LINEAR RELATIONSHIP FOUND BY MAGNETIC RESONANCE IMAGING BETWEEN CEREBROSPINAL FLUID VOLUME AND BODY WEIGHT IN DOGS

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Despite numerous studies on cerebrospinal fluid (CSF) and its importance during hydrocephalus or myelography, no reliable values exist about its overall volume in dogs. In this study, our aim was to measure the intracranial (IC) volume of CSF in dogs and assess its possible relationship with body size and the symmetry of the lateral ventricles. We ran a 3D magnetic resonance imaging (MRI) sequence on the central nervous system of 12 healthy, male mongrel dogs between 3–5 years of age and 7.5–35.0 kg body weight. A validated semi-automatic segmentation protocol was implemented to segment the CSF and measure its volume. Values for the volume of the ventricular compartment were between 0.97 and 2.94 ml, with $62.1 \pm 11.7\%$ in the lateral ventricles, $17.6 \pm 4.9\%$ in the third ventricle, $4.9 \pm 1.6\%$ in the aqueductus mesencephali and $15.5 \pm 6.6\%$ in the fourth ventricle. In 11 cases a significant asymmetry was found between the lateral ventricles. The results suggest that it may be normal for a dog to have one of the lateral ventricles 1.5 times larger than the other. The correlation between body weight and CSF volume was linear, indicating that the current dosage protocols for myelography, based on a hypothetical proportional relationship with body weight, may have to be revised.

Key words: Cerebrospinal fluid, volume, hydrocephalus, dog, MRI

In numerous clinical cases the overall volume and distribution of the cerebrospinal fluid (CSF) may have a very direct effect on patient symptoms and/or diagnosis (Vite et al., 1997; Arany-Tóth et al., 2012). Variations of the normal anatomy of ventricles must also be recognised when evaluating such cases. Despite that, studies of CSF volume and distribution are limited in number and con-

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tradictory due to CSF physiology and measurement challenges. Based on the most recent hypothesis, the CSF and the interstitial fluid of the central nervous system constitute a single functioning unit where the osmotic pressure relations between CSF/interstitial fluid and blood regulate the flow of the molecules (Oresković and Klarica, 2010; Bulat and Klarica, 2011). Consequently, CSF volume cannot be accurately measured post mortem because the altered osmotic conditions and the lack of blood pressure rapidly change the pre-existing values.

There are no studies that have aimed to measure the overall CSF volume of dogs. The ventricular volume of English Bulldogs was measured by MRI in one study (Vite et al., 1997). Due to the slice thickness, the high prevalence of congenital and acquired hydrocephalus (Selby et al., 1979) in this breed, and the existing neurological symptoms and anatomical anomalies in the subjects, these results cannot be extrapolated to the entire species. The volume of the lateral ventricles has also been measured in beagles (Kii et al., 1997; Vullo et al., 1997), another breed known for the high prevalence of congenital and acquired hydrocephalus (Cammermeyer, 1961).

Anecdotal radiographic evidence suggests that the lateral ventricles may be asymmetric in a large percent of healthy dogs, which makes the evaluation of hydrocephalus difficult by adding anatomical variations. The aforementioned study of Kii et al. (1997) on beagles reported that one lateral ventricle was significantly larger than the other in 90% of the subjects.

Asymmetry of the lateral ventricles was studied in different breeds (Labrador Retrievers, DeHaan et al., 1994; English Bulldogs, Ryan et al., 2014). However, the classification of symmetry was based on the subjective observation of MRI images; therefore slight levels of asymmetry may have been evaluated inaccurately. These studies used 5 mm thick slices and T1 weighting, which makes the results potentially unreliable (Harris et al., 1992; Deliganis et al., 2001).

The extracranial (EC) CSF compartment was measured on the subjects of the current study (Reinitz et al., 2015). A preliminary study was performed first to develop and validate the measurement methods (Reinitz et al., 2013) used in that and the current study.

In the present study, we sought to quantify the *in vivo* intracranial (IC) CSF volume and the distribution of the CSF among the ventricles, and particularly to compare the lateral ventricles to each other. Overall, we aimed to determine the distribution of the CSF among the compartments and identify the relations between body size and overall CSF volume in healthy dogs. Understanding this and the distribution of the CSF may help clinicians in diagnosing early stages of hydrocephalus and also in calculating the safe dosage for injecting drugs or contrast media into the subarachnoid (SA) space.

Materials and methods

Subjects

The research was approved by the Institutional Animal Care and Use Committee of the Veterinary Faculty of Szent István University (VF). Twelve healthy, male, mongrel dogs aged 3–5 years were recruited for the study. The owners were given a written description of the planned procedure and were provided opportunities to have their questions answered. Each owner gave a written permission to conduct the measurements, with all costs and risks borne by the VF.

Only dogs that had healthy physiological values and were found free of any clinical symptoms (Houston, 2000; Houston and Radosits, 2000; Garosi, 2004) during the detailed examination conducted on the day of the MRI by the veterinarians of the VF were permitted to participate in the study. Each dog was in average nutritional condition. Withers height and body weight (BW) values were recorded using calibrated, regularly verified equipment.

Image acquisition

General anaesthesia was induced with propofol (Diprivan 1% inj., Astra-Zeneca Limited, London, United Kingdom; 6 mg/kg body weight) and maintained with the inhalation of isoflurane (Abbott Lab. Ltd., Kent, United Kingdom; 1.2–2% end-tidal isoflurane in 1.5–2.0 l/min oxygen) after intubation. The duration of anaesthesia from intubation until the cessation of isoflurane inhalation was less than 45 minutes. The subjects were placed in dorsal recumbency to conduct an MRI examination using a 1.5 T MRI system (Siemens Magnetom Avanto, Siemens AG, Erlangen, Germany). Following the method of Condon et al. (1986), water containers with a quantified amount of water were placed against each subject's spine and were measured with the subjects. First, a routine clinical diagnostic sequence was executed to ensure that no subclinical disorders were visible in the region of interest. Following this, the skull was measured using a T2 weighted 3D SPACE (Sampling Perfection with Application optimized Contrast using different flip-angle Evolution) MRI sequence with the centre of the field set to the estimated centre of the brain. This sequence created a high difference in signal intensity between the CSF and the other tissues. A 12-channel head matrix coil was used. Further settings: plane of measurement: sagittal plane; minimal TR: 1500 ms, TE: 226 ms; turbo factor (echo train length) of 97; flip angle 130; parallel imaging with a GRAPPA acceleration factor of 2; 230 × 230 mm field of view; 310 × 320 acquisition matrix; number of averages 1.9; phase oversampling 80%; slice oversampling 8%; 1.0 mm section thickness (resulting in a voxel of 0.7 × 0.7 × 1.0 mm); interpolated voxel size 0.35 × 0.35 × 1.0 mm; acquisition time: 4 minutes and 4 seconds. Flow compensation was applied in the direction of slice selection, and the sequence resulted in 72 slices of the subject's cranium (Fig. 1).
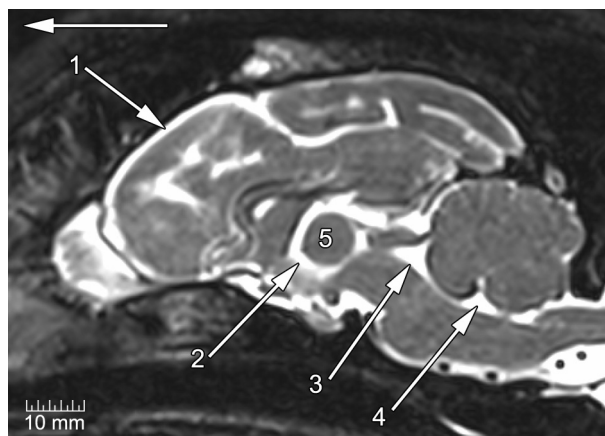
Fig. 1. 3D SPACE MRI image of the cranial region of subject no. 6 in the midsagittal plane. Areas with high signal intensity represent the cerebrospinal fluid. The arrow on the top left corner points cranially. 1: fissura longitudinalis cerebri; 2: third ventricle; 3: recessus colliculi caudales; 4: pars intermedia of the fourth ventricle; 5: adhesio interthalamica

After the procedure, the subjects were monitored for three months, and no signs related to the procedure were recorded. During this period the subjects underwent physical and neurological examinations every two weeks, performed by the veterinarians of the VF. Additionally, no signs that might have existed in a subclinical form during the MRI examination were registered.

Segmentation and volume measurement

The MRI data were evaluated by a veterinary anatomist. A free open source image analyser (Fedorov et al., 2012) was used for segmentation and measurement.

The caudal border of the foramen magnum was used to demarcate the border between EC and IC regions. The window level values were set to have the CSF clearly distinguishable from the nearby tissues, with the anatomical landmarks also clearly visible (W = 520; L = 194), and the same setting was used in every series. The IC SA space and the ventricular compartment were measured separately with a similar method and settings.

A semi-automatic segmentation method was implemented using the 'Threshold' function (range: 99–1004). The resulting selections were adjusted manually (using the 'Paint' and 'Wand' tools) on every slice, starting with the sagittal images, followed by the axial images which were obtained through the transformation of the sagittal images. Depending on the size of the cranium, 105–160 axial images covered the ventricular region, and 196–287 images covered the IC SA compartment with 0.35 mm spacing in both procedures. The 'Make Model' function was used to create the 3D model of the final selections.

During this process, each slice was viewed to verify the segmentation. Examples of the reconstructed models are shown in Figs 2A and 2B. Volume values of the selections were obtained using the 'Label Statistics' module. Once the total volume of the ventricles was measured, the selection was modified: the ventricles were individually deselected using the 'Erase Label' tool (order of deselection: right lateral ventricle, left lateral ventricle, third ventricle, aqueductus mesencephali). After the deselection of each ventricle, the volume measurement of the remaining selection was performed again, which allowed us to calculate the volume of the deselected ventricle. The IC SA space was not divided further.
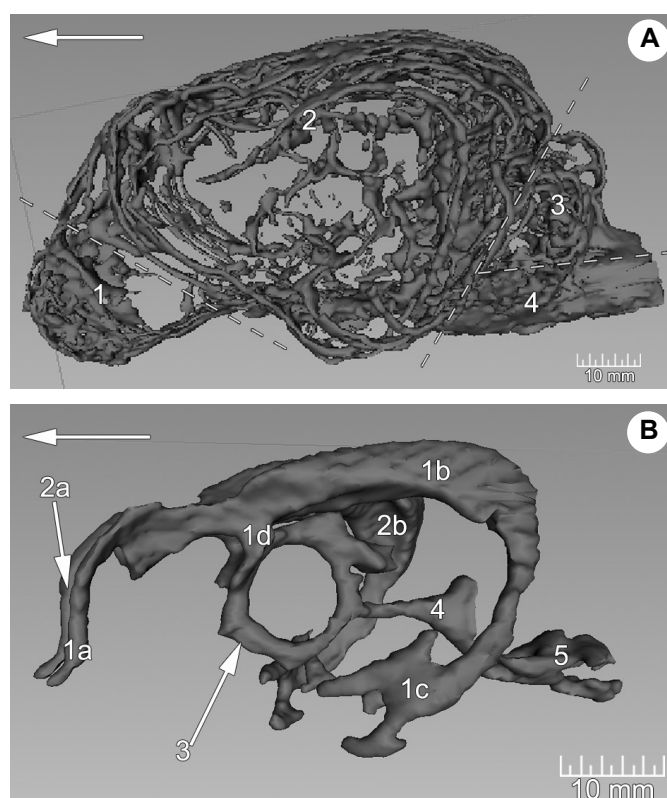
Fig. 2. (A) 3D reconstruction model of the cerebrospinal fluid in the intracranial subarachnoid space of subject no. 6 as viewed in 3D Slicer. Left lateral view. The arrow on the top left corner points cranially. 1: region of the rhinencephalon; 2: region of the cerebrum; 3: region of the cerebellum; 4: region of the pons and the medulla oblongata. (B) 3D reconstruction model of the cerebrospinal fluid inside the ventricles of subject no. 6 as viewed in 3D Slicer. Left lateral view. The arrow on the top left corner points cranially. The left lateral ventricle mostly covers the right lateral ventricle. 1a: recessus olfactorius of the left lateral ventricle; 1b: pars centralis of the left lateral ventricle; 1c: cornu temporale of the left lateral ventricle; 1d: foramen interventriculare sinister; 2a: recessus olfactorius of the right lateral ventricle; 2b: cornu temporale of the right lateral ventricle; 3: third ventricle; 4: aqueductus mesencephali; 5: fourth ventricle

Statistical analysis

Statistical analysis was performed within a statistical environment (R version 3.1, The R Foundation for Statistical Computing, Vienna, Austria) by the Department of Biomathematics and Informatics of the VF. Linear regression was used to specify the relations between the physical measurements and the volumetric data, and a paired *t*-test was used to evaluate differences between the left and right lateral ventricles. Following the statistical analysis of the IC data, results of the IC measurements were combined with those of the EC measurements (Reinitz et al., 2015), and the combined data were analysed using the same methods.

Results

During the preliminary study (Reinitz et al., 2013), we validated the measurement process with a Plexiglas model of the canine SA space following the method of Lee et al. (2001), resulting in 99.96% accuracy. Additionally, the volume of water in the aforementioned containers was measured with every subject using the same segmentation algorithm, resulting in $99.8 \pm 3.1\%$ accuracy.

The final models of the ventricles corresponded to the anatomical descriptions (Fitzgerald, 1961), with all major anatomical structures present and without any further unidentifiable structures. For the IC SA space, all major grooves of the brain were clearly visible, but we were unable to segment several portions of the IC SA space between these grooves, as shown in Fig. 2B.

The measured volume values were between 0.97–2.94 ml in the ventricular compartment and between 8.44–22.62 ml in the IC SA space. The individual results of the IC CSF volume in each compartment and the physical measures of the subjects are shown in Table 1. The following correlation was found between the volume of the IC SA (V_{ICSA}) space and the BW in kilograms (P = 0.009; adjusted r^2 = 0.468): (V_{ICSA}) = BW $\times$ 0.62 + 0.12 (Equation 1).

Of the total ventricular compartment volume, the mean combined volume of the lateral ventricles was $62.1 \pm 11.7\%$, the mean volume of the third ventricle was $17.6 \pm 4.9\%$, the mean volume of the aqueductus mesencephali was $4.9 \pm 1.6\%$ and the mean volume of the fourth ventricle was $15.5 \pm 6.6\%$. No significant correlation was found between physical measures and the volume of the ventricles, or between physical measures and the proportional distribution of the IC CSF compartments.

After combining the results of the current study with the results of the EC measurements (Reinitz et al., 2015), the following correlation was found between BW in kilograms and the total CSF volume (V_{Total}) in ml (P = 1.94×10^{-5}, adjusted r^2 = 0.836): V_{Total} = BW $\times$ 1.39 + 17.5 (Equation 2). Due to their collinearity with BW, adding either the length of the spinal cord or shoulder height did not improve the model.

Table 1

Distribution and volume of the cerebrospinal fluid (CSF) in the intracranial (IC) region

Subject no.	Body weight (kg)	Withers height (cm)	Left lateral ventricle (ml)	Right lateral ventricle (ml)	Third ventricle (ml)	Aqueductus mesencephali (ml)	Fourth ventricle (ml)	IC SA* space (ml)	Total IC CSF volume (ml)
1	13	43	0.31	0.22	0.21	0.06	0.17	8.44	9.41
2	20.2	54	0.34	0.29	0.38	0.07	0.46	15.18	16.72
3	14	45	1.36	0.94	0.3	0.06	0.28	8.75	11.69
4	35	59	0.26	0.35	0.24	0.07	0.14	22.62	23.68
5	19	46	0.88	1.17	0.24	0.08	0.18	11.25	13.8
6	16.5	53	0.35	0.27	0.25	0.06	0.23	9.77	10.93
7	13	38	0.62	0.91	0.37	0.09	0.31	9.52	11.82
8	26	55	0.48	0.35	0.34	0.13	0.37	12.49	14.16
9	20	47	0.59	0.85	0.34	0.11	0.42	12.26	14.57
10	26.5	51	0.86	0.67	0.29	0.11	0.23	19.49	21.65
11	19	49	0.46	0.45	0.26	0.08	0.24	10.36	11.85
12	7.5	26	0.62	0.72	0.36	0.07	0.15	12.12	14.04

*subarachnoid

Mean percentages and standard deviations of the compartmental distributions of CSF are shown in Table 2. There was no significant correlation between BW and the proportional quantity of CSF compartments.

Table 2

Regional distribution of the cerebrospinal fluid (CSF) in dogs

Region	Mean regional distribution of the CSF (%)	Standard deviation (%)
Extracranial	66.99	5.15
Intracranial	28.57	4.91
Ventricular	4.45	1.96

Discussion

MRI studies to measure the volume of the ventricles in dogs were performed in English Bulldogs (Vite et al., 1997), Beagles (Kii et al., 1997; Vullo et al., 1997), and a small group (n = 3) of dogs with unspecified breeds (Daniel et al., 1995). English Bulldogs showed significantly larger ventricular volumes (mean: 11.4 ml after excluding the subject with pathologically confirmed hydrocephalus) than other breeds or our group. The septum pellucidum was deficient

in every English Bulldog and the authors concluded that either all subjects of this group had a subclinical hydrocephalus, or the size of the lateral ventricle is larger in this breed. Only the lateral ventricles were measured in the beagles and no significant difference was found compared to our results (P = 0.111 between the entire groups, P = 0.354 between the males only). Compared to the study of Daniel et al. (1995) on unspecified breeds, the difference between our mean value and theirs is 1.2 ml, and the groups show no significant difference (P = 0.204).

The potential asymmetry of the lateral ventricles adds an important aspect to the evaluation of hydrocephalus. In our group the mean volume of the lateral ventricles was similar (P = 0.937, 95% CI: –0.14; 0.13). Within individuals, a significant difference was found between the left and right sides in 11 dogs (91.7%). In six cases (50%) the left lateral ventricle was larger, and in five cases (41.7%) the right lateral ventricle was larger; in one case (8.3%) the two sides did not differ significantly (left side: 0.46 ml, right side: 0.45 ml). Excluding the case with equal lateral ventricle sizes, the average scale between the smaller and the larger lateral ventricle was 1:1.34 (SD: 0.1) with the largest difference being 1:1.47 and the smallest difference being 1:1.16. In the male group (n = 9) of the aforementioned study on beagles (Kii et al., 1997) the left lateral ventricle was larger in six cases and the right lateral ventricle was larger in two cases; in one case, the two sides did not differ significantly in size. The average ratio of smaller to larger lateral ventricle volume was 1:1.41 (SD: 0.25) after excluding the subject with equal lateral ventricle sizes. The largest ratio was 1:1.80 and the smallest ratio was 1:1.10. Due to possible differences in the sex and hormonal stages in females (Grant et al., 1987), the female Beagle group was not compared to our group in this regard. However, the high prevalence of congenital and acquired hydrocephalus in beagles may affect these results (Cammermeyer, 1961). Asymmetry of the lateral ventricles was studied in male Labrador Retrievers (n = 62; BW = 35–50 kg) of unknown age using MRI (DeHaan et al., 1994). In this study only 39% of the subjects were found to have asymmetric lateral ventricles, without specifying which side was larger. However, the classification of symmetry was based on subjective observation of the MRI images; therefore small levels of asymmetry may have been evaluated inaccurately. Measurement of the volume of ventricle was performed using T1-weighted sequence and 5 mm spacing in the aforementioned studies (Daniel et al., 1995; Kii et al., 1997; Vite et al., 1997; Vullo et al., 1997), although anaesthesia-related artefacts may interfere with CSF in T1-weighted images (Deliganis et al., 2001). Also, due to the complex anatomy of the ventricles, 5 mm thick slices may include brain parenchyma and CSF as well, resulting in under- or overestimation of CSF volume (Harris et al., 1992). These factors along with the aforementioned clinical observations (Cammermeyer, 1961; Selby et al., 1979) make comparisons between these and our studies potentially difficult to evaluate.

As for total CSF volume, the practical implication of Equation 2 is that among adult male dogs with average nutritional condition, ranging between 3–5 years of age and 7.5–35.0 kg BW, a dog of twice the BW of another has approximately 1.5 times more CSF. Although a body mass index (BMI) measurement cannot be obtained from mongrel dogs due to inevitable variations in body frames, we believe the tendency for CSF volume to not scale directly proportionally with the BW can be generalised to the entire species. However, a larger sample size and diversity of dogs should be studied to evaluate this statement and fully characterise the CSF volume–BW relationship.

The distribution of the CSF among the compartments showed no correlation with physical body measurements, indicating that CSF distribution is probably similar among all dogs. As for the proportional quantities of CSF among the different regions, there are no data on dogs with which we could compare our measurements.

There are numerous factors that may interfere with MRI-based CSF volume measurements. In this study we aimed to limit or control these factors as much as possible in order to reveal the real physiological conditions. As each subject passed a complete physical and neurological examination in the present study, our results were unlikely to be influenced by pathological or external influences. The overall CSF volume is proportionally much greater in infants than adults (Ropper, 2004) and begins to increase in the elderly due to numerous factors (Wisco et al., 2008; Royle et al., 2013); thus, we only studied young adult dogs. Purebreds and females were also excluded to avoid possible hormonal effects (Grant et al., 1987) or any known (Cammermeyer, 1961; Selby et al., 1979) or unknown breed variations.

In the short duration of anaesthesia used in the present study, the used anaesthetics do not affect the physiology of the CSF (Artru, 1984; Parma et al., 1989) in dogs.

Recumbency may also affect CSF measurements (Bijsterbosch et al., 2013). However, no effort was made in the present study to reduce this effect. As dorsal recumbency is the position most widely used in standard clinical procedures, changing recumbency would have made our results incomparable with future measurements performed under clinical conditions. Furthermore, any significant reflow between the compartments because of recumbency would have affected the pressure curve and the blood pressure relations of the SA space, but no such effects have been reported.

Existing data suggest that it may be normal for a dog to have one of the lateral ventricles 1.5 times larger than the other. Our findings on the IC distribution of the CSF may help the early diagnosis of hydrocephalus or may prevent false diagnosis of unilateral hydrocephalus. Myelography and other procedures, with contrast/drug injection into the SA space may also benefit from our findings. The official dosage calculations for these procedures are based on a hypo-

thetical proportional relationship between BW and CSF. Based on the relation between the CSF volume and the BW described in Equation 1 and Equation 2, dosage systems may be revised to increase patient safety. However, further studies are required taking into consideration potential intersexual and interbreed differences. Due to numerous factors that make postmortem measurements questionable, we suggest that physiological values for every species should be re-evaluated using *in vivo* imaging methods. Our method is one to be considered for such measurements and the provided IC and combined CSF volume values for dogs may also serve as a baseline for further canine studies.

Acknowledgements

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