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Short Communication

Dogs with macroadenomas have lower body temperature and heart rate than dogs with microadenomas

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ABSTRACT

Pituitary macroadenomas compress the hypothalamus, which partly regulates heart rate and body temperature. The aim of this study was to investigate whether heart rate and/or body temperature could aid in clinically differentiating dogs with macroadenomas from dogs with microadenomas (i.e. small non-compressive pituitary mass). Two groups of dogs diagnosed with pituitary-dependent hyperadrenocorticism (i.e. Cushing's disease) were included. Heart rate and body temperature were collected on initial presentation before any procedure. Dogs with macroadenoma had a significantly lower heart rate and body temperature ($P < 0.01$) compared to dogs with microadenoma. We suggest that the combined cut-off values of 84 beats per minutes and 38.3 °C in dogs with Cushing's disease, especially with vague neurological signs (nine of 12 dogs = 75%), might help to suspect the presence of a macroadenoma.

Pituitary-dependent hyperadrenocorticism (*i.e.* Cushing's disease) in dogs can be caused by large (macroadenoma) or small (microadenoma) pituitary tumours. In addition to endocrine manifestations, macroadenomas can cause neurological signs because they expand into the pituitary stalk and compress and invade the hypothalamus, third ventricle and thalamus (Behrend, 2015). It is often difficult to suspect a macroadenoma because early neurological signs (such as lethargy, reduced appetite, delayed response to stimulation, loss of interest in household activities and episodes of disorientation) are non-specific and perceived as 'ageing' by owners. More definitive neurological signs eventually occur (ataxia, tetraparesis, head pressing, pacing, circling, etc.), probably when the brain compensatory mechanisms become overwhelmed (Nelson et al., 1989; Wood et al., 2007).

Previous studies reported dysfunction of the autonomic nervous system in dogs with macroadenomas, including impaired heart rate and body temperature regulation, which might result from the compression of the hypothalamus (Verstraete and Thoonen, 1939; de Lahunta et al., 2015).

We hypothesized that dogs with macroadenomas would have lower heart rates and body temperature and that such findings could help differentiate macroadenomas from microadenomas in dogs with pituitary hyperadrenocorticism. Therefore, we compared heart rates and body temperatures between dogs with pituitary macroadenomas and microadenomas.

Dogs presented to the Internal Medicine Unit, National Veterinary School of Alfort (France) and at the Queen's Veterinary School Hospital, University of Cambridge (United Kingdom) were included between 1st January 2006 and 30th June 2011.

All dogs were diagnosed with hyperadrenocorticism using adrenocorticotropic hormone (ACTH) stimulation test, low-dose dexamethasone suppression test, ACTH plasma concentration measurement, serum biochemistry, hematology and adrenal glands imaging with CT or ultrasound. All dogs underwent brain imaging by CT or magnetic resonance imaging (MRI). We took advantage of the routine practice, in our institutions, to

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Table 1
Signalment (bodyweight, age and sex) of dogs with macroadenomas and microadenomas.

	Median	25th Percentile	75th Percentile	Min	Max
		Bodyweight (kg)			
Macroadenoma	22.5	12.8	35	5	44
Microadenoma	7	5	12	3	27
		Age (years)			
Macroadenoma	9	8	12	5	15
Microadenoma	11	9	12	7	14
	Male	Female			
Macroadenoma	23	6			
Microadenoma	15	15			

combinepituitary and adrenal CT scans in dogs investigated for hyperadrenocorticism. We diagnosed macroadenomas in dogs that had a pituitary height/brain area ratio (P/B) $\geq 0.40 \times 10^{-2}\,mm^{-1}$, as previously described (Granger et al., 2005). Conversely dogs diagnosed with microadenomas had a P/B ratio $< 0.40 \times 10^{-2}\,mm^{-1}$.

For all dogs, attending clinicians recorded heart rate, body temperature and bodyweight within 2 weeks prior to brain imaging. In dogs presenting with obvious neurological signs, a neurology specialist performed the neurological examination and recorded any neurological deficit identified through history or physical examination. In dogs without obvious neurological signs, an internal medicine specialist performed the clinical examination. We did not consider autonomic nervous system signs (low body temperature or low heart rate) as neurological signs at the time of the study. The data were analysed with SAS using a P value of 0.05 to denote significance. Medians and interquartile ranges are reported for quantitative data. We investigated the association between macroadenoma and body temperature and between macroadenoma and heart rate by using a multivariate linear regression, including potential confounders (association with body temperature (or heart rate) with a P value < 0.20). The candidate variables included as potential confounders were: sex, age, bodyweight and sterilization. We compared groups with Mann–Whitney test and proportions with Fisher's Exact Test. The association between two quantitative variables was tested with Spearman's correlation test. Finally, we examined the optimal threshold values for heart rate and body temperature using Receiver Operating Characteristic analysis.

We recruited 59 dogs into the study: 29 in the macroadenoma group and 30 in the microadenoma group (Table 1). Dogs with macroadenomas had lower heart rates and lower body temperatures than dogs with microadenomas ($P < 0.05$ for both comparisons; Figs. 1 and 2). Plotting the heart rate against the body temperature resulted in more widespread dispersion of the plot of the macroadenoma group compared to the microadenoma group (Fig. 3).

The crude difference estimated by the univariate linear regression between the two groups (macroadenoma vs. microadenoma) was estimated to be $-0.52\,°C$ ($P < 0.01$) and -19 bpm ($P < 0.01$) respectively for body temperature and heart rate. In both models, only the bodyweight was identified as a potential confounder. After adjustment for bodyweight, the temperature difference $\Delta = -0.65\,°C$ and heart rate difference $\Delta = -18$ bpm remained significant ($P < 0.01$ and $P = 0.04$).

The most discriminating thresholds for both parameters were determined from receiver operating characteristic (ROC) curves (Table 2). Using these thresholds identified with ROC (84 bpm and 38.3 °C), a greater proportion of dogs with macroadenomas had

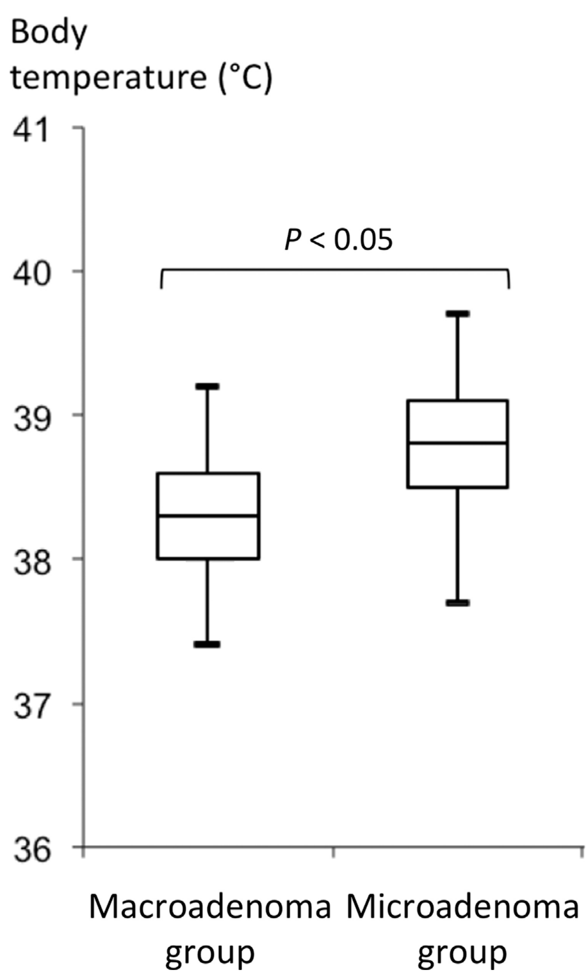

Fig. 1. Box plot of body temperature in 29 dogs with macroadenomas and 30 dogs with microadenomas. The box represents interquartile range (25th–75th percentile). The bars represent the minimum and maximum data values. Median values are indicated by horizontal lines.

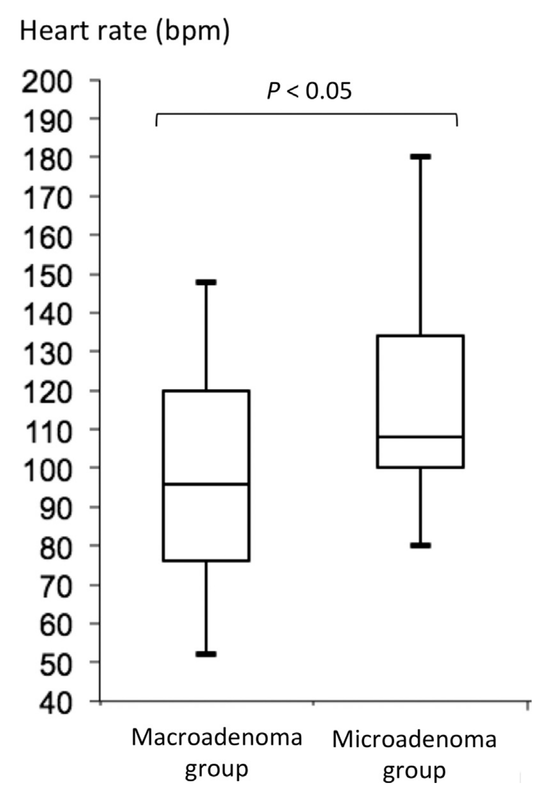

Fig. 2. Box plot of heart rate in 29 dogs with macroadenomas and 30 dogs with microadenomas. See Fig. 1 for legend.