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Chapter 2

Scope and Outline of the investigations
**SCOPE**

Congestive Heart Failure (CHF) constitutes the most common cardiovascular disorder in dogs. Similar to humans, chronic activation of the renin-angiotensin-aldosterone system (RAAS) plays a pivotal role in the pathophysiology of canine CHF. A rich body of literature has established that RAAS peptides oscillate with a circadian periodicity in rodents and humans (Cugini et al., 1981, 1985, 1986, 1987; Kawasaki et al., 1990). During sleeping hours, renin secretion increases and is probably the main controller of blood pressure (BP). In contrast, little is known about the periodicity of these variables in dogs. A thorough comprehension of the chronobiology of the renin-angiotensin system and the regulation of BP can improve therapeutic management of CHF, as it enables the selection of the time of drug administration that yields optimal efficacy with minimal adverse effects.

Systems pharmacology is a discipline that aims at the understanding of the interactions between sub-parts of a biological system (cell, tissue, animal, or animal sub-population) and the functioning of the system as a whole. In this context, modeling and simulation techniques are increasingly relied upon to ensure adequate management of cardiovascular diseases in human patients.

The ambitions of the present research are threefold: i) first, to build a mechanistic representation of the chronobiology of the renin cascade in relation to BP and renal sodium-potassium handling in dogs, ii) then, to evaluate the effect of various feeding patterns (i.e. dietary sodium intake and feeding time) on the periodicity of these systems, and iii) finally, to quantify the perturbations in dynamics of the systemic RAAS following inhibition of the angiotensin-converting enzyme (ACE) with the benchmark CHF medication benazepril.

**OUTLINE**

The modeling work presented in Chapter 3 provides the first chronobiological characterization of the circulating RAAS, in relation to changes in BP and the exchanges of urinary electrolytes in dogs (Mochel et al., 2013a). A series of cosine and surge functions were found to describe and predict the time-variations of the diverse endpoints with high performances, as shown by the quality of the model diagnostics. The use of nonlinear mixed-effects (NLME) allowed borrowing information from the densely sampled plasma biomarkers (i.e. renin activity (RA)) to improve knowledge on the dynamics of the (more sparsely sampled) urinary variables. Another core value of NLME modeling lies in its ability to separate the (between- and within-subject) variability from the measurement error (noise), in order to determine population characteristics that can explain the sources of variation between individuals.
Specifically, dietary sodium was found to impact the tonic and phasic secretion of renin, suggesting that varying feeding time could potentially exert influence on the chronobiology of the systemic RAAS.

This hypothesis is being further explored in Chapter 4 of the PhD dissertation, which compiles results from two experiments on the time variations of RA, urinary electrolytes (Study a), and BP (Study b) under different meal times (07:00, 13:00, and 19:00 for Study a vs. 07:00 and 19:00 for Study b) (Mochel et al., 2014a). The effect of varying feeding schedules on the dynamics of the RAAS and BP was quantified by introducing a phase shift parameter in the NLME models. Our data showed that environmental triggers such as timed feeding have a marked influence on the chronobiology of RA, urinary electrolytes and BP. Precisely, introducing a 6- or 12-h delay in the dogs' feeding schedule caused a shift of similar magnitude in the rhythm of these biomarkers, as confirmed by the model-based estimates of the phase shift parameter (95% CI: (04:20–06:12), vs. (10:06–14:36) for Study a and Study b, respectively).

Although most of the pre-clinical investigations for dose selection of benazepril have used ACE activity as a surrogate marker of efficacy in dogs, recent publications suggest that this may not be a sensitive approach to properly assess the modulatory effect of ACE inhibitors on the RAAS (e.g. Van de Wal et al., 2006). To the best of our knowledge, very little information on the relation between benazeprilat, RA, angiotensin II (AII), and aldosterone (ALD) is available from the literature in dogs. Investigations on the modulatory properties of benazepril on the dynamics of the circulating RAAS are reported in Chapters 5 and 6 of this thesis. 

Chapter 5 discloses the results of a pilot efficacy study on the dynamics of the renin-angiotensin cascade following oral administration of benazepril (10 mg PO q24h), using a low-sodium diet as an experimental model of RAAS activation (Mochel et al., 2013b). Data from a follow-up pharmacokinetic (PK)-pharmacodynamic (PD) study using a semi mechanism-based PK/PD model, which includes a description of the periodic nature of RA, AII, and ALD during placebo treatment and the subsequent changes in dynamics following inhibition of ACE (benazepril 5 mg PO q24h), provides a quantitative framework for further characterization of the effect of ACE inhibition on the systemic RAAS in Chapter 6 of the thesis dissertation (Mochel et al., 2014b). The disposition kinetics of the benazepril active metabolite, benazeprilat, was characterized using a nonlinear binding model to plasma ACE, while a combination of immediate-response models was shown to adequately predict the pharmacodynamic effects of benazeprilat. Data from both studies revealed that benazeprilat markedly influences the dynamics of the RAAS, resulting in a marked but transitory decrease in AII and ALD, while increasing RA throughout the observation span. According to the final PK/PD model, benazeprilat
peak concentrations (31 ng/ml) triggered on average a 2.8-fold reduction of All, with a subsequent 2.6-fold increase in RA, and a 2.3-fold decrease in ALD compared with placebo. The elevation of RA was a consequence of benazeprilat-induced interruption of the All-renin negative feedback loop (Geary et al., 1992), while the reduction of All and ALD levels could be one of the drivers of improved survival and quality of life in benazepril-treated dogs.

The results of this research are finally summarized in a final Chapter (Chapter 7), which also outlines the future perspectives of our work. Specifically, the next steps towards characterization of the chronobiology of the RAAS in diseased animal populations are being discussed. These investigations constitute a scientific basis for optimization of drug therapy of CHF by selecting the most appropriate time of dosing.
REFERENCES


