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Aldosterone breakthrough in dogs with naturally occurring myxomatous mitral valve disease

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Abstract *Introduction:* Aldosterone breakthrough (ABT) is the condition in which angiotensin converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers fail to effectively suppress the activity of the renin angiotensin aldosterone system. The objective of this study was to determine if ABT occurs in dogs with naturally occurring myxomatous mitral valve disease receiving an ACEI, using the urine aldosterone to creatinine ratio (UAldo:C) as a measure of renin angiotensin aldosterone system activation.
Animals, Materials and Methods: This study includes 39 dogs with myxomatous mitral valve disease. A UAldo:C cut-off definition (derived from a normal population of healthy, adult, and client-owned dogs) was used to determine the prevalence of ABT in this population. Spearman analysis and univariate logistic regression were used to evaluate the relationship between UAldo:C and ABT (yes/no) and eight variables (age, serum K^+ concentration, serum creatinine concentration, ACEI therapy duration and ACEI dosage, furosemide therapy duration and furosemide dosage, and urine sample storage time). Finally, the UAldo:C in dogs receiving spironolactone, as part congestive heart failure (CHF) therapy, was compared to dogs with CHF that were not receiving spironolactone.
Results: The prevalence of ABT was 32% in dogs with CHF and 30% in dogs without CHF. There was no relationship between either the UAldo:C or the likelihood of ABT

Preliminary results were presented at the 2014 American College of Veterinary Internal Medicine Forum, Nashville, TN, USA, June 2014.

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and the eight variables. Therapy with spironolactone lead to a significant elevation of the UAldo:C.

Discussion: Using the UAldo:C and a relatively stringent definition of ABT, it appears that incomplete RAAS blockade is common in dogs with MMVD receiving an ACEI. The prevalence of ABT in this canine population mirrors that reported in humans. While the mechanism of ABT is likely multifactorial and still poorly understood, the proven existence of ABT in dogs offers the potential to improve the prognosis for MMVD with the addition of a mineralocorticoid receptor blocker to current therapeutic regimens.

Conclusions: Approximately 30% of dogs being treated for heart disease and CHF satisfied the definition of ABT. Identifying patient subpopulations experiencing ABT may help guide future study design and clinical decision-making.

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Abbreviations

ABT	aldosterone breakthrough
ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ARB	angiotensin 1-receptor blocker
CHF	congestive heart failure
MMVD	myxomatous mitral valve disease
MRB	mineralocorticoid receptor blockade/blocker
RAAS	renin angiotensin aldosterone system
RIA	radioimmunoassay
UAldo:C	urine aldosterone to creatinine ratio

Chronic activation of the sympathetic nervous system and renin angiotensin aldosterone system (RAAS) results in sodium and water retention, vasoconstriction (increased preload and afterload), and cardiovascular remodeling. This neurohormonal activation promotes and perpetuates the congestive heart failure (CHF) syndrome. Plasma renin activity and blood concentrations of aldosterone and norepinephrine, which increase as heart disease progresses, are markers and contributors to the hemodynamic derangements of this syndrome [1—5]. Importantly, loop-diuretic therapy, and sodium restriction further stimulate RAAS activation [5—7]. Improved understanding of the pathological consequences of neurohormonal activation has led to beneficial heart failure therapies beyond loop diuretics in veterinary medicine, most notably angiotensin converting enzyme inhibitors (ACEIs) [8—11]. Furthermore, benefits seen with inodilating drugs, such as pimobendan, are likely due, in part, to reduced circulating neurohormone levels produced by improvements in hepatic and renal perfusion, more efficient metabolism and excretion of these compounds, and reduced stimuli for their release. However, despite improved CHF pharmacotherapy, morbidity, and mortality remain high.

When secreted chronically and in excess, aldosterone has been implicated in the increased generation of reactive oxygen species, inflammation, and pathologic remodeling (hypertrophy and fibrosis) in tissues such as myocardium, vascular smooth muscle, and kidneys [12—15]. Aldosterone levels have been found to be increased in people with chronic and acutely decompensated CHF [2,3,6]. It had been presumed that both ACEI and angiotensin 1-receptor blockers (ARB) would effectively blunt aldosterone secretion by reducing the formation of angiotensin II (a major secretagogue of aldosterone). It is now known that ACEI and ARB (alone or in combination) do not always effectively suppress aldosterone secretion in people and this phenomenon is referred to as aldosterone breakthrough (ABT) [16—25]. In humans, ABT is an important, well-accepted, yet poorly understood phenomenon, in those treated with ACEI or ARB for chronic kidney disease, heart failure, and hypertension [16,20,21,25,26].

Despite its acceptance, there is no consensus regarding ABT's exact definition, timing, and prevalence. Creating a definition of ABT requires a reliable screening tool to evaluate aldosterone levels. As previously described by the authors, the urine aldosterone to creatinine ratio (UAldo:C), using spot urine samples, can be used as a surrogate for 24-h urinary aldosterone excretion, allowing assessment of RAAS activity in dogs [27]. Using the UAldo:C, the authors have demonstrated ABT in normal research dogs where, despite ACEI

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