

Literature Review: Aldosterone breakthrough in dogs with naturally occurring myxomatous mitral valve disease

Authors: Ames MK, Atkins CE, Eriksson A, Hess AM
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Prepared by: Prof. emer. Christophe W. Lombard
University of Bern, Dept. of Veterinary Clinical Sciences

Introduction

Aldosterone breakthrough (ABT) is the condition in which angiotensin converting enzyme inhibitors (ACEIs) and/or angiotensin receptors fail to effectively suppress the activity of the renin angiotensin aldosterone system. It has been clearly characterized for dogs thanks to the efforts of the group around Prof. Clarke Atkins from the NC-State University North Carolina. In a series of powerful contributions to the veterinary literature over the last decade, the group of collaborators has developed the tool of “Aldosterone to Creatinine Ratio” (UAldo:C-ratio) and shown it’s usefulness to reflect faithfully the 24-hr Aldosterone excretion via the urine, condition sine qua non to assess the status of RAAS-activation. They have also defined the ratio’s normal range for healthy dogs with neither cardiac disease nor other conditions leading to activation of the RAAS. In this most recent paper, the authors have analysed a series of 39 dogs with various degrees of severity suffering from degenerative mitral valve disease (MMVD). Their hypothesis was that ABT indeed occurs in canine patients with MMVD, and the goal was to determine how commonly it occurs, and to compare the ratio in dogs with CHF receiving ACEI-therapy to those receiving ACEI plus Spironolactone, a competitive antagonist at the mineralocorticoid receptor.

Methods and patients

Dogs with MMVD without or with CHF seen at the NC-State Veterinary College or Colorado State CVM over a 2-year period were eligible for enrolment into the present study. CHF was defined as the presence of cardiogenic pulmonary edema, see figure 1 below), necessitating furosemide administration. A board-certified cardiologist confirmed one or both diagnoses (MMVD, CHF) as necessary. Dogs already receiving therapy were prospectively placed into 3 groups, based on their previous history and their drug regimen: Group 1 (no CHF) included dogs on ACEI for at least 1 day, group 2 included dogs with previous CHF on diuretics, ACEI and pimobendan, and Group 3 (also previous CHF) with the same drugs as Group 2 dogs and additional spironolactone. Dogs receiving therapy were not categorized for its duration. Except for angiotensin-receptor blockers, other cardiac and non-cardiac

drugs were allowed, as well as drugs for systemic hypertension and endocrine diseases.

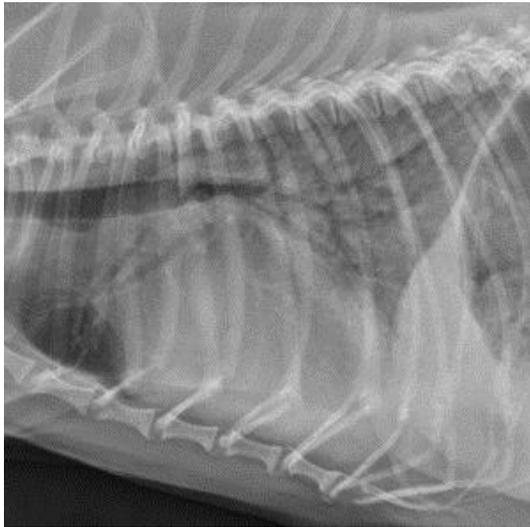


Fig. 1 Lateral thoracic radiograph of a dog with cardiogenic pulmonary edema

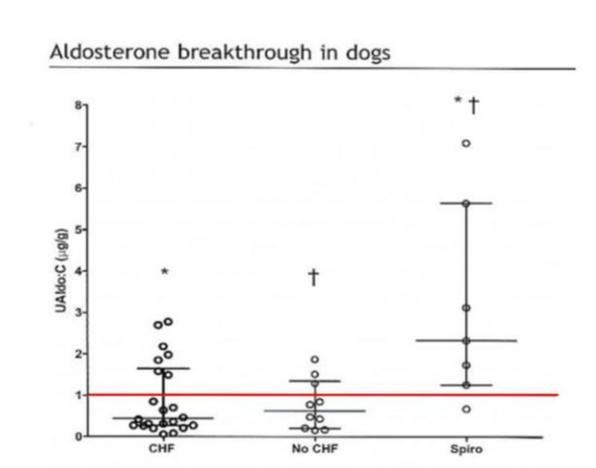


Fig 2 UAldo:C-ratios of the 3 groups of dogs. The red line indicates the upper limit of normal 1ug/g

Blood and urine were handled according to good clinical practice (GCP), urine frozen at -70 C until analysed in batches at a later time. The urine Aldosterone concentration was measured with a previously validated radioimmunosassay (RIA). The same veterinary diagnostic laboratory measured the Aldosterone- as well as the urinary creatinine concentration (standard colorimetric assay). The normal upper limit for the UAldo:C-ratio had been previously determined to be lower or equal to 1.0 ug/g in 34 healthy laboratory dogs and 21 client-owned normal, >5year old, healthy dogs. Therefore, the definition of ABT was a UAldo:C-ratio > 1.0 ug/g. The relationship between the UAldo:C-ratio and 8 variables (age, serum K⁺-levels serum creatinine concentration, ACEI-therapy duration and dosage, furosemide therapy duration and dosage, and urine sample storage time) was evaluated with the Spearman test. The other performed statistical procedures appeared state-of-the-art and adequate.

Results

Forty-one dogs were enrolled and 39 dogs were admitted into one of the 3 previously defined categories. The UAldo:C-ratios of all dogs from each group are shown as scatter plots (median and interquartile ranges), see figure 2. The group no CHF had a total of 10 dogs, with 3 of them (30%) with UAldo:C-ratio values above 1.0 ug/g. The CHF-Group had a total of 22 dogs with 7 of them (32%) showing UAldo:C-ratios above 1.0 ug/g. And the Spiro-Group had 7 dogs with 1 dog's UAldo:C-ratio within the normal range. Statistically significant differences were evident between medians of the CHF- and the Spiro-group (t), and the No CHF- and the Spiro-group (*), while the difference between CHF- and No CHF-group did not reach significant levels.

Discussion

ABT of both the CHF- and the No CHF-groups were 32% and 30% respectively and indicate an important percentage of breakthrough in dogs on ACEI's, some without

and some with additional furosemide therapy. The duration of such therapy was not properly assessed, and the numbers of evaluated dogs for such a determination, if possible over time, wasn't given here, which represents a certain weakness of the study. Equally, there is no calculation of power given, and the total number of assessed dogs is rather low. Nevertheless, the study results indicate that ABT represents a serious problem in dogs on ACEI-therapy that should possibly be addressed by modification of the therapy in affected dogs.

ABT has been shown to occur despite reduced ACE-activity after the use of ACEI's, which points at other mechanisms for the production of Angiotensin II via non ACE-pathways such as for example Chymase. Also, while Angiotensin II is one of the primary and more potent stimulants for Aldosterone-production, other stimuli for Aldosterone-release (e.g. K⁺ serum levels, renin levels) or its diminished metabolism are potential other mechanisms leading to remaining elevated serum Aldosterone levels. There wasn't any correlation documented to K⁺-levels in this study, and renin levels weren't measured. The elevated levels seen in the Spiro group of this trial stem likely from competitive binding of Spironolactone at the mineralocorticoid receptors and therefore "freeing-up" or displacing some Aldosterone molecules. It is presently not absolutely clear if such receptor blockade is the sole beneficial effect of Spironolactone. The non-receptor mediated effects of Aldosterone remain under investigation. Indeed, beneficial effects (reduced mortality) could be documented in a previous study in dogs (1), although many of these patients were receiving ACEI's simultaneously to Spironolactone. Therefore, a mixed effect of Spiro- and ACEI-treatment is likely responsible for the benefits in the dogs without ABT in that study.

Summary

The reviewer liked this elegant study very much. It documented ABT with rather strict definition in about 30% of dogs receiving ACEI-therapy, mirroring the findings in humans with cardiovascular disease. Although the number of dogs studied is rather small, the statements made and the conclusions derived are solid. There are likely several factors contributing to ABT in individual dogs. A longitudinal study of dogs should be performed, in order to document variability of ABT over time, and attempting to elucidate its precise mechanisms further. Cardiologists should evaluate their patients individually with respect to Aldosterone levels and decide upon additional mineralocorticoid blockade with Spironactone on a case by case base.

Literature cited

- 1) Berney F 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: 331-41