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# Cisternal versus lumbar cerebrospinal fluid lactate concentration in healthy dogs

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**Abstract:** The analysis of cerebrospinal fluid biomarkers provides a wide range of information about the neurological health of a patient. Lactate is a metabolic precursor necessary for brain gluconeogenesis. When oxidative impairment or mitochondrial damage is present, lactate alteration occurs. The rostro-caudal dynamics of cerebrospinal biomarkers along the craniospinal axis in humans and horses was demonstrated in other studies. To the authors' knowledge, no clinical study has, so far, investigated the cerebrospinal fluid lactate concentration in dogs in association with the puncture site. The purpose of this study was to compare the cerebellomedullary cistern and lumbar cistern cerebrospinal fluid lactate concentrations in healthy dogs. Cerebellomedullary and lumbar cerebrospinal fluids were collected for the cell count, total protein determination and lactate analysis from ten healthy Beagle dogs. The results revealed a significantly increased lumbar cerebrospinal fluid lactate concentration when compared with the cerebellomedullary cistern level. The results included: the total nucleated cell count < 5 cells/µl, the red blood cell count < 500 cell/µl, the total proteins < 0.3 g/l, as well as the cerebellomedullary lactate values (1.44 ± 0.06 mM/l) and the lumbar cistern lactate values (1.58 ± 0.1 mM/l). The results of this study highlight useful data that help to understand the physiological lactate variations depending on the cerebrospinal fluid puncture site.

**Keywords:** brain energy metabolism; canine; puncture; rostro-caudal dynamics

The analysis of cerebrospinal fluid (CSF) provides a wide range of information about the neurological health of a patient. The routine analysis of CSF in veterinary neurology includes the cell number, type and total proteins (Di Terlizzi and Platt 2009). However, non-traditional markers such as the lactate have been sparking interest in human and veterinary medicine, providing additional information about intracranial and metabolic disorders (Pang and Boysen 2007; Witsberger et al. 2012; Caines et al. 2013). Lactate is a metabolic precursor necessary for brain gluconeogenesis (Magistretti and Pellerin 2000). When oxidative impairment or mitochondrial damage is present, lactate alteration occurs (Sugi et al. 1975; Pugliese et al. 2005). The cerebrospinal fluid lactate (CSFL) concentration was found to be increased as a result of cerebral metabolic dysfunction in a variety of diseases, such as cognitive dysfunction syndrome, cerebral ischaemia, head trauma and a variety of CNS (cen-

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tral nervous system) inflammatory and neoplastic diseases (Sugi et al. 1975; Pugliese et al. 2005; Pang and Boysen 2007; Caines et al. 2013).

Despite the number of studies examining how the pathology influences the CSFL concentration, there are few reports with limited populations describing the CSFL physiologic ranges in dogs (Pugliese et al. 2005; Il-Hwan et al. 2008; Witsberger et al. 2012; Caines et al. 2013; Galan et al. 2013). These reports are just available for samples obtained from the cerebellomedullary cistern (CMC). Nevertheless, it is known that CSF is often obtained at the lumbar site, even for intracranial diseases.

The circadian rhythm and rostro-caudal dynamics of CSF biomarkers have been demonstrated to exist along the craniospinal axis in humans (Vaughn et al. 1988; Reiber 2003; Tarnaris et al. 2011). In veterinary literature, it has been reported that the CSFL concentration from the CMC samples in horses is lower than that in the lumbar samples (Andrews et al. 1990), suggesting the presence of a rostrocaudal gradient also in this species. We hypothesise that the lumbar CSFL concentration could be higher than the cerebellomedullary one in dogs. To the author's knowledge, no clinical study has so far investigated the CSFL concentration in dogs in association with the puncture site. The aim of this study was to determine whether the CSFL concentration was different between the CMC and lumbar cistern (LC) samples in healthy dogs.

## MATERIAL AND METHODS

Ten healthy, adult (3.5–4.5 years old) laboratory Beagle dogs underwent both an CMC and an LC puncture. This study followed the European legislation (86/609/EU) and the experimental protocol was approved by the Ethics and Welfare Animal Committee of the University of Cordoba (Córdoba, Spain). The animals' welfare was our priority, and, thus, all efforts were made to minimise the animals' distress.

In this study, no premedication prior to the general anaesthesia was performed with the aim at avoiding biased samples due to the use of different anaesthetic drugs. A general anaesthesia was induced and maintained either with propofol or isoflurane as follows: (1) with 6 mg/kg to 8 mg/kg of propofol (Propofol-Lipuro 1%; Braun Vet Care, Barcelona, Spain) and followed by a constant rate infusion that ranged between 0.4 mg/kg/min and 0.6 mg/kg/min, or (2) with isoflurane (Isovet; B Braun Vet Care, Barcelona, Spain) in 100% oxygen using a circle rebreathing system (Excel 210SE; Ohmeda, Louisville, Kentucky, USA), maintaining an end-tidal between 1.3% and 1.5%. The heart rate, blood pressure and blood oxygenation were monitored during the anaesthesia. All ten of the dogs recovered satisfactorily after each procedure.

All the CSF samples were collected by two investigators, firstly from the LC and subsequently from the CMC following a standard technique (Di Terlizzi and Platt 2009), using a 20-gauge, 1.5 inch-long disposable spinal needle (Becton-Dickinson and Company, New Jersey). All the samples were collected within the first 15 min after the induction, once the anaesthetic depth was adequate for the procedure. A total volume of 1.5 ml CSF (less than 0.2 ml per kg of body weight) was obtained from each dog between the two puncture sites. Each of the two samples (i.e. one from the CMC and the other from the LC) were further divided into two different aliquots. On the one hand, one aliquot from each puncture site was immediately analysed for the cell count (Neubauer haemocytometer Zuzi; Auxilab, Beriain, Spain) and also for the total protein spectrophotometric determination [pyrogallol red colorimetric reaction (Atom A15; Biosystems, Barcelona, Spain)]. On the other hand, the remaining aliquots were sent to an external laboratory (Idexx Laboratories, Barcelona, Spain) for the lactate analysis [molecular absorption spectrometry (ADVIA 1800, Siemens Healthcare, Barcelona, Spain)]. The statistical analysis consisted of the Kolmogorov-Smirnov test to verify the normal data distribution. The Student's *t*-test was performed in order to compare the CMC and LC lactate concentrations for the related samples. The software SPSS v18.0 (SPSS Inc., IBM Chicago, Il, USA) was used for the data analysis. The statistical significance was set at $P \leq 0.05$.

## RESULTS

Five male spayed and five female neutered dogs were used in this study. The median age was 4 years. All the CSF samples were clear and colourless. In all the cases, the CSF samples showed values within the physiological limits for the total nucleated cell count (TNCC), the red blood cell count (RBCC)

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Table 1. Values of all the indicators analysed in cerebellomedullary cistern (CMC) and lumbar cistern (LC)

| | CMC | LC |
|---|---|---|
| Cell count (cells/µl) | 2.33 | 2.7 |
| Total proteins (g/l) | 0.088 | 0.193 |
| Lactate (mM/l) | 1.44 | 1.58 |

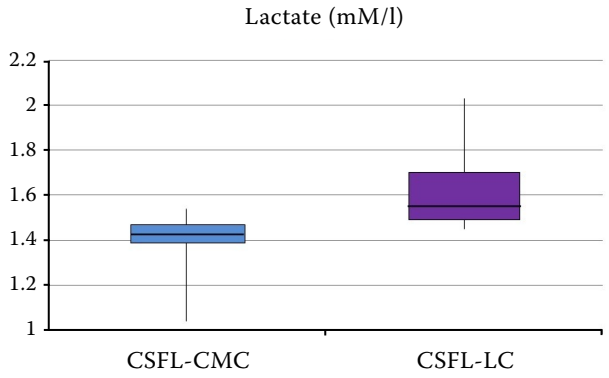


Figure 1. Box plot indicating the lactate CSF concentrations in ten dogs and the differences between the puncture site (CMC *vs* LC). The boxes show the interquartile range (IQR), with the median presented by the centre line. The whiskers represent the maximum and minimum measurements, up to 1.5 × IQR (Interquartile Range). The CSFL-CMC group is indicated in blue. The CSFL-LC group is shown in purple. In this study, it a Student's *t*-test has been used in order to compare the CMC and LC lactate concentrations for the related samples. The statistical significance was set at $P \leq 0.05$

and the proteins, with references of < 5 cells/µl, < 500 cell/µl and < 0.3 g/l, respectively (Table 1). The mean ± SD CMC lactate concentration was 1.44 ± 0.06 mM/l (minimum 1.04 mM/l – maximum 1.6 mM/l), and the mean ± SD LC lactate concentration was 1.58 ± 0.1 mM/l (minimum 1.45 – maximum 2.03 mM/l) (Figure 1). The CSFL concentration was significantly higher in the lumbar samples than in the cisternal samples ($P = 0.001$).

## DISCUSSION

In humans and dogs, the rostro-caudal dynamics of CSF markers have been described (Vaughn et al. 1988; Reiber 2003; Tarnaris et al. 2011). Although no significant differences have been found between the CMC and LC markers in previous studies, an increasing trend in the LC lactate concentration has been observed when compared with the CMC lactate (Tarnari et al. 2011).

The same finding has been described in horses which present a higher CSFL concentration in the LC samples than in the CMC ones (Andrews et al. 1990).

The CFSL concentrations in this study were similar to those reported in previous studies (Sugi et al. 1975; Pugliese et al. 2005; Il-Hwan et al. 2008; Witsberger et al. 2012; Caines et al. 2013; Galan et al. 2013). However, like previous studies, a wide variation in the physiological concentrations was observed. The age and anaesthetic drugs have been described as possible influences on the CSFL in Pugliese et al. (2005) and Horn and Klein (2010). Recent studies like Seisdedos et al. (2019) reflect a significant variation between the CSFL concentrations due to the anaesthetic agent used (either propofol or isoflurane) and the anaesthesia time of the puncture (either 15 min or 3 h after the anaesthesia induction). Animals with similar ages and only two different anaesthetic protocols have been used in this study, in accordance with concurrent research projects, in order to minimise the variability observed among the studies. It has been proposed that there could be variations in the CSFL concentration between different breeds, thus, for the sake of avoiding bias, we have exclusively used Beagles. Horn and Klein (2010) found that isoflurane increases the CSFL concentration in mice, proportionally to the anaesthesia time. In this study, the puncture has been performed immediately after the induction; therefore, the influence by the anaesthetic duration on the CSFL could be considered as minimal.

Our findings suggest that the CSFL concentration is higher in the lumbar samples. The limited number of animals makes further studies necessary to establish the dynamics of this metabolite along the spinal axis. Nevertheless, it is in the authors' opinion that our results emphasise the importance of a deep understanding of the CFSL concentration for the complete interpretation of the pathological changes of this metabolite, as well as their significance.

Further studies including other breed types, different age groups and a larger number of animals should be taken in order to define breed-dependent and age-dependent reference values for the CSFL concentration in both the CMC and LC.

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## Conflict of interest

The authors declare no conflict of interest.

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