Transcranial Doppler ultrasound analysis of resistive index in rostral and caudal cerebral arteries in dogs

Minho Seo, Hojung Choi, Kichang Lee, Mincheol Choi, Junghee Yoon*

College of Veterinary Medicine, Seoul National University, Seoul 151-742, Korea

Transcranial Doppler (TCD) was carried out to determine the resistive index (RI) values of normal canine cerebral arteries and its reproducibility and to evaluate the change of cerebral vascular resistance following diuretics administration. RI values of rostral cerebral artery (RCA) were compared between fontanelle window and temporal window. Normal ranges and reproducibility of the RI values were examined in the rostal cerebral artery (RCA) and caudal cerebral artery (CCA). And after administration of diuretics, TCD-derived RI values were measured at RCA and CCA. Cerebral vascular RI values of RCA and CCA were 0.55 ± 0.05 and 0.55 ± 0.03 in the normal dogs, respectively. There was no significant difference of RI between male and female; between fontanelle window and temporal window. Reproducibility of RI measurements between intraobserver and interobserver were relatively high. The RI of RCA and CCA were significantly increased 15 minutes after mannitol administration ($p < 0.01$) and returned to baseline values by 30 minutes, but it did not significantly change after furosemide and saline administration. The results suggest that TCD is a useful test which can obtain reproducible results from any window and has the advantage of detecting subtle changes in cerebral vascular resistance.

Key words: Transcranial Doppler ultrasound, diuretics, dogs

Introduction

The use of Doppler ultrasound to estimate blood flow velocity was described in 1960, but it was only in the 1980s that it was appreciated that sufficient ultrasound would pass through the skull to allow the detection of blood flow within the intracranial circulation [1]. To achieve sufficient bone penetration, low frequency (2 MHz) ultrasound is used. This increases tissue penetration at the cost of poor spatial resolution. Therefore, even with more recent transcranial duplex scanners, two dimensional B mode images are of low spatial resolution, and in adults the technique primarily provides useful information about blood flow velocity. Using various bone windows, where the barrier to the ultrasound is thinnest, it is possible to insonate the proximal middle, anterior, posterior cerebral arteries, the distal internal carotid artery, and the intracranial vertebrobasilar system. Location is achieved by the use of pulsed Doppler ultrasound allowing determination of the depth of the insonated vessel [1,5].

Transcranial Doppler (TCD) has a number of advantages as a method of evaluating cerebral hemodynamics. It is relatively cheap and non-invasive, allowing repeated measurements and continuous monitoring. It has a high temporal resolution making it ideal to study rapid changes in cerebral hemodynamics [1,5]. The parameters evaluated at TCD include direction of flow, velocity, and vascular resistance. Dynamic changes in the pulsatility index (PI) and the resistance index (RI), as calculated from TCD data, allow for an assessment of the forces acting on the terminal vasculature of the brain [12,24,32]. TCD is commonly accepted as a method for evaluation of intracranial arterial stenosis or occlusions and of arterial vasospasm after subarachnoid hemorrhage [2,30]. Preliminary reports suggested that TCD readings also might correlate with intracranial pressure (ICP) elevation in patients with severe brain edema and brain death after head injury, and in hydrocephalic infants [12,15]. Previous studies demonstrated a significant correlation between ICP and RI and reported that changes in the RI appear to be useful indicators of elevated ICP [12,24]. In addition, there was no significant difference between RI measurements from fontanelle window and temporal window. Therefore, RI measurements using TCD can be obtained from any window [4].

In human, numerous cerebral vessels have been mapped and their TCD parameters have been characterized using TCD [1,5,6,13,18]. However, a few veterinary reports have evaluated TCD of the canine brain in a limited population of patients [28]. Location of RCA and CCA were reported in B-mode ultrasound of dog and were adjacent to lateral

*Corresponding author
Tel: 82-2-880-1265; Fax: 82-2-880-8662
E-mail: heeyoon@snu.ac.kr

ventricle and third ventricle [16]. Furthermore, these studies were not conducted in conscious dogs. Specific normal cerebral blood velocity parameters, as determined by TCD, have not been reported in the veterinary literature for the conscious dog, but are necessary for this diagnostic methodology to achieve its full potential.

The use of diuretic agents for the reduction of elevated ICP has been found to be effective and is widely recognized as a suitable means of management of this condition [3,14,21,23,31]. Mannitol, an osmotic diuretic, has been commonly used clinically and experimentally for this purpose, either on its own or in combination with other diuretic agents. Furosemide, a distal loop diuretic, has been used to lower ICP when used alone, although there is conflicting experimental evidence for this in the normal and edematous brain [22]. The effect of diuretics has been evaluated by cerebral blood velocity parameter using TCD, but has not been evaluated by RI of the cerebral vessel. This study was performed to assess the feasibility of RI measurement in the cerebral vasculature of normal conscious dogs from fontanelle and temporal windows using TCD, and the change of cerebral vascualr resistance following administration of diuretic agents.
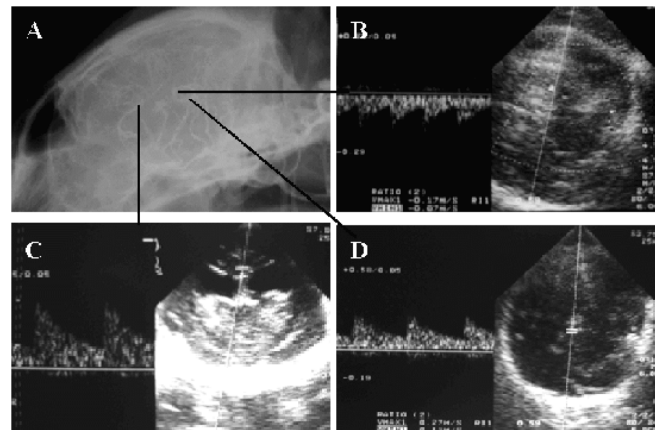
Materials and Methods

Experimental animals

Thirty seven clinically healthy dogs (aged from 3 months to 10 years old; weighed from 0.82 to 4.20 kg) were used for normal RI values of rostral cerebral artery (RCA) and sixteen dogs (aged from 5 months to 7 years old; weighed from 1.40 to 4.30 kg) were used for normal RI values of caudal cerebral artery (CCA). All dogs fulfilled the following inclusion criteria: no arrhythmia or ischemic heart disease with electrocardiographic examination, heart rate in the range of 70-160/s, no pulmonary disease, no hepatic disease, hematocrit values within the range of 35-57%, and normal blood pressure determined indirectly [19]. Ten dogs were used for reproducibility and drug induced cerebral vascular resistance changes. The dogs were housed indoor for minimum 1 month and were fed a standardized diet (Nestle Purina, Korea). All dogs were screened and considered normal based on complete neurologic and physical examinations prior to use in the study. The experimental protocol was approved by the Animal Care and Use Committee at Seoul National University.

Duplex Doppler imaging technique

Doppler sonography was performed with Toshiba SSA-260A scanner (Toshiba, Japan), using a electronic sector probe of 3.75 MHz. Standard Doppler power level was used with a range gate length of 1.5 mm, pulse repetition frequency of 4500 Hz, medium gain setting, and wall filtering of 100 Hz. All dogs were given minimum 30

Fig. 1. Angiography of cerebral vasculature (A) and Doppler images of the rostral cerebral artery (C), left caudal cerebral artery (B), and right caudal cerebral artery (D).

minutes for adapting to experimental environment. And dogs remained in a sitting position throughout the trial period. Coupling gel was applied above the zygomatic arch and transverse scan was performed. The exact positioning of the ultrasound probe was rather critical in most subjects. A satisfactory signal could only be obtained in a restricted region above the zygomatic arch, from 1 to 5cm in front of the ear. An ultrasonic window had to be located in each individual by searching this region to obtain the maximum amplitude of the Doppler signals. In order to obtain the Doppler signal in the RCA and CCA in transverse scans, the sample volume was located at the sulci of the corpus callosum, hyperechoic midline structure dorsal to lateral ventricle and around the third ventricle, hyperechoic structure continued to be seen in the midline (Fig. 1). After consecutive equivalent-appearing Doppler waveforms were obtained, the RI was calculated. The RI was obtained by dividing the difference between the peak systolic (PSV) and the end diastolic velocities (EDV) by the peak systolic velocity:

$$RI = (PSV - EDV)/PSV$$

The RI was calculated for each vessel as an average value obtained from three similar-appearing Doppler waveforms to reduce the effects of physiologic variation.

Transcranial Doppler window

The RI of RCA was obtained from fontanelle window and temporal window in 17 dogs.

Reproducibility

Intraobserver variation was calculated based on RI measurements performed 3 times every other 7 day in 10 dogs. Interobserver variation was calculated based on RI measurements performed from two observers in 10 dogs.

Two observers participated in this study had over five year experience and dedication to diagnostic imaging, particularly ultrasonography. RI was obtained from RCA and CCA. Variation was determined by intraclass correlation coeffecient.

Drug induced cerebral vascular resistance change

Ten dogs were used for evaluation of cerebral vascular resistance change induced following administration of diuretics using ultrasound. Mannitol, an osmotic diuretic, and furosemide, a distal loop diuretic, were used to induced cerebral vascular resistance change. Twenty percent mannitol (Cheiljedang, Korea) was given in 1 g/kg dose IV at 2 ml/kg/min, and furosemide (Lasix®, Handok Pharm., Korea) in 1 mg/kg IV. In addition, 0.9% saline is given in same dose and rate as mannitol for controlling increased volume. The RIs of RCA and CCA were obtained prior to the infusion, after completion of the infusion and at 15, 30, 45, and 60 min. Withdrawal periods between each medication were over 7 days.

Statistical analysis

Data were reported as means ± standard deviation (SD). The RI measurement values of CCA are the average of right and left CCA. Statistical analysis was performed using the SPSS statistical computer program. The RIs in the RCA and CCA obtained from male and female were compared using independent t-test. The RI in RCA obtained from fontanelle window and temporal window were compared using independent t-test. In order to minimize interindividual variability of physiological response, we compared baseline values with subsequent measurements after the administration of diuretics. Changes in RI were compared with baseline value with ANOVA and the Scheffe post-hoc test.

Results

Duplex Doppler imaging of the cerebral vasculature

The mean RI value, standard deviation, and value range for RCA and CCA were listed in Table 1. There was no significant difference of RI between male and female. The RIs of RCA from fontanelle window and temporal window were 0.55 ± 0.04 and 0.56 ± 0.04, respectively. There was no significant difference of RI between the windows. With regard to intraobserver and interobserver variation, the intraclass correlation coefficient between measurements for the RI values was summarized in Table 2. There was no significant difference between RI values of RCA and CCA, these values were reproducible. The RI values of CCA were relatively more reproducible than those of RCA in interobserver variation.

Drug induced cerebral vascular resistance change

Every single measurement was performed within 3 minutes. The RI of RCA ($p < 0.01$) and CCA ($p < 0.01$)

Table 1. Normal mean RI values of RCA and CCA in dogs

Variable	n	Mean±SD	Range
RCA	37	0.55±0.05	0.46~0.64
Male	13	0.54±0.06	0.46~0.64
Female	24	0.55±0.05	0.47~0.64
CCA	16	0.55±0.03	0.50~0.60
Male	8	0.55±0.03	0.50~0.58
Female	8	0.56±0.02	0.53~0.60

SD: standard deviation, RCA: rostral cerebral artery, CCA: caudal cerebral artery

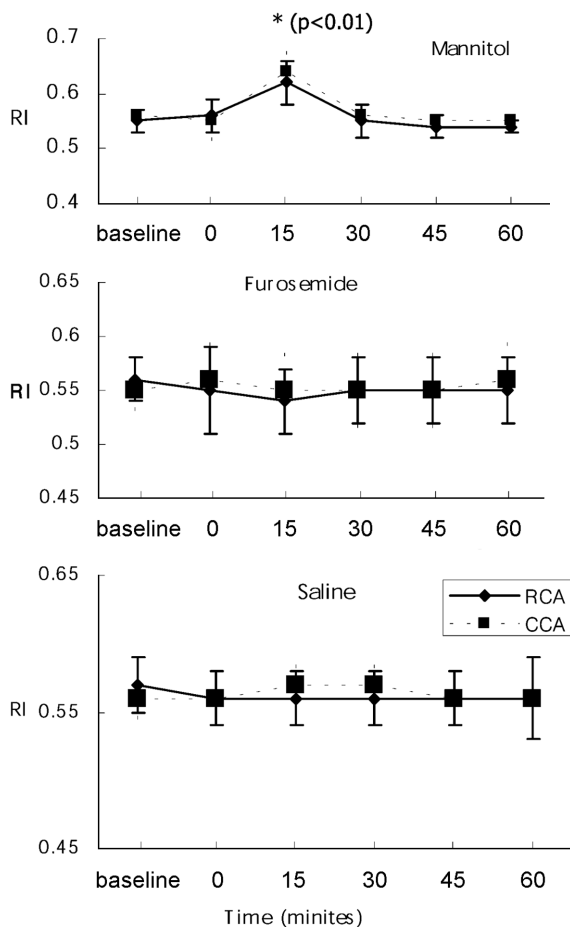**Table 2.** Reproducibility of the RI values of RCA and CCA in dogs

Parameter		Mean	SD	Reliability coefficient (κ)
Intraobserver	RCA			
	first	0.57	0.02	
	second	0.55	0.02	0.81
	third	0.56	0.02	
	CCA			
	first	0.56	0.02	
	second	0.56	0.02	0.62
	third	0.55	0.02	
Interobserver	RCA			
	one	0.56	0.03	0.62
	other	0.55	0.02	
	CCA			
	one	0.56	0.02	0.92
	other	0.56	0.02	

RCA: rostral cerebral artery, CCA: caudal cerebral artery

were significantly increased 15 min after the administration of mannitol and returned to baseline value, 0.56 by 30 min, whereas not significantly changed after furosemide and saline administration (Fig. 2).

Discussion

In human, normal limits of TCD-induced RI measurements in the cerebral vessels were reported. The RIs have positive correlation with ICP, therefore RI was useful as noninvasive indicators of an elevated ICP [24,28]. However, normal limits of RI measurements in cerebral vessels of the normal conscious dogs were not reported. A variety of neurological disorders was associated with intracranial hypertension. Invasive ICP measurements in intracranial cerebrospinal fluid (CSF) spaces or in brain parenchyma were accepted as the gold standard in neurosurgery and these methods called for general or at least local anesthesia and carried the common risks of surgical procedures, such as intracerebral bleeding or infection [9]. Therefore, some attempts have

Fig. 2. The RI of rostral cerebral artery (RCA) and caudal cerebral artery (CCA) at baseline and at various times following the start of mannitol (1 g/kg), furosemide (1 mg/kg), and saline (5 ml/kg) infusion. Values are means ± standard deviation.

been made to establish reliable noninvasive techniques for ICP measurement which may be considered an alternative to invasive methods [25].

TCD has the advantage of being noninvasive, easily handled, and working in real time. Monitoring of cerebral blood flow velocity (CBFV) with the TCD technique, however, has several limitations and possible sources of errors. Variability of TCD velocities depends strongly on the skill of the investigator and the angle of insonation [5], since it is sometimes difficult to determine the angle of the probe to the intracerebral vessel with a high degree of accuracy, absolute velocity measurements are difficult to compare.

Brain imaging can be assessed using a craniotomy or open fontanelle as an acoustic window in adult dogs [16] and neonates [17]. The B-mode ultrasonographic characteristics of both the normal and hydrocephalic canine brain have been described [16,33]. Although numerous cerebral vessels have been mapped and their TCD parameters characterized using TCD in human, few veterinary reports have evaluated

TCD of the canine brain, even in a limited population of patients. In transverse scan at the level of the interthalamic adhesion, pulsations seen on real-time images were remarkable in the sulci of the corpus callosum and around the third ventricle [16]. The RCA extends rostrocaudally along the dorsal surface of the corpus callosum. The CCA extends dorsomedially along the lateral surface of the brain stem and supplies the choroid plexus of the third ventricle. The RCA and the CCA are responsible for the pulsations. RI measurements can be obtained at the distal branch of these vessels. They may reflect the resistance of distal cerebral arteries. The normal canine cerebral vessels identified in this study are the RCA and CCA. The RCA is difficult to be identified using transtemporal window, but easy in transverse and sagittal scans of dogs with open fontanelle using transfontanelle window. But the CCA is easily identified in transverse scans using transtemporal window. This may be related to extension of the cerebral arteries. In addition, color Doppler imaging (CDI) may help identify these vessels. For these reasons, preferred cerebral artery is the RCA in transfontanelle window and the CCA in transtemporal window. There was no significant difference between RI measurements from transfontanelle window and transtemporal window [4]. Therefore, RI measurements using TCD can be obtained from any window and an ultrasonic window had to be located in each individual by searching preferred window to obtain the maximum amplitude of the Doppler signals. This is similar to the result of this study. In this study, the mean RI values of the RCA and CCA were 0.55 ± 0.05 and 0.55 ± 0.03. The mean RI values of dogs are similar to the mean RI values (0.5-0.6) of human [29]. In human, the mean RI value of the intracranial arteries in term infants during the first 24h of life was 0.75 ± 0.10 [28]. The data corresponded to the known downward trend of the RI during the first year of life [29]. After fontanelle closure, the mean RI was decreased to the range between 0.50 and 0.60. RI values were in the range of 0.8-0.75 for prematures, 0.7-0.65 for term babies, and gradually decreased during the first few months of life to reach adult values. In dogs, there is no study reported about normal RI values of intracranial arteries. In the present study, dogs below 3 months are excluded because they would be expected to have a higher RI. We thought that the mean RI values of this study were the RI values of intracranial arteries in normal adult dogs [11]. It was thought that RI values of normal dogs under 3 months are studied.

High reproducibility is critical for the TCD system, especially if this methodology is used to detect small difference in the blood velocity parameters that may occur in intracranial disease, and in the evaluation and comparisons of various medical and/or surgical treatment. In this study, high reproducibility was demonstrated in selected cerebral arteries in normal conscious dogs. Therefore, these measurements were highly reproducible, and might permit

valid comparisons to the blood flow parameters of certain intracranial diseases that possess vascular resistance changes.

This study was sought to demontrate the cerebral blood flow velocity correlates of a hemodynamic effect of mannitol and furosemide using TCD. Dosage and rate of mannitol and furosemide are based on the study reported by Roberts *et al* [26]. They found that the higher mannitol dose (1 g/kg), resulting in a greater blood-brain osmotic gradient, proved to be the most efficacious in ICP reduction and rapid administration (2 ml/kg/min) produced higher peak serum concentrations of mannitol and more profound lowering of ICP than the same dose delivered at slower rates.

We observed that RI of the RCA and the CCA increased 15 min after the administration of mannitol and returned to baseline values by 30 min. This data were similar to the result of study reported by Soriano *et al.* [32]. Mannitol has been shown to increase the cerebral blood flow due to a transient hypervolemia, decrease blood viscosity due to hemodilution, and alter red blood cell deformity [8,10,27]. The end result of these effects is a reflex vasoconstriction of the cerebral arterioles, which allows a decrease in cerebral blood volume, and therefore, a decrease in the ICP [21]. Therefore, changes of RI values after mannitol except initial effect would be related to change of cerebral blood flow and vasoconstriction, which is normal autoregulation of cerebral vessels.

The RI of the RCA and CCA after infusion of furosemide did not significantly change in this study. Most investigators have assumed that furosemide reduces ICP by decreasing brain sodium levels and water transport as well as lowering CSF volume by adversely affecting cation transport into the ventricular cavity. Many clinical and experimental studies appear to indicate that furosemide reduce ICP in the normal and edematous brain [7,20]. However, the result of the present study is not consistent with previous studies, but may be related to vasoconstriction without sharp change of ICP secondary to cerebral blood flow.

This study suggests that TCD may have several promising applications in veterinary neurology. Quantitative assessment of the RI of RCA and CCA prove to be useful and sufficiently reproducible, which this non-invasive and clinically easy-to-perform technique may give physiologic and pathophysiologic information in a number of cerebral diseases.

References

1. **Aaslid R, Markwaler TM, Nornes H.** Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 1982, **57**, 769-774.

2. **Aaslid R, Haber P, Nornes H.** Evaluation of cerebrovascular spasm with transcranial Doppler ultrasound. J Neurosurg 1984, **60**, 37-41.

3. **Albright AL, Latchaw RE, Robinson AG.** Intracranial and systemic effects of osmotic and oncotic therapy in experimental cerebral edema. J Neurosurg 1984, **60**, 481-489.

4. **Allison JW, Faddis LA, Kinder DL, Roberson RK, Glasier CM, Seibert JJ.** Intracranial resistive index(RI) values in normal term infants during the first day of life. Pediatr Radiol, 2000, **30**, 618-620.

5. **Arnolds BJ, Reutern GMV.** Transcranial Doppler sonography. Examination technique and normal reference values. Ultrasound Med Biol 1986, **12**, 115-123.

6. **Bishop CCR, Powell S, Rutt D, Browse NL.** Transcranial Doppler measurement of middle cerebral artery blood flow velocity: A validation study. Stroke 1986, **17**, 913-915.

7. **Buhrley LE, Reed DJ.** The effect of furosemide on sodium-22 uptake into cerebrospinal fluid and brain. Exp Brain Res 1972, **14**, 503-510.

8. **Burke AM, Quest DO, Chein S, Cerri C.** The effects of mannitol on blood viscosity. J Neurosurg 1981, **55**, 550-553.

9. **Czech T, Korn A, Reinprecht A.** Clinical evaluation of a new epidural pressure monitor. Acta Neurochir, 1993, **125**, 169-172.

10. **Donato T, Shapira Y, Artru A, Powers K.** Effect of mannitol on cerebrospinal fluid dynamics and brain tissue edema. Anesth Analg 1994, **78**, 58-66.

11. **Fontaine S, Lafortune M, Cattin F, Patriquin H.** The role of transcranial Doppler in diagnostic neuroimaging. J Radiol 1998, **79**, 213-225.

12. **Goh D, Minns RA, Hendry GMA, Thambyayah M, Steers AJW.** Cerebrovascular resistive index assessed by Duplex Doppler sonography and its relationship to intracranial pressure in infantile hydrocephalus. Pediatr Radiol 1992, **22**, 246-250.

13. **Hart R, Haluszkiewicz E.** Blood flow velocity using transcranial doppler velocimetry in the middle and anterior cerebral arteries: Correlation with sample volume depth. Ultrasound Med Biol 2000, **26**, 1267-1274.

14. **Hartwell RC, Sutton LN.** Mannitol, intracranial pressure, and vasogenic edema. Neurosurgery 1993, **32**, 444-450.

15. **Homburg AM, Jakobsen M, Enevoldsen E.** Transcranial Doppler recordings in raised intracranial pressure. Acta Neurol Scand 1993, **87**, 488-493.

16. **Hudson JA, Cartee RE, Simpson ST, Buxton DF.** Ultrasonographic anatomy of the canine brain. Radiology 1989, **30**, 13-21.

17. **Hudson JA, Simpson ST, Cox NR, Buxton DF.** Ultrasonographic examination of the normal canine neonatal brain. Vet Radiol 1991, **32**, 50-59.

18. **Lunt MJ, Jenkinson DF, Kerr D.** Transcranial Dopper blood velocity mesurement-The effect of changes in velocity profile. Ultrasound Med Biol 2000, **26**, 1145-1151.

19. **Meurs KM, Miller MW, Slater MR, Glaze K.** Arterial blood pressure measurement in a population of healthy geriatric dogs. J Am Anim Hosp Assoc 2000, **36**, 497-500.

20. **Millison C, James HE, Shapiro HM.** Intracranial hypertension and brain oedema in albino rabbits. Part 2: Effects of acute therapy with diuretics. Acta Neurochir 1981, **56**, 167-181.

21. **Muizerlaar JP, Lutz III HA, Becker DP.** Effect of mannitol on ICP and CBF and correlation with pressure auroregulation

in severely head-injured patients. J Neurosurg 1984, **61**, 700-706.

22. **Pollay M, Fullenwider C, Roberts A, Stevens A.** Effect of mannitol and furosemide on blood-brain osmotic gradient and intracranial pressure. J Neurosurg 1983, **59**, 945-950.

23. **Qureshi AI, Wilson DA, Traystman RJ.** Treatment of elevated intracranial pressure in experimental intracerebral hemorrhage: Comparision between mannitol and hypertonic saline. Neurosurgery 1999, **44**, 1055-1064.

24. **Rainov NG, Weise JB, Burkert W.** Transcranial Doppler sonography in adult hydrocephalic patients. Neurosurg Rev 2000, **23**, 34-38.

25. **Reid A, Marchbanks RJ, Bateman DE, Martin AM, Brightwell AP, Pickard JD.** Mean intracranial pressure monitoring by an audiological technique: a pilot study. J Neurol Neurosurg Psychiatry 1989, **52**, 610-612.

26. **Roberts PA, Pollay M, Engles C, Pendleton B, Reynolds E, Stevens FA.** Effect on intracranial pressure of furosemide combined with varying doses and administration rates of mannitol. J Neurosurg 1987, **66**, 440-446.

27. **Rudehill A, Lagerkranser M, Lindquist C, Gordon E.** Effects of mannitol on blood volume and central hemodynamics in patients undergoing cerebral aneurysm surgery. Anesth Analg 1983, **62**, 875-880.

28. **Seibert JJ, McCowan TC, Chadduck WM, Adametz JR, Glasier CM, Williamson SL, Taylor BJ, Leithiser RE, McConnell JR, Stansell CA, Rodgers AB, Corbitt SL.** Duplex pulsed Doppler US versus intracranial pressure in the neonate: clinical and experimental studies. Radiology 1989, **171**, 155-159.

29. **Seibert JJ, Glasier CM, Leithiser RE.** Transcranial Doppler using standard duplex equipment in children. Ultrasound 1990, **8**, 167-196.

30. **Seiler RW, Grolimund P, Aaslid R, Huber P, Nornes H.** Cerebral vasospasm evaluated by transcranial ultrasound correlated with clinical grade and CT-visualized subarachnoid hemorrhage. J Neurosurg 1986, **64**, 594-600.

31. **Silver P, Nimkoff L, Siddiqi Z, Estrada R, Sagy M.** The effect of mannitol on intracranial pressure in relation to serum osmolality in a cat model of cerebral edema. Intensive Care Med 1996, **22**, 434-438.

32. **Soriano SG, McManus ML, Sullivan LJ, Rockoff MA, Black PM, Burrows FA.** Cerebral blood flow velocity after mannitol infusion in children. Can J Anaesth 1996, **43**, 461-466.

33. **Spaulding KA, Sharp NJH.** Ultrasonographic imaging of the lateral cerebral ventricle in the dog. Vet Radiol 1990, **31**, 59-64.