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

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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
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 vascular 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 an 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 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:

$$RI = \frac{(PSV - EDV)}{PSV}$$

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 coefficient.

**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) 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 carried the common risks of surgical procedures, such as intracerebral bleeding or infection [9]. Therefore, some attempts have
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

![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.](image-url)
valid comparisons to the blood flow parameters of certain intracranial diseases that possess vascular resistance changes.

This study was sought to demonstrate 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.

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