Pharmacodynamics of the renin-angiotensin aldosterone system (RAAS) and blood pressure in relation to food intake in dogs

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NOVARTIS

Background

- **Situation:** Recent data from **human** patients receiving **ACE inhibition therapy** have shown the importance of **chronobiology** for the effective management of **RAAS-related diseases**
- **Opportunity:** Accumulating knowledge on the **chronobiology** of the **RAAS** and blood pressure (**BP**) provides a strong scientific rationale for determining the **optimum dosing time**, thereby making the **best usage** of available **cardioactive** therapeutics

Objectives

- Investigate the effect of **feeding schedules** on the **pharmacodynamics** of renin activity (**RA**), **BP**, renal sodium (**$U_{Na,fe}$**) and potassium (**$U_{K,fe}$**) handling in dogs
- Use the data generated in dog data to **better understand** the **biology** of the **renin cascade** and **BP in humans**(†)

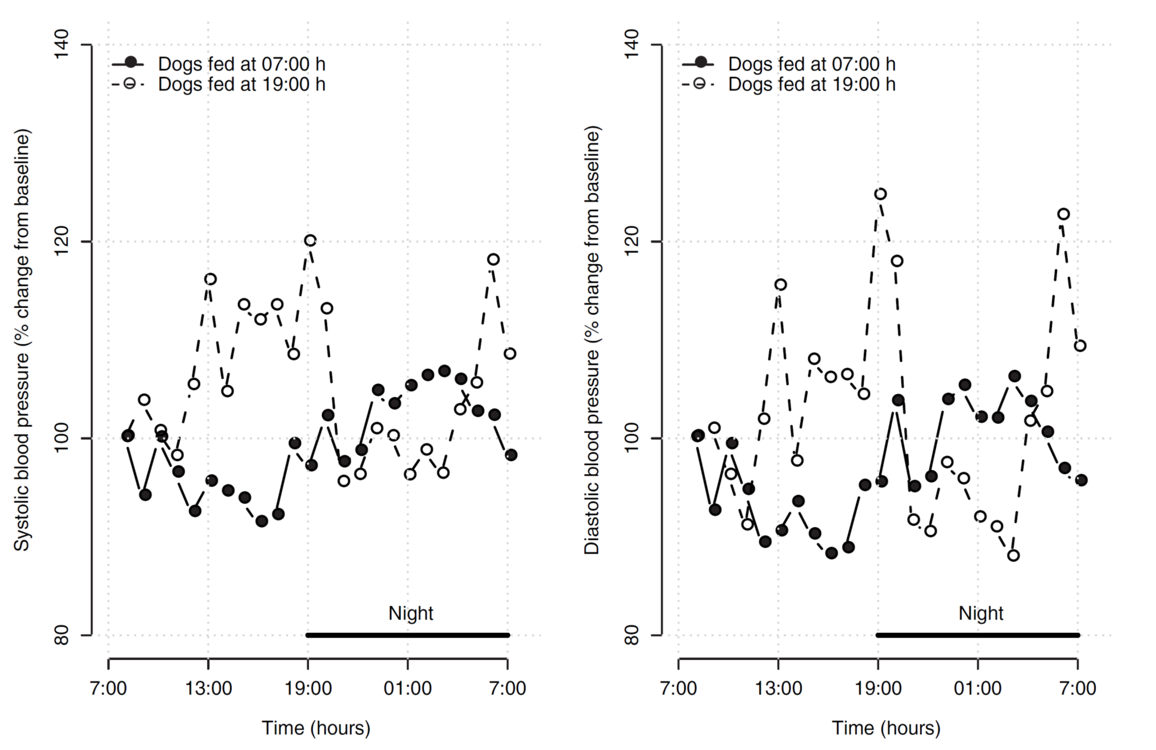
(†)Activation of the RAAS is one of the key neurohumoral responses to the reduced cardiac output observed in the course of congestive heart failure (CHF) in both species[1]

Methods

- Measurements for characterization of the **RAAS** were drawn from **18 dogs** fed a normal-sodium diet at either **07:00**, **13:00** or **19:00** h, while **BP** was recorded continuously from **6** telemetered beagle dogs fed a similar diet at **07:00** or **19:00** h
- Data derived from **intensive blood** and **urine sampling**, as well as **continuous BP** monitoring were collected throughout a **24-hour** time period, and analyzed by means of **NLME models**, using NONMEM version 7.2[2]

Results

Figure 1. Circadian changes in systolic and diastolic blood pressure under various feeding schedules



Circadian changes in systolic and diastolic BP under various feeding schedules. Average systolic (left pane) and diastolic (right pane) BP versus time profile in dogs fed a normal-sodium diet (0.5% sodium) at 07:00 h (continuous line) and 19:00 h (dashed line). Systolic and diastolic BP oscillated in parallel throughout the observation span. Similar to renin and urinary electrolytes, introducing a time-delay in the dogs feeding schedule triggered a shift in the periodicity of BP

RA, $U_{Na,fe}$, $U_{K,fe}$, systolic, and diastolic BP oscillate with a **circadian periodicity** in dogs. A **cosine** model with a **fixed 24-h period** was found to fit the variations of **RA, $U_{K,fe}$ and BP** well, whereas cyclic changes in **$U_{Na,fe}$** were best characterized by means of a **combined cosine** and **surge** model, reflecting a postprandial excretion of Na (i.e peak natriuresis)

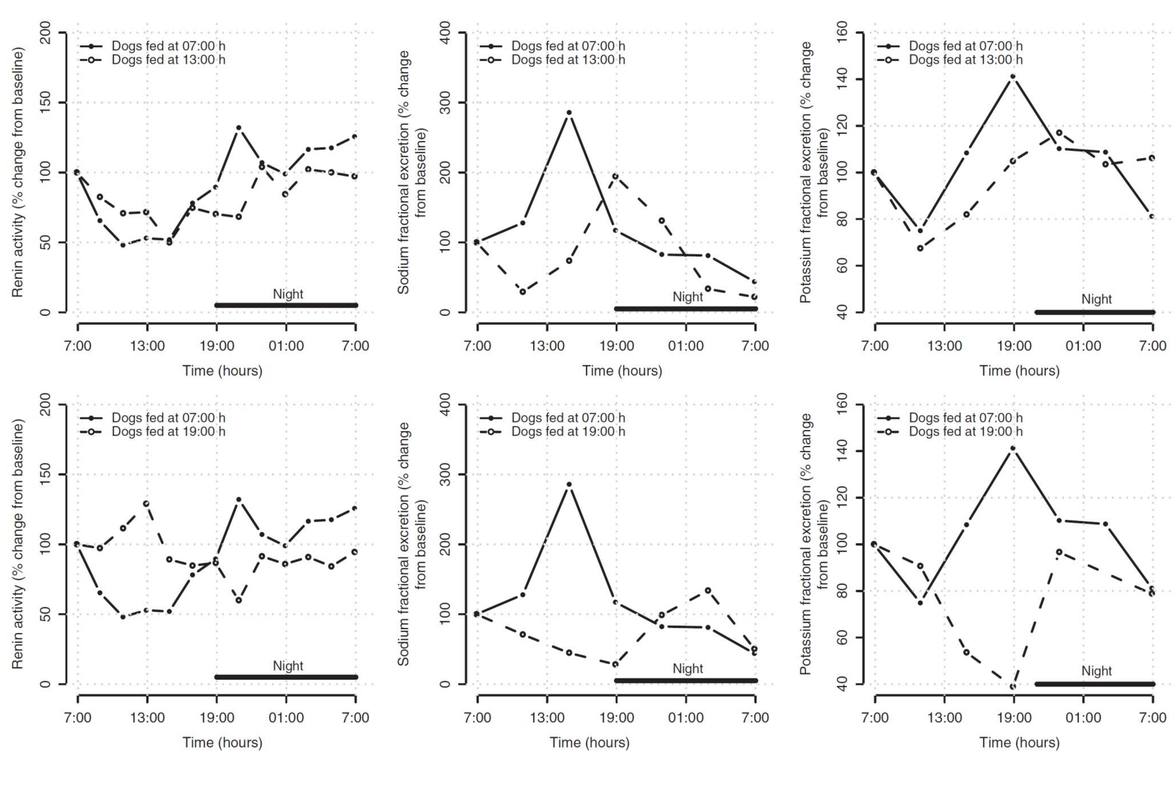
Our data show that **feeding time** has a marked influence on the chronobiology of the renin cascade, urinary electrolytes, and BP. Introducing a 6- or 12-h delay in the dogs feeding schedule caused a **shift** of similar magnitude in the **rhythm** of these biomarkers

Because of the known sensitivity of the renin cascade and BP to changes in sodium intake, we hypothesize that the **synchronizing** effect of food could be mediated in part by **dietary sodium**

Table 1. Parameter estimates of the final mathematical models

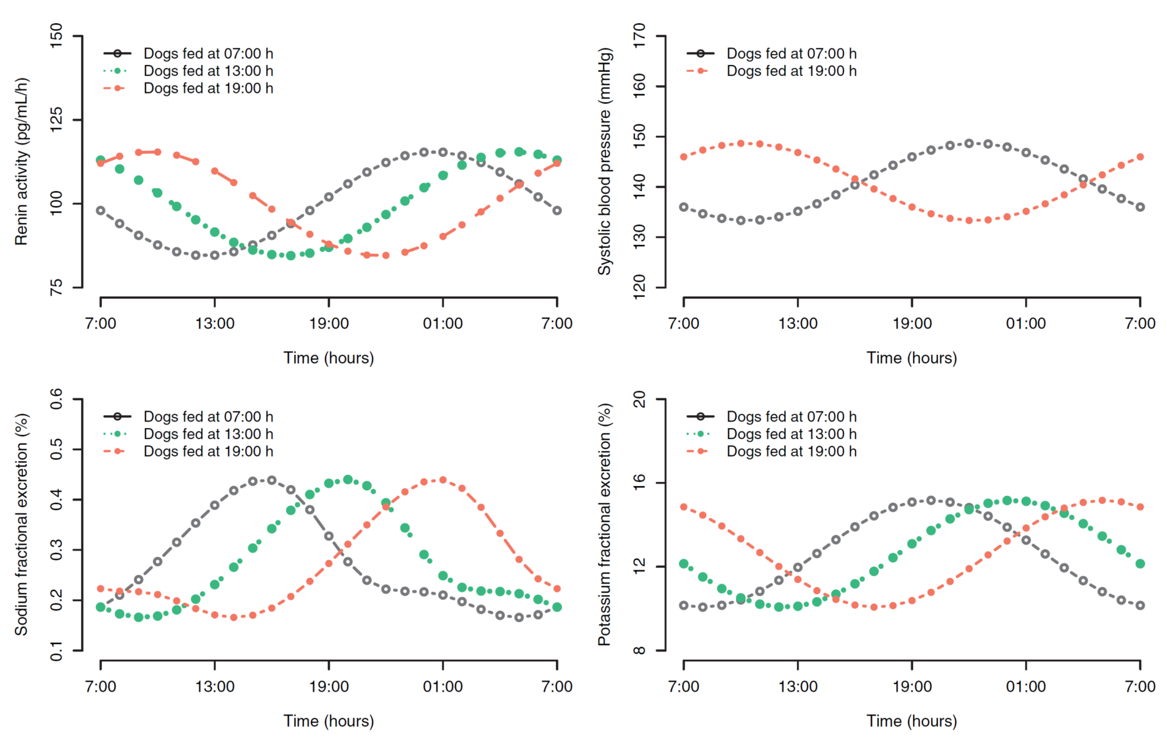
Dependent variable	Parameter	Point estimate	RSE	90% CI
Renin activity (RA)	Mesor	100 (pg/mL/h)	13%	(78-121)
	Amplitude	16 (pg/mL/h)	16%	(11.8-20.2)
	Acrophase	24:30 (h)	5%	(24:03-24:57)
	Phase shift	**05:06 (h)**	**11%**	**(04:27-06:06)**
Potassium fractional excretion ($U_{K,fe}$)	Mesor	12.6 (%)	4%	(11.7-13.4)
	Amplitude	2.5 (%)	21%	(1.6-3.3)
	Acrophase	20:00 (h)	10%	(18:46-21:14)
	Phase shift	**05:06 (h)**	**11%**	**(04:27-06:06)**
Sodium fractional excretion ($U_{Na,fe}$)	Baseline	0.30 (%)	7%	(0.26-0.33)
	Amplitude	0.15 (%)	18%	(0.11-0.19)
	Acrophase	08:44 (h)	16%	(07:44-09:44)
	Phase shift	**05:06 (h)**	**11%**	**(04:27-06:06)**
	Width of surge	5:30 (h)	22%	(03:30-07:30)
Systolic BP (SBP)	Mesor	141 (mmHg)	7%	(125-157)
	Amplitude	4 (mmHg)	9%	(3.4-4.6)
	Acrophase	22:20 (h)	5%	(21:10-23:30)
	Phase shift	**12:32 (h)**	**9%**	**(10:30-14:12)**
Diastolic BP (DBP)	Mesor	78 (mmHg)	8%	(68-88)
	Amplitude	7 (mmHg)	17%	(5.0-8.9)
	Acrophase	22:20 (h)	5%	(21:10-23:30)
	Phase shift	**12:32 (h)**	**9%**	**(10:30-14:12)**

Figure 2. Circadian changes in renin, urinary sodium and potassium fractional excretion under various feeding schedules



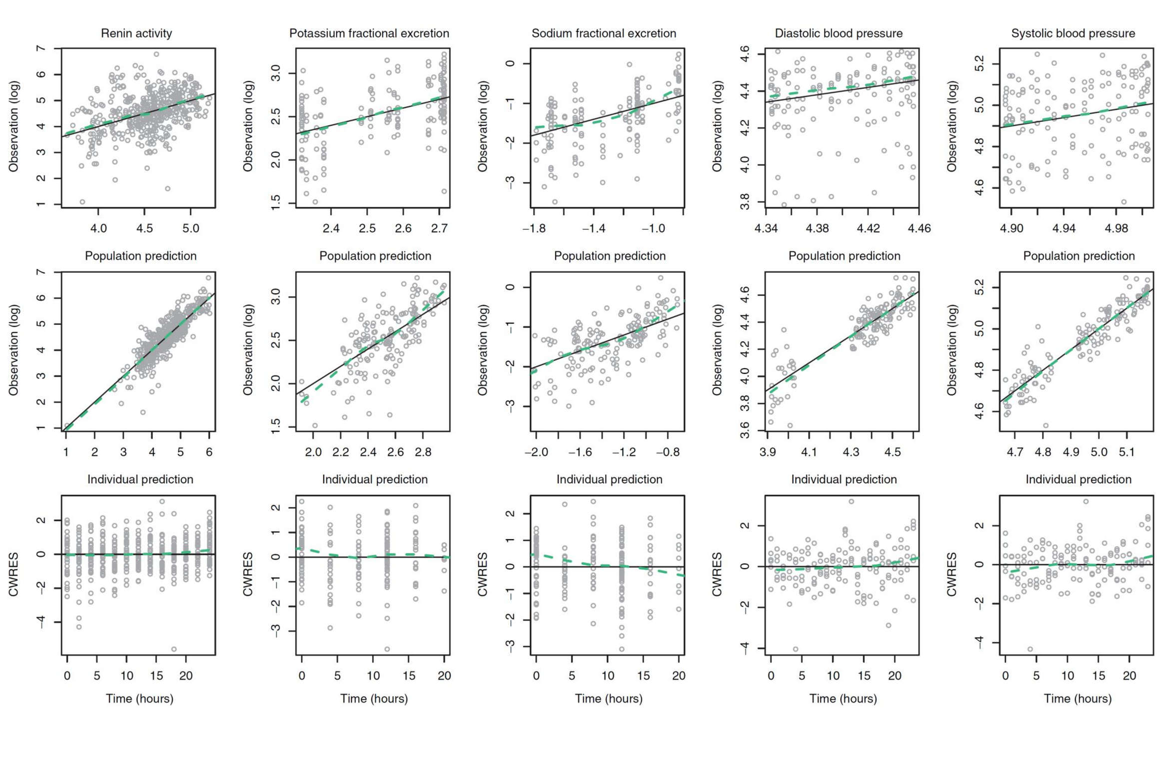
(Top) Average plasma RA (left pane), urinary sodium (middle pane) and potassium (right pane) fractional excretion in dogs fed a normal-sodium diet (0.5% sodium) at 07:00 h (continuous line) and 13:00 h (dashed line). (Bottom) Average plasma RA (left pane), urinary sodium (middle pane) and potassium (right pane) fractional excretion in dogs fed a normal-sodium diet (0.5% sodium) at 07:00 h (continuous line) and 19:00 h (dashed line)

Figure 3. Predicted influence of feeding schedules on the chronobiology of RA, BP and urinary electrolytes in healthy dogs



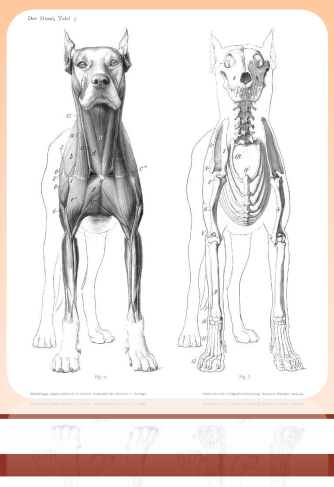
Simulated RA (top left pane), systolic BP (top right pane), sodium (bottom left pane) and potassium (bottom right pane) fractional excretion using typical parameters estimates from the mathematical models. Continuous grey line with open circles: dogs fed at 07:00 h; dotted green line with closed circles: dogs fed at 13:00 h; dashed red line with closed circles: dogs fed at 19:00 h

Figure 4. Standard goodness-of-fit diagnostics from the final mathematical models



Scatter plot of population (top panel) and individual predictions (middle panel) versus observations (log scale), and conditional weighted residuals (bottom panel, CWRES) of population predictions. From left to right: RA, $U_{K,fe}$, $U_{Na,fe}$, DBP and SBP. Solid black line: identity line. Dashed line: regression line. For CWRES, the x-axis represents time after feeding onset

Conclusions and Perspectives



- The **timing** of **food intake** appears to be **pivotal** to the **circadian organization** of the **renin** cascade and **BP**
- This **synchronizing effect** could be mediated by **feeding-related signals** capable of entraining circadian **oscillators** downstream of the suprachiasmatic nucleus
- Further research on the chronobiology of the RAAS and BP in **dog patients** receiving **ACE inhibition** therapy is required
- These additional information would help determining the **time** of **drug administration** that **optimizes efficacy** while **minimizing** the occurrence of **adverse effects** in CHF dogs

References

[1] Sisson DD. Vet Clin North Am Small Anim Pract. 2004;34(5):1105-26

[2] Mochel JP et al. Chronobiol Int. 2013;30(9):1144-59

Acknowledgments

The investigations on RAAS periodicity were conducted at the Centre de Recherche Sante Animale SA of Novartis Animal Health. The telemetry study was performed at Novartis Institutes of Biomedical Research

This study was supported by Novartis Pharma AG, Basel, Switzerland

Poster presented at the Population Approach Group Europe (PAGE), June 07-10 2016, Lisbon (Portugal)