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Postgraduate School of Veterinary Science**

**Subarachnoid pressure changes  
in dogs during myelography**

**Thesis of PhD Dissertation**

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## INTRODUCTION

In addition to the advancements in diagnostic 3D imaging techniques, contrast radiography of the subarachnoid space, a relatively simple and effective diagnostic method, is still a useful tool for the diagnosis of compressive spinal lesions. One of the main disadvantages of myelography, compared to 3D imaging, is that it is an invasive procedure. Even when performed properly, tonic-clonic seizures, protracted recovery, and central nervous system depression may occur after the examination. Adverse effects and complications are more common in large dogs, and when atlanto-occipital puncture is used, or when the duration of postmyelographic anesthesia is short. Large volumes of contrast medium more often produce adverse effects than smaller volumes. The prevalence of seizures after myelography varies between 1% and 21.4%, even when using second-generation iodinated compounds. Understanding the characteristics of the side effects may help to prevent and/or reduce them. Iodinated contrast media can cause chemical irritation and meningitis; this is well documented as a possible cause of clinical signs in. We suspected, that pressure increase of the cerebrospinal fluid (CSF) space may contribute to a reduction of cerebral circulation and thus the development of neurological complications following myelography.

Cerebral perfusion pressure represents the gradient acting across the cerebrovascular bed; it is one of the determinants of cerebral blood flow. The CPP can be calculated as the difference between the mean arterial pressure and the intracranial pressure ( $CPP = MAP - ICP$ ). The intracranial pressure and the cisternal subarachnoid pressure have a high correlation and can be used alternatively with regard to nor-

mal intracranial anatomy. The normal value of intracranial pressure in healthy, anaesthetized, laterally recumbent dogs is in the range of 5-12 mmHg. An increase of the intracranial pressure reduces the CPP, which induces compensation in the form of systemic hypertension. Providing that the CPP is normal, the cerebral blood flow (CBF) depends on the diameter of cerebral arteries;  $CBF = MAP/CVR$  ( $CVR = \text{cerebrovascular resistance}$ ). The vascular response is adjusted to the metabolic requirements of the brain and controlled by vascular and chemical autoregulatory mechanisms, the latter mainly based on the blood  $PaCO_2$ . Systemic hypertension results in cerebral vasoconstriction, whereas systemic hypotension causes cerebral vasodilatation to maintain the cerebral blood flow at a constant rate. The CBF is independent of the systemic blood pressure within a wide range (50-150 mmHg). Outside the capability of autoregulation ( $MAP < 50$  mmHg or  $> 150$  mmHg) the blood flow is directly proportional to the cerebral perfusion pressure. With a MAP of less than 50-60 mmHg, this may result in cerebral hypoperfusion even if the intracranial pressure is normal. Anaesthetic management can influence the cerebral blood flow at several points e.g. MAP,  $PaCO_2$ , hypothermia, as well as the direct effect of anaesthetics on the cerebrovascular autoregulation. The increased intracranial pressure and the effect of anaesthesia during myelography result in a unique haemodynamic situation, which has been rarely discussed or investigated in the literature.

The recommended volume of contrast medium to be used for myelography via atlanto-occipital puncture is 0.3-0.6 mL/kg if a thoracolumbar, and 0.2-0.3 mL/kg if a cervical lesion is suspected. When using lumbar puncture, administering lower volumes (0.2-0.3 mL/kg) has become common practice. There are recommendations regarding

the rate of administration, but the reported values fall between 2 and 10 mL/min. Volume load induces an exponential intracranial pressure change with the rate of change of pressure as a function of contrast medium volume being proportional to intracranial volume. A measure of the rate of change is the pressure-volume index (PVI), which expresses the volume of fluid that, upon intrathecal injection, increases the intracranial pressure by a factor of 10. The PVI is a good indicator of the volume load bearing capacity of the intracranial space. Its value depends on anatomic parameters but is also influenced by the presence of disease. In people, the PVI of healthy adults differs markedly from children. The PVI can be calculated from the volume of injected fluid and the intracranial pressure change. Numerous clinical trials have demonstrated that the pressure in the cisternal and intracranial fluid spaces is practically the same. Therefore, measurement of cisternal pressure is a rapid and simple method that provides reliable data on the intracranial cerebrospinal fluid pressure as well, provided that no intracranial obstruction of cerebrospinal fluid circulation is present.

The aim of this study was to evaluate the cardiovascular and respiratory parameters of dogs during cisternal myelography with special attention to the changes in the cerebral haemodynamics. The effects of isoflurane anaesthesia were also evaluated during the procedure. Furthermore, we sought to quantify the degree of pressure increase in the cerebrospinal fluid space during cisternal myelography. The data were examined to determine if a correlation existed between this pressure increase and various body parameters or lesion characteristics. Besides, we aimed to compare the contrast volume calculated using the recorded parameters to those recommended in the literature.

## MATERIALS AND METHODS

According to the regulation of the Institutional Animal Care Committee all procedures were performed with the dog owners' approval. Dogs enrolled in the study had been referred for myelography to the Radiology Unit of the clinic with clinical signs of spinal chord dysfunction. Further inclusion criteria were a minimum body weight of 5 kg, myelography performed with a cervical puncture and no concurrent cerebral or other systemic disease. Routine hematology and blood biochemistry were performed prior to the contrast procedure. The dogs were premedicated with intravenous (IV) butorphanol (0.1 mg kg<sup>-1</sup>,) and diazepam (0.25 mg kg<sup>-1</sup>, IV) and anaesthesia was induced with propofol (3-5 mg kg<sup>-1</sup>, IV). Endotracheal intubation was performed with low pressure-high volume cuffed tube and cuff pressure was set to 20-30 cmH<sub>2</sub>O. General anaesthesia was maintained with isoflurane in oxygen delivered via a small animal circle circuit rebreathing system using a vaporizer (Isotec 3, Datex-Ohmeda GE Healthcare, London, UK) and the oxygen flow rate was set to 1-2 l/min. In the first 10-20 minutes the vaporizer was set to 3% until the end of the contrast injection, resulting an increasing ET<sub>ISO</sub> to 2-3%. Upon finishing the contrast administration vaporizer was set back and isoflurane level was adjusted between 1-2% ET<sub>ISO</sub> based on the depth of anaesthesia (palpebral reflex, eye position, heart rate (HR), respiratory rate (RR), and muscle tone). Continuous drip infusion (lactated Ringer solution, 10 ml kg<sup>-1</sup> h<sup>-1</sup>) was administered in parallel with the anaesthesia. Mechanical ventilation was not used. If the ET<sub>CO<sub>2</sub></sub> rose above 60 mmHg, manually assisted ventilation was started. The dorsal pedal artery was cannulated for invasive blood pressure

measurement. With the dogs in lateral recumbency a 22G spinal needle was placed in the cisterna magna allowing CSF collection (0.5-1 ml) for analysis. Thereafter, a digital pressure sensor (Druck PTX/PMP 1400, GE®, London, UK), was connected to the needle for registration of the CSF pressure 120 seconds before, during and 120 seconds after the administration of contrast, at a frequency of 10 s<sup>-1</sup>. The pressure gauge was set to the horizontal level of the needle. The accuracy was validated on a water column before and after the procedure. For the injection, a second needle was introduced into the cerebromedullary cistern and 0.3 ml kg<sup>-1</sup> prewarmed (38°C) iohexol solution (Omnipaque®, 300 mg/ml, GE Healthcare, London, UK) was administered at a rate of 4,1 ml min<sup>-1</sup> with a syringe pump (IVAC P6000, IVAC Medical Systems, Hampshire, UK). Trend data for the systolic (SP) and diastolic (DP) blood pressure, ETCO<sub>2</sub>, SpO<sub>2</sub>, HR, RR, ECG, and oesophageal temperature were recorded at a frequency of 1 min<sup>-1</sup> during anaesthesia (InnoCare-T, Innomed Medical Co., Budapest, Hungary). End tidal isoflurane concentration was also monitored (SurgiVet® V9400, SurgiVet, Waukesha, Wisconsin, USA). The mean arterial pressure was calculated according to the equation  $MAP=DP+1/3(SP-DP)$ . The MAP<sub>0</sub> was defined as the value of the mean arterial pressure at the beginning of the contrast injection and the MAP<sub>max</sub> as the peak value for the arterial pressure wave following the injection. The value of resting subarachnoid pressure (SaP<sub>0</sub>) was the average of values in the 2-minute interval before administration of the contrast medium. The highest value after administration (SaP<sub>max</sub>) and value 2 minutes after administration (SaP<sub>120</sub>) also were determined. The PVI of individual dogs was calculated by the following formula:

The cerebral perfusion pressure was calculated as the difference between the MAP and SAP during the period when SAP data were available (120 seconds before, during and 120 seconds after the injection). The preinjection ( $CPP_0$ ) and lowest ( $CPP_{min}$ ) values were recorded. The CPP, MAP and SAP values were graphed for waveform analysis. Based on the graph, the length of the critical CPP period ( $CPP < 50 \text{ mmHg}$ ) was calculated. Individuals were evaluated for the presence of apnoea, bradycardia, tachycardia and hypertension during and immediately after the injection. Bradycardia/tachycardia, hypo/hypertension was defined as a change of 20% from the baseline values. Apnoea was defined as cessation of spontaneous breathing for at least 30 seconds. The presence and type of compressive lesion, location (C1-5, C6-T2, T3-L3, or L4-S) and final diagnosis were recorded. The neurologic signs were scored on a modified Frankel scale, from 0 to 5. There were no side effects associated with the measurement procedures used in this study. Recording of postmyelographic seizures was not complete, thus could not be assessed in this study.

We calculated Pearson's correlation coefficient between pressure values and basic clinical data, and determined a linear regression equation for the body weight-pressure-volume-index relation. The significance level was set to 0.05. The effect of compression on the PVI value was evaluated with the analysis of covariance test (ANCOVA). Maximum subarachnoid pressure ( $SAP_{max}$ ), mean arterial pressure (MAP), and minimum cerebral perfusion pressure ( $CPP_{min}$ ) were compared to their corresponding baseline values by paired samples bootstrap t-tests, accompanied by 95% bootstrap BCa confi-



dence intervals. Spearman's rank correlation was used to evaluate the relationship between body weight,  $CPP_{min}$ ,  $SAP_{max}$ , and the number of clinical signs (apnoea, hypertension and bradycardia).

## RESULTS

Twenty-three breeds were represented with a mean body weight of  $21 \pm 14$  kg (range: 6-56 kg). The mean age of the animals was  $7 \pm 3$  (2-13) years; there were 32 males and 11 females in the study group. The severity of clinical signs was as follows: score 0 (paraplegia without deep pain sensation), 10 dogs; score 1, 6 dogs; score 2, 6 dogs; score 3, 6 dogs; score 4, 12 dogs; score 5 (spinal hyperesthesia), 5 dogs. The lesions were distributed as follows: 2 in the C1-5 region, 2 in C6-T2, 24 in T3-L3, and 2 in L4-S. There were 15 dogs without compressive lesions.

### *Subarachnoid pressure and PVI values*

The subarachnoid pressure and PVI values are in Table 1. Correlations between pressure and body parameters are summarised in Table 2.

*Table 1: Subarachnoid pressures and PVI*

<b>Parameter</b>	<b>Value</b>	<b>Range</b>
SaP <sub>0</sub> (mm Hg)	$9 \pm 3$	3-16
SaP <sub>max</sub> (mm Hg)	$70 \pm 32$	24-146
SaP <sub>120</sub> (mm Hg)	$40 \pm 14$	19-72
PVI mL	$6,65 \pm 3,87$	2,28-19,02

*Table 2. Correlations between pressure and body parameters*

	SAP <sub>0</sub>	SAP <sub>max</sub>	SAP <sub>120</sub>	PVI
bodyweight	0,43	0,75	0,53	0,94
crown-ramp lenght	0,36	0,71	0,46	0,87

There was not a significant association between age, location of the lesion, severity of clinical signs score, or gender with any recorded pressure parameter ( $r = -0.39$ - $0.38$ ).

Due to the strong correlation, the PVI for an individual dog can be estimated from the regression equation ( $PVI = 1.556 + 0.267 \times \text{body weight kilogram}$ ). If the PVI is known, the volume of injection resulting in a specific intracranial pressure value can be calculated. Based on the above, a table presenting the fluid volumes that belong to the maximum pressure threshold values can be compiled. Figure 3 represents contrast dose as a function of body weight necessary to achieve subarachnoid pressures of 40, 50 and 60 mm Hg respectively.

Pressure-volume index values were significantly lower for patients with compressive lesions ( $P = 0.0204$ ).

### *Mean arterial pressure*

The mean of the MAP<sub>0</sub> was  $72 \pm 20$  (34-122) mmHg. The adjustments of isoflurane concentration, changes in body position and eventual painful manoeuvres resulted in a very variable shape and range of the overall MAP curve over time. In thirty (70%) dogs the MAP curve started to increase during contrast administration and reached a peak in the following 60-120 seconds. Then it returned, with a rapid decrease, to approximately its original level. The total duration of the MAP

wave was generally 5-10 minutes. In thirteen (30%) dogs, there was no apparent change of the MAP detected during the injection. The mean increase of MAP was  $25 \pm 23$  (-8-73) mmHg after the injection, reaching a maximum of  $97 \pm 25$  (43-162) mmHg ( $MAP_{max}$ ) ( $p < 0.0001$ , 95% CI: (18.4, 31.9)).

### *Cerebral perfusion pressure*

Prior to the contrast injection the value of the calculated CPP was  $64 \pm 20$  (25-115) mmHg. Eleven (26%) of the 43 dogs had a CPP under 50 mmHg. At the end of contrast administration the mean  $CPP_{min}$  was  $14 \pm 34$  (-47-102). The mean decrease of the CPP was  $50 \pm 28$  (-30-108) mmHg during the injection ( $p < 0.0001$ , 95% CI: (41.6, 58.1)). The period of cerebral hypoperfusion (CPP < 50 mmHg) lasted for the entire measurement period (ca. 6 minutes) in six dogs (14%). Eighteen (42%) dogs had a discrete period of hypoperfusion of  $147 \pm 110$  sec (10-480). Nine dogs (21%) had a CPP lower than 50 mmHg before the injection that exceeded the threshold after the injection. Another five dogs (12%) had a CPP over 50 mmHg before the injection, but it did not increase above that during the following two minutes. In five dogs (12%) the CPP did not fall under 50 mmHg during the entire measurement period. Plotting the  $CPP_{min}$  against body weight shows a negative correlation between them (Spearman's  $\rho = -0.77$ ,  $p < 0.0001$ ).

### *Heart rate*

Twelve out of 43 dogs (28%) showed a marked drop in their heart rate related to the contrast injection. In some of these dogs, the bradycardia started with a 5 to 10 second period of slight tachycardia, and then the HR decreased dramatically, and was as low as 40-60 /min. The duration of bradycardia was between 3 to 10 minutes. Eight dogs showed slight tachycardia (20-40% of base line value) without the following bradycardia. Twenty three dogs did not exhibit any specific changes in the heart rate.

### *Respiratory rate*

The RR generally reflected the depth of anaesthesia. Twelve out of 43 dogs (28%) had a period of apnoea (30-120 seconds) following the contrast injection.

### *ETCO<sub>2</sub>*

The mean value of ETCO<sub>2</sub> during anaesthesia was calculated for each dog from the successive measurements obtained during one-minute intervals. The mean ETCO<sub>2</sub> for the entire group of 43 dogs was 47±9 mmHg (26-68) during anaesthesia. The oxygen saturation did not decline below 90% in any of the animals.

Nine dogs showed the clinical signs of the Cushing's triad (apnoea, hypertension and bradycardia); 20 dogs showed at least one of those parameters, and 14 dogs had none of the above mentioned clinical signs. Positive correlation was found between body weight and clini-

cal signs ( $\rho=0.67$ ,  $p<0.0001$ ),  $SAP_{max}$  and clinical signs ( $\rho=0.65$ ,  $p<0.0001$ ), whereas CPPmin and clinical signs were in negative correlation ( $\rho= -0.73$ ,  $p<0.0001$ ).

## DISCUSSION

### *Cerebral perfusion pressure*

In this study, the average value of 72 mmHg for the mean arterial pressure, before injection, reflects a moderate degree of hypotension. The dose dependent hypotensive effect of isoflurane is well documented in dogs. The mean calculated preinjection CPP value ( $CPP_0=64$  mmHg) was close to the accepted lower limit of the normal range; nine out of the 43 dogs had a CPP value between 50-60 mmHg, and 11 had values less than 50 mmHg. The  $SAP_0$  in these 20 animals was within normal limits, indicating that the low MAP was the cause of the hypoperfusion. The subarachnoid volume load of 0.3 ml  $kg^{-1}$  of contrast medium resulted in a significant reduction of the CPP. In 13 individuals (30%) the lowest calculated CPP value was negative at the end of the injection procedure, suggesting a severely depleted cerebral circulation. The observations during the post injection period revealed that the CPP exhibited a rapid return toward the original level. The rapid elevation of the CPP can be explained by the SaP decline that correlated with the length of the ischemic period. Some individuals had a rapid decrease of their SaP curve, while others had a more gradual slope. The 120 second period of observation showed a  $60\pm 19\%$  reduction of the SaP in the animals. The other cause of the

increase in CPP is the increase in arterial pressure, which is a physiological response to elevated intracranial pressure that maintains adequate cerebral circulation.

### *Clinical signs of Cushing triad*

The observed transient changes of the heart and respiratory rates are consistent with a sudden increase in the intracranial pressure. The classic response, as described by Cushing in 1901, includes apnoea, hypertension and bradycardia (Cushing's triad). The moderate increase in both the HR and MAP, not followed by bradycardia, demonstrates an early response to increasing ICP. Bradycardia is activated when the CPP and CBF are significantly compromised, especially in the brainstem. This correlates with the extremely low perfusion pressure and very high subarachnoid pressure in the patients reported here. The most severe changes in cardiorespiratory parameters occurred in the large breed dogs. This can be explained by the extremely high subarachnoid pressure and low CPP values in these dogs, as a result of the relatively high volume of contrast medium, used for the procedure.

### *ETCO<sub>2</sub>*

The PaCO<sub>2</sub> is an important factor in cerebral autoregulation. Hypercapnia causes cerebral vasodilatation, which elevates the CBF and thus the ICP. Keeping the PaCO<sub>2</sub> between 28-35 mmHg is a cornerstone of neuroanaesthesia for the prevention of intracranial hyperten-

sion. In this study, the  $\text{ETCO}_2$  was elevated ( $47 \pm 9$  mmHg) relative to the reference values; this finding suggests that controlled hyperventilation might be optimal, for these dogs, to preserve hypo/normocapnia.

Our other objective was to determine the volume of contrast medium that can be used for atlanto-occipital myelography of dogs without causing a marked elevation in subarachnoid pressure. Intracranial pressure monitoring during myelography is not routine. Thus, determining a volume of contrast medium that is unlikely to induce intracranial pressure elevation above a certain magnitude in a given individual would be useful. The pressure elevation induced by volume load is a function of the compliance of intracranial components. Based on our measurements, there was a close association between body weight and the PVI ( $r = 0.94$ ) and thus body weight is a suitable parameter in the prediction of that index.

Using the estimated PVI values, the appropriate volume of contrast medium can be calculated for an animal according to body weight. This calculated volume is unlikely to increase the subarachnoid pressure above a specific pressure limit. In people, it is a basic principle that cerebral perfusion pressure should be kept above 60 mm Hg to maintain brain perfusion. Cerebral perfusion pressure can be calculated as a difference between mean arterial pressure and intracranial pressure. Optimally, dogs under anesthesia have a mean arterial pressure of 80-120 mm Hg. Therefore, in addition to preserving the systemic normotension the clinical aim is to keep the intracranial pressure below 40 mm Hg throughout the procedure. We calculated to allow the maximum permissible theoretical pressure threshold value to be  $\text{SaP}_{\text{max}} = 40$  mm Hg.

The contrast medium volume calculated for a SaP<sub>max</sub> of 40 mm Hg falls in the range of 0.17-0.35 mL/kg, depending on body weight which contradicts the data in the literature, where higher volume of contrast medium is often recommended, irrespective of body weight and at a constant mL/kg.

In our study, the presence of a spinal compressive lesion had a statistically significant effect on the PVI. Thus dogs with compressive lesions require lower doses. The clinical importance of this observation is questionable for several reasons. We suggest using a dose calculated for an average 'spinal population' and to perform individual monitoring for signs of intracranial hypertension to detect 'outliers'. Intuitively, a potential risk of using reduced iodine volume is that diagnostic efficiency may be compromised, owing to poorer filling of the subarachnoid space. To date, no controlled clinical study has been carried out to prove diagnostic reliability of PVI based contrast doses. However our preliminary results with the contrast dose calculated with the PVI method at our clinic and are convincing.

The results of this study showed that spontaneously breathing isoflurane anaesthetized dogs were slightly hypotensive before the onset of myelography. This, combined with an increased intracranial pressure, as a result of the subarachnoid contrast injection, significantly reduced the cerebral perfusion pressure in the majority of the dogs. The presence of the classical signs of increased intracranial pressure (bradycardia, apnoea, and hypertension) correlated well with the severity of the decrease in cerebrovascular flow. As ICP monitoring is rarely performed during routine myelography, these clinical symptoms can be used as signs of impending cerebral ischemia during contrast procedures. The maintenance of the CPP is a crucial factor for the



prevention of neurological complications. The combination of isoflurane with other anaesthetic agents (e.g. opioids) might allow for lower isoflurane concentrations during the procedure. Thus, normotension could be maintained and preserved cerebral autoregulation might prevent increases in the ICP. Respiratory depression and subsequent hypercapnia could be eliminated by controlled ventilation. A moderate forced hypocapnia might contribute to decreased ICP in dogs.

The selection of volumes commonly used in practice is presumably aimed at safely achieving the required diagnostic result but it fails to take into consideration the risk posed by volume load. Our findings indicate that this practice induces a pronounced pressure elevation in the cerebrospinal fluid space, especially when using larger volumes (0.3-0.6 mL/kg) and particularly in large dogs. Furthermore, our results provide a sound basis for the trends we experience and observe in practice. We recommend a modified dose table which better reflects the anatomical and physiological parameters of different sized dogs. However, despite good correlation between body weight and dose, some individuals may experience unexpected pressure-volume parameters. In addition, speed of injection can influence intracranial and cerebral perfusion pressure as well as a number of other factors such as the site and severity of compression and arterial and central venous blood pressure. Thus, our recommendation values should be regarded as reference values and individual circumstances should always be considered.

## PUBLICATIONS REPORTING THE RESULTS OF THE POSTGRADUATE RESEARCH

1. Arany-Toth A, Csebi P, Jensen H.S., Németh T. (2008) Cisternal pressure measurement in dogs during myelography. *Magy Allatorvosok* 130, 698-703. IF: 0,088
  
2. Arany-Tóth A., Csébi P., Reiczigel J., Németh T. (accepted for publication, 2011): Subarachnoid pressures and cardiorespiratory parameters during cisternal myelography in isoflurane anaesthetized dogs. *J Vet Anaesth Analg*, IF: 1,290
  
3. Arany-Tóth A., Csébi P., Reiczigel J., Sére V., Németh T. (accepted for publication, 2012): Pressure-volume index-based volume calculation of contrast medium for atlanto-occipital myelography in dogs. *Vet Radiol Ultrasound*, IF: 1,107

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