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Short communication

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

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Highlights

- Cut-off values of 38.3°C and 84 bpm allowed discrimination between pituitary macroadenomas and microadenomas.
- Fifty nine per cent of dogs with pituitary macroadenomas had a body temperature ≤ 38.3°C.
- Forty one per cent of dogs with pituitary macroadenomas had a heart rate ≤ 84 bpm.
- Seventy five per cent of Cushing dogs with vague neurological signs had a heart rate ≤ 84 bpm or a body temperature ≤ 38.3°C.

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 (9 of 12 dogs = 75%), might help to suspect the presence of a macroadenoma.

Keywords: Canine pituitary neoplasm; Cushing's disease; Hypothermia; Bradycardia; Forebrain.

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 and Glass 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 January 1st 2006 and June 30th 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 combine pituitary 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 body weight 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, body weight and sterilization. We compared groups with

Mann-Whitney test and proportions with Fisher's Exact Test. The association between 2 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; Figure 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 (Figure 3).

The crude difference estimated by the univariate linear regression between the two groups (macroadenoma *versus* 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 body weight was identified as a potential confounder. After adjustment for body weight, 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 either a heart rate ≤ 84 bpm or a body temperature ≤38.3°C or both (P<0.0002 for each comparison, Table 3). No dogs with microadenomas had both a heart rate ≤84 bpm and a body temperature ≤ 38.3°C, whereas 11 dogs with macroadenomas exhibited both of these autonomic signs (Table 3).

No dogs with microadenomas exhibited neurological deficits. Similarly, 9/29 dogs with macroadenomas exhibited no neurological deficits. In the remaining 20 dogs, 12 exhibited vague neurological signs (i.e., only altered mentation and behavioral changes); 9 (75%) of these dogs had a heart rate ≤ 84 bpm or a body temperature ≤ 38.3°C, suggesting autonomic nervous system dysfunction. The remaining 8 dogs with macroadenomas presented with circling, cortical blindness and partial seizures.

Our data show that the heart rate and body temperature are lower in dogs with macroadenomas compared to dogs with microadenomas, and that dogs with hyperadrenocorticism presenting with both a heart rate ≤ 84 bpm and a body temperature ≤ 38.3°C are very likely to have macroadenomas responsible for their endocrine disease. However, the heart rate and the body temperature had a low sensitivity, i.e., a third of dogs (34%) with a macroadenomas had a heart rate > 84 bpm or a body temperature > 38.3°C.

Diencephalic lesions can cause hypothermia or hyperthermia in humans (Carmel 1985) and this might occur in animals. Healthy, smaller-sized or older animals are more likely to develop hypothermia (Lee 2017), therefore we tested and excluded age and bodyweight as potential confounding factors. One possible cause for the difference in heart rate between the two groups is a Cushing reflex secondary to increased intracranial pressure leading to heart rate reduction

(Fitch et al, 1977). Another possible explanation would be a destruction of the hypothalamus by the macroadenoma. Concurrent measurement of the blood pressure in our study dogs would have helped to explore the possible causes of bradycardia, such as the Cushing's reflex. One of the potential weaknesses of the study is that there is an association between HR and BW in dogs (Hezzel et al, 2013). Moreover, in our study, dogs with macroadenomas were larger. We included body weight into our modelling as a potential confounding factor, but the difference in heart rate remained significant after adjustment for body weight. Other limitations to this study include the fluctuating nature of the heart rate and body temperature and the non-standardized method of measurement of heart rate and body temperature. However, we sought to reproduce the routine clinical situation where vital parameters are measured only once during a consultation. Therefore, we purposely collected data only at initial presentation. Standardized methods of measurement of both parameters as well as repetitive measures would require a prospective study.

Because the diagnostic value of these parameters will always remain limited in dogs with clear forebrain neurological dysfunction, it would be of interest to evaluate the temperature and heart rate of dogs with macroadenomas and hyperadrenocorticism, but without obvious neurological signs. We had too few such dogs for meaningful comparison.

In summary, our data revealed that dogs with macroadenomas had a lower heart rates and body temperatures than dogs with microadenomas. In the context of a case diagnosed with hyperadrenocorticism, the finding of a heart rate ≤ 84 bpm or a body temperature ≤ 38.3°C should raise the suspicion of the presence of a macroadenoma.

Conflict of interest statement

The authors disclose no conflict of interest.

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Table 1

Signalment (body weight, age and sex) of dogs with macroadenomas and microadenomas.

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

Table 2

Results of the receiver operating characteristic curve analysis for body temperature (°C: degree Celsius) and heart rate (bpm: beats per minute).

	Area under the curve (95% CI)	Youden index	Associated criterion	Sensitivity (95% CI)	Specificity (95% CI)
Body Temperature (°C)	0.79 (0.66-0.88)	0.49	≤ 38.3	0.62 (0.42 – 0.79)	0.86 (0.69 – 0.96)
Heart rate (bpm)	0.70 (0.57-0.81)	0.38	≤ 84	0.41 (0.23 – 0.61)	0.97 (0.83 – 0.99)

Table 3: Pituitary height/brain area (P/B) ratio, neurological signs, body temperature (°C: degree Celsius) and heart rate (bpm: beats per minute) in dogs with macroadenomas or microadenomas.

	P/B ratio		Body temperature			Heart rate			Heart rate and body temperature	
	Median	Range	Median	Range	Dogs with T ≤ 38.3°C Number (%)	Median	Range	Dogs with HR ≤ 84 bpm Number (%)	Dogs with T ≤ 38.3°C or HR ≤ 84 bpm Number (%)	Dogs with T ≤ 38.3°C and HR ≤ 84 bpm Number (%)
Macroadenoma group N= 29 dogs	1	0.41-1.71	38.3	37-39.2	18 (59%)	96	52-148	12 (41%)	19 (66%)	11 (38%)
No neurological sign N= 9 dogs	0.6	0.41-1.35	38.5	37.6-39	4 (44%)	92	72-140	4 (44%)	4 (44%)	4 (44%)
Vague neurological signs (altered mentation and behavioural changes) N= 12 dogs	0.8	0.45-1.28	38.2	37.7-39.2	8 (67%)	93	60-120	5 (42%)	9 (75%)	4 (33%)
Evident neurological signs (circling, cortical blindness, partial seizures) N = 8 dogs	1	0.58-1.71	38.3	37-39.1	6 (75%)	98	52-148	3 (38%)	6 (75%)	3 (38%)
Microadenoma group N= 30 dogs	0.14	0.14-0.37	38.8	37.7-39.7	4 (13%)	108	80-180	1 (3%)	5 (17%)	0

Figure legends

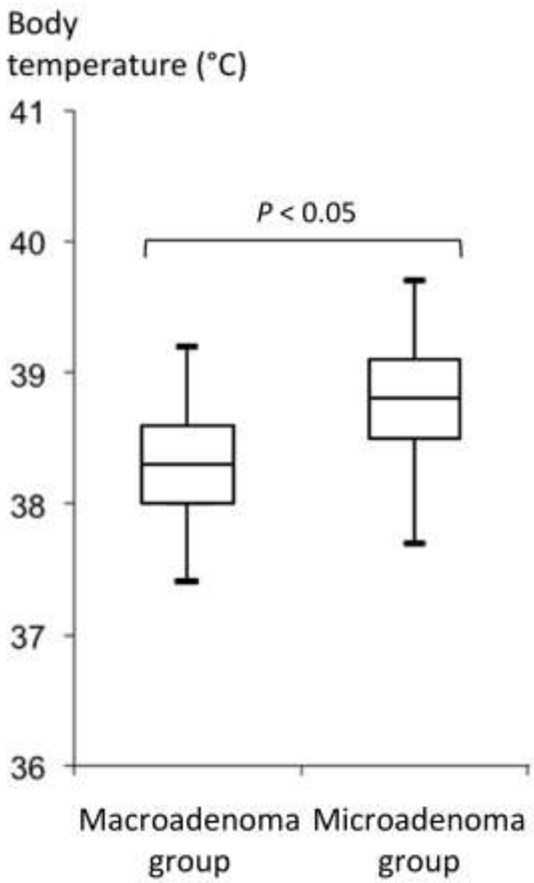

Figure 1: Box plot of body temperature in 29 dogs with macroadenomas and 30 dogs with microadenomas. The box represents interquartile range (25th to 75th percentile). The bars represent the minimum and maximum data values. Median values are indicated by horizontal lines.

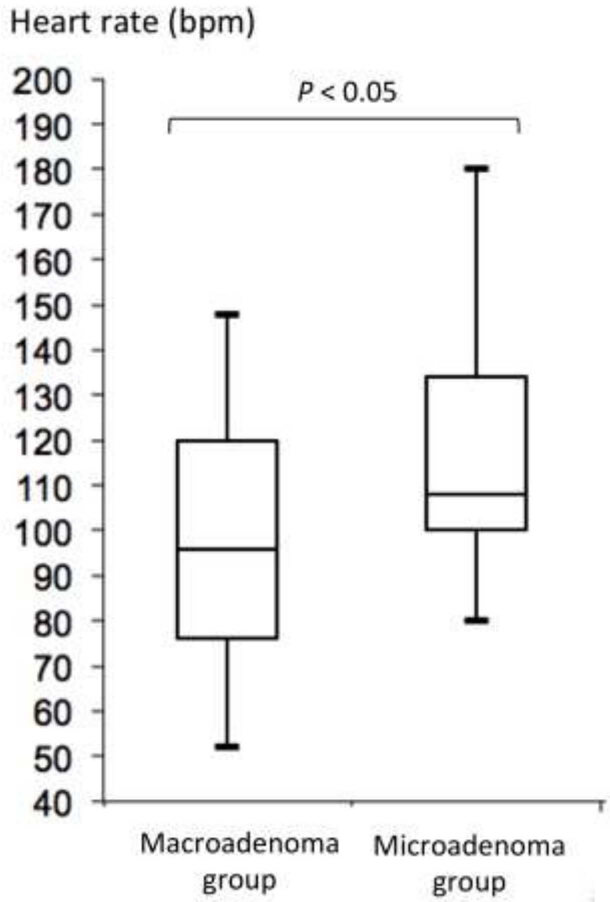

Figure 2: Box plot of heart rate in 29 dogs with macroadenomas and 30 dogs with microadenomas. See Figure 1 for legend.

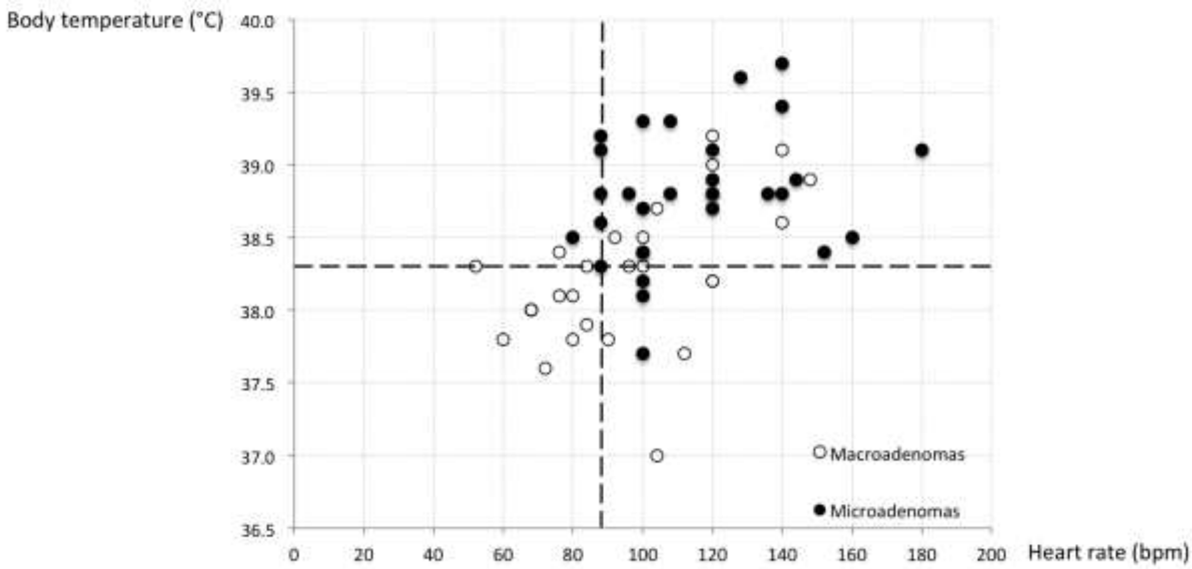

Figure 3: Plot of the heart rate (x-axis) against the body temperature (y-axis) for dogs with macroadenoma (solid circle) and dogs with microadenomas (open circle). Dogs in the microadenoma group are mainly located in the upper right quadrant. Note the dispersion of the data in the macroadenoma group towards the left with 12 dogs with a HR ≤ 84 bpm and 18 dogs with a BT ≤ 38.3°C but only one dog in the microadenoma group with a HR ≤ 84 bpm and 4 with a BT ≤ 38.3°C. Dashed lines on both plots represent the cut off value found using ROC curves for heart rate and body temperature.