy—an angiotensin-converting enzyme inhibitor (ACEI) and

a loop diuretic, with or without beta-blockers and with or without digoxin—led to a significant reduction in morbidity and mortality when compared with standard therapy alone.

These studies showed a significant benefit when additional blockade of the RAAS—in the form of MR blockade—was added to preexisting RAAS blockade with an ACEI. MR blockade is now considered the standard of care in humans with heart failure and low ejection fraction.^{12,13} The benefit seen with additional RAAS blockade in heart failure supports the concept of aldosterone breakthrough (see **Aldosterone Breakthrough**, page 90).

In Dogs

A similar study was performed in 212 dogs with naturally occurring myxomatous mitral valve disease (MMVD) and heart failure. This study demonstrated a 69% reduction in risk for cardiac morbidity and mortality when spironolactone was added to standard therapy (ACEI and furosemide, with or without digoxin) as compared with standard therapy alone (**Figure**).⁵

A separate safety analysis of dogs involved in the aforementioned study demonstrated that, when compared with dogs receiving placebo and standard therapy (loop diuretic, ACEI, and pimobendan), those receiving spironolactone in addition to standard therapy¹⁴:

- Were not at higher risk for adverse events, such as

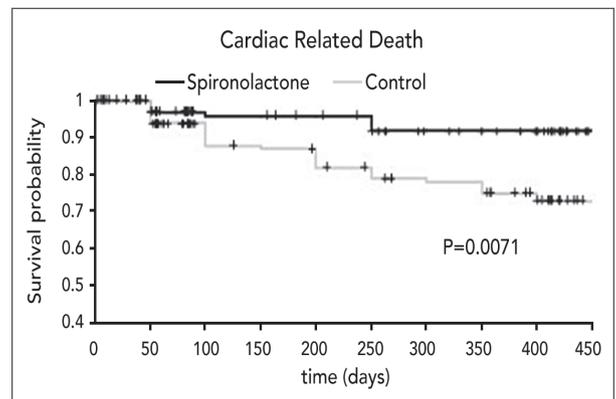


FIGURE. Kaplan-Meier plot of percentage of dogs remaining in the study⁵ over time. Of 212 dogs, 102 were treated with spironolactone in addition to standard therapy and 110 were treated with standard therapy alone. Dogs with myxomatous mitral valve disease treated with spironolactone remained in the study for a significantly longer time period. Adapted from Bernay F, Bland JM, Häggström J, et al. Efficacy of spironolactone on survival in dogs with naturally occurring mitral regurgitation caused by myxomatous mitral valve disease. *J Vet Intern Med* 2010; 24:331-341.

death from renal disease and variations in serum sodium, potassium, urea nitrogen, and creatinine

- Had lower mortality associated with cardiac disease, kidney disease, or both
- Of most importance, did not have a greater incidence of hyperkalemia.

In a study of Doberman pinschers with occult dilated cardiomyopathy (DCM), significant increases in serum potassium concentration (compared to each dog's baseline values) were seen in those receiving both spironolactone and an ACEI.¹⁵ Although we deemed these changes clinically insignificant, in 50% of dogs, the serum potassium concentration exceeded the reference interval. Therefore, regular monitoring of serum electrolytes and renal values (as often as every 3 months) was recommended for Doberman pinschers receiving spironolactone and an ACEI.

Overall, regular monitoring of serum electrolytes and renal values is prudent in all animals receiving vasodilators and diuretics, including spironolactone and ACEIs. Finally, spironolactone in combination with ACEI therapy appears to be safe when used to treat dogs with naturally occurring asymptomatic MMVD, as well as those with occult DCM without preexisting azotemia.^{15,16}

INDICATIONS

Dogs with MMVD

The 2009 consensus statement from the American College of Veterinary Internal Medicine defines the stages of heart disease and failure (**Table**) and provides guidelines for therapy of dogs with MMVD.¹⁷

- The guidelines recommend spironolactone as an adjunctive therapy in dogs with ACVIM stage D2 (refractory heart failure managed on outpatient basis) MMVD.
- A majority of panelists used spironolactone to treat ACVIM stage C2 (heart failure managed on outpatient basis) MMVD, although consensus (100% agreement) was not reached.
- A minority of panelists advocated the use of spironolactone in dogs with ACVIM stage B2 MMVD.

Spironolactone is approved within the European Union as adjunctive therapy for canine heart failure, secondary to MMVD. Clinical trials are currently evaluating the effects of spironolactone in combination with an ACEI in the treatment of dogs with stage B2 and C MMVD.^{4,18}

Dogs with DCM & Congenital Heart Disease

There are currently no consensus statements regard-

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the **ACVIM Guidelines for the Diagnosis and Treatment of Canine Chronic Valvular Heart Disease** at <http://onlinelibrary.wiley.com/doi/10.1111/j.1939-1676.2009.0392.x/full>.

TABLE.

ACVIM Classification of Heart Disease & Failure in Dogs¹⁷

STAGE	DEFINITION
Stage A	Identifies patients at high risk for developing heart disease but currently no identifiable structural disorder of the heart (eg, a cavalier King Charles spaniel without a heart murmur)
Stage B	Identifies patients with structural heart disease (eg, typical murmur of mitral valve regurgitation present) but no clinical signs caused by heart failure
Stage B1	Refers to asymptomatic patients that have no radiographic or echocardiographic evidence of cardiac remodeling
Stage B2	Refers to asymptomatic patients that have hemodynamically significant valve regurgitation, as evidenced by radiographic or echocardiographic findings of left-sided heart enlargement
Stage C	Denotes patients with past or current clinical signs of heart failure associated with structural heart disease
Stage C1	Identifies patients that require acute, hospital-based therapy
Stage C2	Identifies patients that can be managed as outpatients
Stage D	Refers to patients with end-stage disease with clinical signs of heart failure caused by chronic valvular heart disease that are refractory to standard therapy*; such patients require advanced or specialized treatment strategies in order to remain clinically comfortable
Stage D1	Identifies patients that require acute, hospital-based therapy
Stage D2	Identifies patients that can be managed as outpatients

* As defined by the panel in the guidelines



Aldosterone Breakthrough

The positive results from studies of MRBs in patients with heart failure and low ejection fraction support the existence of aldosterone breakthrough (ABT): the phenomenon in which RAAS blockade with an ACEI—with or without an angiotensin-receptor blocker (ARB)—is incomplete and aldosterone levels rise despite RAAS suppressive therapy.

UAldo:C Ratio

We use the urine aldosterone-to-creatinine (UAldo:C) ratio, which correlates to 24-hour urine aldosterone excretion,²⁸ to assess RAAS activation in clinical patients and experimental RAAS activation,²⁹⁻³⁵ and propose a cutoff value of 1 mcg/g. This value is the mean +2 standard deviation of the UAldo:C ratio in a population of young (1–2 years of age) normal dogs from North Carolina State University Veterinary Hospital and Colorado State University Veterinary Hospital.³⁶

Definition

There is no consensus regarding the definition (and, therefore, incidence), mechanism, and clinical implications of ABT in humans with chronic cardiovascular or renal disease, although its existence and importance are uniformly accepted.³⁷ However, we suggest 2 definitions for ABT—based on UAldo:C ratio:

1. UAldo:C ratio that increases relative to baseline values, despite therapy with ACEI or ARB or
2. UAldo:C ratio that exceeds an absolute cutoff value.

Incidence

Preliminary data from our clinics suggest that ABT occurs in dogs with heart failure due to naturally occurring heart disease, with an incidence of approximately 40%. This percentage is similar to that found in our model of RAAS activation as well as the incidence of ABT in humans receiving an ACEI. ABT also appears to occur early in the disease course.³⁷

Monitoring the UAldo:C ratio may, therefore, help optimize an individual patient's pharmacotherapy and determine whether spironolactone should be added as an adjunctive therapy to improve RAAS blockade.

ing the use of spironolactone in other diseases, such as DCM, heartworm disease, and congenital heart disease. Logic supports spironolactone's utility and its history, along with research data, support its safety.

Heart Failure with HFpEF

The role of spironolactone in the treatment of heart failure due to ventricular diastolic dysfunction and preserved systolic function (heart failure with preserved ejection fraction [HFpEF]) is an area of ongoing research.

The association between hyperaldosteronism and development of myocardial fibrosis in human and experimental animal models of hypertension is well established.¹⁹ Small studies in humans with HFpEF have shown that MR blockade with spironolactone improved diastolic function.^{20,21}

However, in a recently completed large study in humans with HFpEF, the addition of spironolactone

to existing heart failure therapy did not result in a significant survival benefit or reduction in hospitalization for heart failure, although there were substantial geographic differences in patient response.²² The incidence of hospitalization for heart failure was lower in the spironolactone group.

Cats with HCM

Hyperaldosteronism and activation of the RAAS, in particular, are implicated in the pathologic ventricular remodeling and diastolic myocardial dysfunction in hypertrophic cardiomyopathy (HCM) in humans.²³

Aldosterone is elevated in Maine coon cats with asymptomatic HCM,²⁴ and use of spironolactone (2 mg/kg PO Q 24 H for 4 months) for asymptomatic HCM in cats has been evaluated.²⁵ Unfortunately, this study did not show reduction in left ventricular mass or improvement in an echocardiographic parameter of diastolic function, and 4 of the 13 cats treated with spironolactone developed ulcerative facial dermatitis.

A double-blinded, placebo-controlled clinical trial has evaluated the use of spironolactone (1.7–3.3 mg/kg PO Q 24 H) in cats with heart failure due to cardiomyopathy (the majority of cats had HCM).²⁶ All cats were also receiving furosemide and benazepril. The results of this study demonstrated an improved survival rate of 15 months in cats receiving spironolactone when compared to those receiving placebo. Also, at interim analysis²⁷ ($n = 16$ cats enrolled), no cat receiving spironolactone had experienced ulcerative facial dermatitis.

IN SUMMARY

Based on clinical and research data, we use spironolactone in almost all instances in which ACEIs are used, which includes dogs with the following:

- ACVIM stage B2 MMVD: Cardiac enlargement, but before onset of heart failure (pulmonary edema)
- ACVIM stage C2 and D2 MMVD: At-home therapy of CHF
- Systemic hypertension
- Occult and symptomatic DCM
- Proteinuric renal disease.

Although preliminary data are promising, we do not feel there is yet adequate evidence for routine use of spironolactone in cats.

ABT = aldosterone breakthrough; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; CHF = congestive heart failure; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy;

HFpEF = heart failure with preserved ejection fraction; MMVD = myxomatous mitral valve disease; MR = mineralocorticoid receptor; MRB = mineralocorticoid receptor blocker; RAAS = renin-angiotensin-aldosterone system; UAldo:C = urine aldosterone-to-creatinine

Footnote

- a. Unpublished data from the ongoing Ceva Animal Health LLC, BESST: Benazepril Spironolactone Study.

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Spironolactone: Key Points

- The optimal dosage of spironolactone in dogs appears to be 2 mg/kg PO Q 24 H.
- Spironolactone in combination with ACEI therapy appears to be safe when used to treat dogs with naturally occurring asymptomatic MMVD or occult DCM without preexisting azotemia.
- Bioavailability of spironolactone in dogs is highest when it is administered with food.
- Regular monitoring of serum electrolytes and renal values is prudent in all animals receiving vasodilators and diuretics, including spironolactone and ACEIs.
- Monitoring the UAldo:C ratio may help optimize an individual patient's pharmacotherapy and determine whether spironolactone should be added as an adjunctive therapy to improve RAAS blockade.



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