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Transcranial Doppler Ultrasound Examination in Dogs with Suspected Intracranial Hypertension Caused by Neurologic Diseases

K. Sasaoka, K. Nakamura, T. Osuga, T. Morita, N. Yokoyama, K. Morishita, N. Sasaki, H. Ohta, and M. Takiguchi

Background: Transcranial Doppler ultrasound examination (TCD) is a rapid, noninvasive technique used to evaluate cerebral blood flow and is useful for the detection of intracranial hypertension in humans. However, the clinical usefulness of TCD in diagnosing intracranial hypertension has not been demonstrated for intracranial diseases in dogs.

Objectives: To determine the association between the TCD variables and intracranial hypertension in dogs with intracranial diseases.

Animals: Fifty client-owned dogs with neurologic signs.

Methods: Cross-sectional study. All dogs underwent TCD of the basilar artery under isoflurane anesthesia after magnetic resonance imaging (MRI). Dogs were classified into 3 groups based on MRI findings: no structural diseases (group I), structural disease without MRI evidence of intracranial hypertension (group II), and structural disease with MRI evidence of intracranial hypertension (group III). The TCD vascular resistance variables (resistive index [RI], pulsatility index [PI], and the ratio of systolic to diastolic mean velocity [Sm/Dm]) were measured.

Results: Fifteen, 22, and 13 dogs were classified into groups I, II, and III, respectively. Dogs in group III had significantly higher Sm/Dm (median, 1.78; range, 1.44–2.58) than those in group I (median, 1.63; range, 1.43–1.75) and group II (median, 1.62; range, 1.27–2.10). No significant differences in RI and PI were identified among groups.

Conclusions and Clinical Importance: Our findings suggest that increased Sm/Dm is associated with MRI findings of suspected intracranial hypertension in dogs with intracranial diseases and that TCD could be a useful tool to help to diagnose intracranial hypertension.

Key words: CNS disorders; Intracranial pressure; Repeatability; Ultrasonography.

Intracranial hypertension is defined as a continuous increase in intracranial pressure above the reference range.[1] It can be caused by various intracranial diseases (eg, trauma, hemorrhage, infarction, ischemia, edema, masses, encephalopathy, status epilepticus). Intracranial hypertension can cause lethal damage to the brain as a result of decreased cerebral blood flow and mechanical compression of brain structures.[2,3] Therefore, rapid diagnosis and appropriate treatment of intracranial hypertension are important.[4,5]

The diagnosis of intracranial hypertension has been confirmed by direct intracranial pressure measurement in the neurointensive care of humans, but this method is invasive and can cause complications.[4] Direct intracranial pressure management rarely has been used to diagnose increased intracranial pressure in veterinary medicine because it is often considered too invasive.[6] Although several clinical signs (eg, low level of consciousness, absence of brainstem reflexes, abnormal motor activity and posture, Cushing response) alert veterinarians to the possibility of intracranial hypertension, these signs are nonspecific and can be absent.[7,8] Magnetic resonance imaging (MRI) findings are good indicators of intracranial hypertension, but these findings are also nonspecific.[7,9] Previously reported MRI findings indicative of intracranial hypertension include effacement of cerebral sulci,[10] brain herniation,[11,12] compression of the cerebrospinal fluid (CSF) space,[12] and brain shifting.[9]

Abbreviations:

AUC	area under the receiver operating characteristic curve
CI	confidence interval
CSF	cerebrospinal fluid
CV	coefficient of variation
Dm	diastolic mean velocity
EDV	end diastolic velocity
ICC	intraclass correlation coefficient
MRI	magnetic resonance imaging
PI	pulsatility index
PSV	peak systolic velocity
RI	resistive index
ROC	receiver operating characteristic
Sm/Dm	ratio of systolic to diastolic mean velocity
Sm	systolic mean velocity
TCD	transcranial Doppler ultrasound examination
Vm	mean velocity

From the Laboratory of Veterinary Internal Medicine, Department of Veterinary Clinical Sciences, (Sasaoka, Osuga, Morita, Yokoyama, Sasaki, Ohta, Takiguchi); Veterinary Teaching Hospital, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, Hokkaido, Japan (Nakamura, Morishita).

This study was performed at the Veterinary Teaching Hospital, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, Japan.

Corresponding author: M. Takiguchi, Laboratory of Veterinary Internal Medicine, Department of Veterinary Clinical Sciences, Graduate School of Veterinary Medicine, Hokkaido University, N18 W9 Sapporo, Hokkaido 060-0818, Japan; e-mail: mtaki@vetmed.hokudai.ac.jp

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Transcranial Doppler ultrasound examination (TCD) is a rapid, noninvasive modality used to evaluate cerebral arterial blood flow, and has been used mainly in the field of neurointensive care in humans.[13,14] Increased intracranial pressure causes decreased cerebral perfusion pressure, which alters cerebral arterial flow waveforms.[15,16] Two TCD vascular resistance variables commonly used to evaluate altered cerebral waveforms are the resistive index (RI) and the pulsatility index (PI).[17,18] Additionally, the ratio of systolic to diastolic mean velocity (Sm/Dm) is another vascular resistance variables that is reported to be a sensitive index for detection of changes in arterial compliance and resistance of the ophthalmic artery.[19]

In veterinary medicine, the RI was reported to be correlated with intracranial pressure measured directly in experimental intracranial hypertension.[16,20] However, there have been no reports of the clinical usefulness of TCD in the diagnosis of intracranial hypertension in dogs. Previous studies demonstrated alterations of Doppler waveforms of cerebral arteries in dogs with hydrocephalus, hepatic encephalopathy, and granulomatous meningoencephalitis, but the relationship between the Doppler waveform and intracranial hypertension was not determined in these studies.[21–23] Thus, a clinical study evaluating the ability of TCD to detect suspected intracranial hypertension is needed. In addition, it needs to be clarified whether intracranial structural diseases without intracranial hypertension affect TCD variables in dogs.

Therefore, the overall aim of our study was to evaluate the usefulness of TCD in the diagnosis of intracranial hypertension in dogs with intracranial diseases. Specific aims were to: (1) determine the association between TCD variables and MRI findings of dogs with suspected intracranial hypertension, and (2) determine the association between TCD variables and the presence of intracranial structural diseases.

Materials and Methods

Study Population

Client-owned dogs were prospectively and consecutively recruited between October 2011 and October 2012 at the Hokkaido University Veterinary Teaching Hospital. Dogs were included in this study: (1) if they were suspected to have intracranial disease and (2) if they underwent MRI under isoflurane general anesthesia. All dogs underwent TCD under isoflurane anesthesia after brain MRI. Dogs were excluded if Doppler waveforms could not be obtained from the basilar artery or if their clinical condition was poor and sedation or anesthesia for MRI was considered to be contraindicated.

Owner interviews and physical examinations were performed to obtain the following data: sex, age, body weight, and clinical history. After blood and neurologic examinations, dogs underwent MRI under isoflurane general anesthesia. All physical and neurologic examinations were performed by an experienced neurologist at Hokkaido University Veterinary Teaching Hospital (HO), with emphasis on signs suggestive of intracranial hypertension, such as alteration in the level of consciousness, gait abnormalities, postural reaction deficits, pupil size abnormalities, absence of pupillary light reflexes, deficits in the menace response, and Cushing response.[1,7] After brain MRI, CSF was collected by cisternal puncture if dogs were not suspected to have intracranial hypertension based on the absence of MRI findings indicative of intracranial hypertension (see below). For each dog, clinical diagnosis was determined on the basis of clinical data including MRI findings.

Magnetic Resonance Imaging

Magnetic resonance imaging was performed using a single 0.4 Tesla unit.[a] Before MRI examination, all included dogs were sedated with midazolam (0.1 mg/kg IV) and butorphanol tartrate (0.2 mg/kg IV). General anesthesia was induced with propofol (7 mg/kg IV) and maintained after intratracheal intubation with isoflurane (end-tidal concentration, approximately 1.5%) in 100% oxygen. Each dog received lactated Ringer's solution IV (10 mL/kg/h). End-tidal CO_2 was maintained between approximately 25 and 35 mmHg using mechanical ventilation. Mean arterial blood pressure was maintained ≥60 mmHg. These physiologic variables were monitored using a Vitals monitor.[b] If dogs were suspected to have intracranial hypertension on the basis of MRI findings, they were given 1 g/kg mannitol IV over 30 min during MRI. Transverse T1W pre- and postcontrast, T2W, and FLAIR sequences and sagittal T2W sequences were routinely obtained. The MRI findings were reviewed by an experienced veterinarian (HO) who was unaware of the TCD variables. The MRI findings indicative of intracranial hypertension were recorded according to the following criteria: (1) effacement of the cerebral sulci,[10] (2) brain herniation (foramen magnum, transtentorial, subfalcine),[11,12] (3) compression of CSF space (third ventricle, fourth ventricle),[12] and (4) displacement of the lamina quadrigemina.[9] Dogs were suspected of having intracranial hypertension if any ≥2 of the above-mentioned MRI findings were identified.[9,24]

On the basis of the MRI findings, dogs were classified into 3 groups to elucidate the relationships among intracranial structural diseases, suspected intracranial hypertension, and TCD variables. Dogs in group I had no structural disease of the brain. Dogs in group II had intracranial structural diseases (eg, neoplasia, encephalitis, cerebrovascular brain disease, hydrocephalus) without suspected intracranial hypertension. Dogs in group III had intracranial structural diseases with suspected intracranial hypertension. Group I dogs were considered controls for groups II and III because group I dogs had no abnormal findings on MRI.

Transcranial Doppler Ultrasound Examination

After MRI, TCD was performed with an ultrasound machine[c] using a 4–11-MHz convex probe[d] under the same anesthetic conditions as used for MRI. Administration of mannitol was started soon after detection of MRI findings indicative of intracranial hypertension, and TCD was performed 0 to 30 minutes after administration of mannitol. Dogs were positioned in left lateral recumbency with their heads flexed at a 90° angle to visualize the basilar arteries through the transforaminal window. After B-mode examination with a sagittal view, color flow Doppler was performed to identify the basilar artery (Fig 1A). The basilar arterial Doppler waveforms were obtained using 6.0-kHz pulse repetition frequencies, a 94-Hz wall filter, 2.5-mm sample width, and angular correction at <40 degrees.[20,25] The obtained Doppler waveforms were recorded with simultaneous electrocardiograms, and then manually traced to determine the TCD variables, including peak systolic velocity (PSV), end diastolic velocity (EDV), mean velocity (Vm), systolic mean velocity (Sm), and diastolic mean velocity (Dm). In addition, TCD vascular resistance variables, including resistive index (RI) and pulsatility index (PI), were calculated as

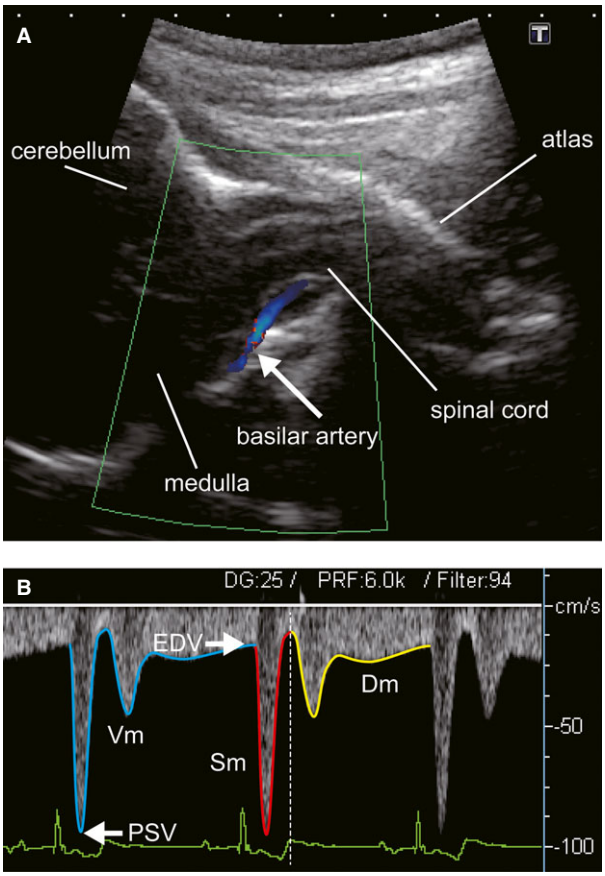

Fig 1. Transcranial Doppler ultrasound examination (TCD) images. Basilar artery flow is identified below medulla on a sagittal view of color flow Doppler **(A)**. Measurement of basilar arterial flow by pulsed Doppler **(B)**. Systolic mean velocity (Sm) and diastolic mean velocity (Dm) are discriminated by an end-T wave of ECG.

follows: RI = (PSV – EDV)/PSV, and PI = (PSV – EDV)/Vm.[20] The ratio of systolic to diastolic mean velocity (Sm/Dm) also was calculated as a vascular resistance variable (Fig 1B).[19] Heart rate was calculated using the R-R intervals on simultaneous electrocardiograms. The means of 5 consecutive cardiac cycles were calculated for all TCD variables. During TCD, physiologic variables including mean arterial pressure and end-tidal CO_2 also were recorded.

Assessment of Repeatability

Six laboratory dogs (2 males and 4 females; ages, 2–12 years; body weight, 10.3–12.4 kg) were used. All dogs were confirmed as healthy on the basis of physical, neurologic, and blood examinations. Each dog was anesthetized with isoflurane as described above. After a stabilization period, each dog underwent TCD performed by 1 observer (KS) 3 times at 15-minute intervals. Each time, the TCD variables were determined as described above.

Statistical Analysis

Statistical analysis was performed using commercially available software.[e,f] All continuous variables were expressed as median (range). Determination of the normal distribution of data was evaluated by means of a Shapiro–Wilk test, and assumption of the homogeneity of variances was determined by Bartlett's test. If the data distribution was determined to be normal and the variance homogeneous, the overall difference among groups was determined by 1-way analysis of variance (ANOVA), and post hoc multiple comparisons were made by the Tukey–Kramer HSD test. When the distribution was determined not to be normal or variance not homogeneous, the overall difference among groups was determined by the Kruskal–Wallis test (nonparametric 1-way ANOVA), and post hoc multiple comparisons were made by the Steel-Dwass test. Categorical variables were compared by Fisher's exact test. Spearman's rank correlation test was used to investigate correlations between variables. Receiver operating characteristic (ROC) analysis with the Mann–Whitney *U*-test and Bonferroni correction for multiple testing was used to assess the ability to use TCD variables to detect dogs with suspected intracranial hypertension among those with neurologic signs. The area under the ROC curve (AUC) and 95% confidence interval (CI) were calculated for each variable. Optimal cutoff values were chosen for each TCD variable based on the highest Youden index. For the optimal cutoff value of each variable, sensitivity and specificity were calculated. For all tests, significance was set at $P < 0.05$.

Intraobserver repeatability was assessed by the coefficient of variation (CV) and intraclass correlation coefficient (ICC). Repeatability was considered to be acceptable when the CV was <15%[26] and the ICC was >0.70.[27]

Results

Study Population

Fifty-nine client-owned dogs with neurologic signs were recruited. Six dogs were excluded because sedation or anesthesia for MRI was considered to be contraindicated. Of the remaining 53 dogs, 3 dogs (Golden Retriever, 28.7 kg; French Bulldog, 12.4 kg; and American Cocker Spaniel, 9.7 kg) were excluded because Doppler waveforms could not be obtained from the basilar artery. Consequently, Doppler waveforms could be obtained from 50 dogs (50/53, 94%). Of the 50 finally enrolled dogs, there were 14 intact males, 16 castrated males, 8 intact females, and 12 spayed females. The median age was 7 years (range, 2–13 years), and median body weight was 5.8 kg (range, 1.3–33.3 kg). The most commonly represented breed was Miniature Dachshund (n = 8), followed by Chihuahua (6), mixed breed (5), Toy Poodle (4), Maltese (4), Shetland Sheepdog (3), Miniature Schnauzer (3), Golden Retriever (2), French Bulldog (2), Yorkshire Terrier (2), and 1 each of Australian Shepherd, Bearded Collie, Cavalier King Charles Spaniel, English Cocker Spaniel, Japanese Spitz, Labrador Retriever, Norfolk Terrier, Papillon, Shiba, Shih Tzu, and Welsh Corgi. Clinical diagnoses included idiopathic epilepsy (n = 17), intracranial neoplasia (14), encephalitis (9), cerebrovascular disease (6), and hydrocephalus (4).

On the basis of the MRI findings, 15, 22, and 13 dogs were classified into groups I, II, and III, respectively. As for MRI findings indicative of intracranial hypertension, effacement of the cerebral sulci was identified in 7 dogs; brain herniation in 13 dogs (foramen magnum in 10 dogs; transtentorial in 5 dogs; subfalcine in 4 dogs);

compression of the CSF space in 16 dogs (third ventricle in 13 dogs; fourth ventricle in 9 dogs); and displacement of the lamina quadrigemina in 10 dogs (Table 1). Any 1 of the MRI findings was recorded in 9 dogs: These dogs were categorized into group II. Meanwhile, among dogs in group III, 6 had any 2 of the MRI findings; 3 had any 3 of the MRI findings; and 4 had all of the 4 findings.

The proportion of the dogs that had abnormalities on neurologic examination in each group was dependent on the distribution of clinical diagnosis in the group. Five dogs (5/22, 23%) in group II and 4 dogs (4/13, 31%) in group III exhibited neurologic abnormalities suggestive of intracranial hypertension, such as low level of consciousness, pupil size abnormalities, absence of pupillary light reflexes, and deficits in the menace response. No dogs showed the Cushing response. None of the data on the study population except for clinical diagnosis was different among groups (Table 1). All dogs diagnosed with idiopathic epilepsy were classified into group I (control group).

Comparison of the TCD Variables

Of the TCD vascular resistance variables, only Sm/Dm was significantly different among the groups (Table 2, Fig 2, $P = 0.01$). The Sm/Dm was significantly higher in group III (median, 1.78; range, 1.44–2.58) than in group I (control group: median, 1.63; range, 1.43–1.75; $P = 0.02$) and group II (median, 1.62; range, 1.27–2.10; $P = 0.02$). On the other hand, no significant difference was found between groups I and II ($P = 0.96$). Regarding the other variables, including RI and PI, no significant differences were observed among groups.

No differences in TCD variables were identified between dogs with neurologic abnormalities suggestive of intracranial hypertension (n = 10) and without such neurologic abnormalities (n = 40). The medians (ranges) of RI were 0.73 (0.59–0.81) and 0.72 (0.57–0.89) in dogs with and without the neurologic abnormalities, respectively. The medians (ranges) of PI were 1.60 (1.02–2.74) and 1.55 (1.03–4.41) in dogs with and without neurologic abnormalities, respectively. The medians (ranges)

Table 1. Demographic data, physiologic variables, neurologic examination findings, clinical diagnoses, and MRI findings of 50 dogs that underwent transcranial Doppler ultrasound examination.

Variable	Group I (Control Group) (n = 15)	Group II (n = 22)	Group III (n = 13)	Overall *P*-value
Age (years)	7 (2–13)	6 (3–13)	8 (2–13)	0.88
Body weight (kg)	5.9 (2.4–24.1)	5.5 (1.7–33.3)	5.2 (1.3–20.6)	0.50
Sex				0.43
Male (No. intact)	9 (4)	15 (9)	6 (1)	
Female (No. intact)	6 (2)	7 (2)	7 (3)	
Physiologic variables during TCD				
Mean arterial pressure (mmHg)	65 (58–80)	75 (55–98)	70 (56–94)	0.43
End-tidal CO_2 (mmHg)	36.0 (32.0–38.0)	34.5 (23.0–43.0)	33.0 (26.0–38.0)	0.09
Heart rate (rpm)	76.3 (58.3–147.4)	75.6 (48.5–125.0)	82.1 (40.7–158.7)	0.89
Neurologic examination				
Low level of consciousness	0	1	2	
Gait abnormalities	0	6	3	
Postural reaction deficits	0	9	4	
Pupil size abnormalities	0	1	1	
Absence of pupillary light reflexes	1	1	1	
Deficits in the menace response	1	4	3	
Clinical diagnosis				<0.001
Idiopathic epilepsy	15	2	0	
Intracranial neoplasia	0	7	7	
Encephalitis	0	6	3	
Cerebrovascular disease	0	6	0	
Hydrocephalus	0	1	3	
MRI findings				
Effacement of the cerebral sulci	0	0	7	
Brain herniation	0	3	10	
Foramen magnum	0	2	8	
Transtentorial	0	0	5	
Subfalcine	0	1	3	
Compression of CSF space	0	4	12	
Third ventricle	0	4	9	
Fourth ventricle	0	0	9	
Displacement of the lamina quadrigemina	0	2	8	

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

Continuous data are expressed as the median (range). All overall *P*-values were determined by the Kruskal–Wallis test (continuous variables) or Fisher's exact test (categorical variables).

Table 2. Transcranial Doppler ultrasound examination variables for 3 groups.

Variable	Group I (Control Group) (n = 15)	Group II (n = 22)	Group III (n = 13)	ANOVA or Kruskal–Wallis	Overall *P*-value
PSV (cm/s)	76.4 (41.5–97.9)[a]	64.2 (34.3–99.3)[a]	81.7 (46.9–111.3)[a]	A	0.24
EDV (cm/s)	20.1 (13.4–33.1)[a]	19.9 (8.6–39.4)[a]	17.3 (8.9–39.0)[a]	A	0.84
Vm (cm/s)	34.2 (19.1–49.9)[a]	33.5 (13.7–56.8)[a]	27.7 (13.9–68.4)[a]	K	0.68
Sm (cm/s)	47.6 (24.9–64.7)[a]	44.9 (18.4–78.2)[a]	41.5 (22.0–95.8)[a]	A	0.60
Dm (cm/s)	30.0 (17.5–44.6)[a]	28.0 (11.4–48.2)[a]	23.6 (11.8–50.9)[a]	A	0.79
RI	0.72 (0.62–0.78)[a]	0.71 (0.57–0.80)[a]	0.75 (0.59–0.89)[a]	A	0.16
PI	1.57 (1.09–2.12)[a]	1.47 (1.03–2.41)[a]	1.84 (1.02–4.41)[a]	K	0.47
Sm/Dm	1.63 (1.43–1.75)[a]	1.62 (1.27–2.10)[a]	1.78 (1.44–2.58)[b]	K	0.01

A, ANOVA; Dm, diastolic mean velocity; EDV, end diastolic velocity; K, Kruskal–Wallis test; PI, pulsatility index; PSV, peak systolic velocity; RI, resistive index; Sm, systolic mean velocity; Sm/Dm, ratio of systolic to diastolic mean velocity; Vm, mean velocity.

Continuous data are expressed as the median (range). Values with different superscript letters indicate significant differences among groups.

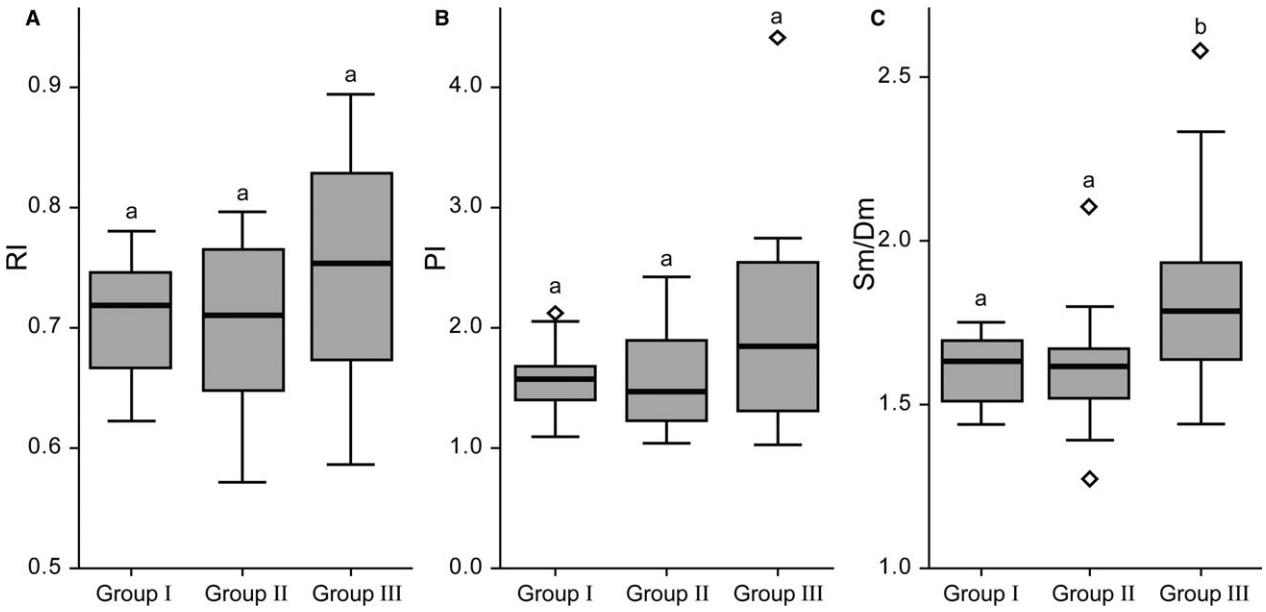

Fig 2. Box and whisker plot of transcranial Doppler ultrasound examination (TCD) variables in 3 groups: **(A)** resistive index (RI); **(B)** pulsatility index (PI); **(C)** ratio of systolic to diastolic mean velocity (Sm/Dm). The box represents the interquartile range (IQR) from the 25th to 75th percentile. The upper and lower whiskers represent the highest datum still within 1.5 IQR of the upper quartile and the lowest datum still within 1.5 IQR of the lower quartile, respectively. The individual dots beyond the whiskers represent outliers. Medians with different letters indicate significant differences among groups.

for Sm/Dm were 1.64 (1.42–2.10) and 1.63 (1.27–2.58) in the dogs with and without neurologic abnormalities, respectively.

Correlation Between Number of Identified MRI Findings Indicative of Intracranial Hypertension and TCD Variables

We considered that a large number of MRI findings indicative of intracranial hypertension identified in enrolled dogs indicated more severe intracranial hypertension. A significant positive correlation was found between the number of identified MRI findings indicative of intracranial hypertension and Sm/Dm (Spearman's $\rho = 0.38$, $P = 0.007$). No significant correlations were observed between the number of identified MRI findings and other TCD variables. However, values of RI and PI increased as the number of identified MRI findings increased (Fig 3).

ROC Analysis

The ROC analysis was performed to evaluate the ability to use the TCD vascular resistance variables to detect dogs with suspected intracranial hypertension (group III) among dogs with neurologic diseases (groups I, II, and III). The ROC analysis indicated that only Sm/Dm could be used to detect dogs in group III among all enrolled dogs (Bonferroni-corrected $P < 0.05$). The AUC was 0.66 (95% CI, 0.47–0.85) for

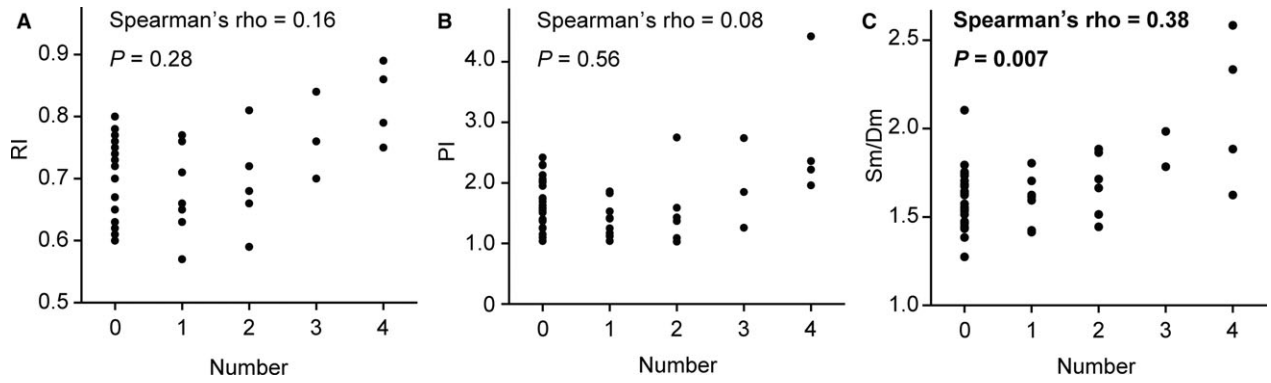

Fig 3. Correlations between the TCD variables ((**A**) RI, (**B**) PI, and (**C**) Sm/Dm) and number of identified MRI findings indicative of intracranial hypertension (horizontal axis). The MRI findings indicative of intracranial hypertension were effacement of the cerebral sulci, brain herniation, compression of CSF space, and displacement of the lamina quadrigemina. Spearman's rho and *P*-value are included for each plot.

RI, 0.61 (95% CI, 0.40–0.82) for PI, and 0.79 (95% CI, 0.63–0.95) for Sm/Dm (Table 3, Fig 4).

Assessment of Repeatability

The TCD could be performed in all laboratory dogs under general anesthesia. All CV values were <10%, whereas all ICC values were >0.70 (Table 4).

Discussion

Our results suggest that TCD vascular resistance variables can be used to detect dogs with intracranial hypertension. Although no significant differences in TCD vascular resistance variables were detected between dogs without intracranial structural diseases (group I) and those with intracranial structural diseases without suspected intracranial hypertension (group II), we found that Sm/Dm was significantly higher in dogs with suspected intracranial hypertension (group III).

In our study, RI, PI, and Sm/Dm increased as the number of identified MRI findings indicative of intracranial hypertension increased. However, RI and PI did not significantly differ between dogs with and without suspected intracranial hypertension. Previous experimental studies in dogs have shown that increased intracranial pressures measured directly are associated with an increase in RI obtained by TCD.[20] In humans, a correlation between directly measured intracranial pressures and PI has been shown in neurointensive care studies involving patients with intracranial hypertension after traumatic brain injury.[17,28] The discordance between our results and these findings may have been caused by a difference in the study population: Dogs with severe clinical status precluding general anesthesia were excluded from the study.

Our findings indicate that intracranial hypertension may be diagnosed on the basis of increased Sm/Dm. The Sm/Dm in the ophthalmic artery has been reported as an indicator of systemic atherosclerosis in humans.[19] In atherosclerosis in humans, high values of Sm/Dm reflect a decrease in diastolic flow because of decreased arterial compliance with preserved systolic velocity.[19,29] Our study is the first to report the use of Sm/Dm as a variable of TCD in dogs. We hypothesized that Sm/Dm also would reflect the alterations in cerebral blood flow observed in intracranial hypertension: As intracranial pressure increases, the resultant decrease in cerebral blood flow alters the Doppler waveforms of the cerebral artery so that the diastolic velocity is decreased with the systolic velocity being preserved.[15,16] Considering that no significant differences in Dm were observed among the groups, the relative changes in diastolic velocity might occur in individual Doppler waveforms, and Sm/Dm was reflected as a ratio of these relative changes.

Our findings indicate that Sm/Dm may be a more sensitive variable to detect intracranial hypertension compared with RI and PI. A previous study evaluating Doppler waveforms of the ophthalmic artery showed that Sm/Dm can be more sensitive for the detection of

Table 3. Area under the receiver operating characteristic curve (AUC) and optimal diagnostic cutoffs to detect dogs with suspected intracranial hypertension among dogs with neurologic diseases.

Variable	AUC	95% CI	Sensitivity	Specificity	Cutoff	*P*-value
RI	0.66	0.47–0.85	0.38	0.95	0.79	0.09
PI	0.61	0.40–0.82	0.38	0.92	2.21	0.23
Sm/Dm	0.79	0.63–0.95	0.62	0.92	1.78	0.002

AUC, area under the receiver operating characteristic curve; CI, confidence interval; PI, pulsatility index; RI, resistive index; Sm/Dm, ratio of systolic to diastolic mean velocity.

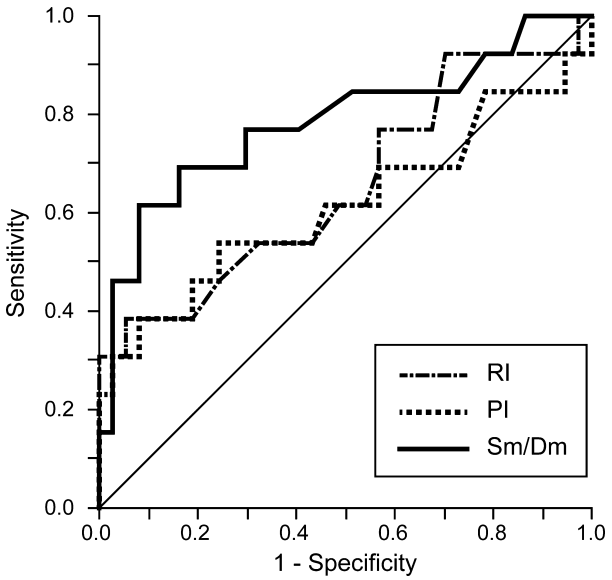

Fig 4. Receiver operating characteristic (ROC) curves of RI, PI, and Sm/Dm for the detection of dogs with suspected intracranial hypertension among 50 dogs with neurologic diseases.

Table 4. Repeatability of transcranial Doppler ultrasound examination variables in healthy laboratory dogs.

Variable	Mean (range)	Intraobserver SD	CV (%)	ICC
Heart rate (rpm)	78.9 (69.8–95.1)	2.4	3.0	0.92
PSV (cm/s)	79.0 (65.2–113.6)	7.1	9.0	0.74
EDV (cm/s)	22.5 (14.8–32.8)	1.4	6.4	0.95
Vm (cm/s)	33.9 (25.1–46.5)	2.5	7.3	0.86
Sm (cm/s)	44.2 (32.9–60.7)	3.9	8.9	0.79
Dm (cm/s)	29.0 (21.4–40.3)	2.1	7.2	0.90
RI	0.72 (0.64–0.81)	0.02	2.2	0.90
PI	1.70 (1.29–2.35)	0.10	5.8	0.88
Sm/Dm	1.54 (1.40–1.69)	0.05	3.2	0.82

CV, coefficient of variation; Dm, diastolic mean velocity; EDV, end diastolic velocity; ICC, intraclass correlation coefficient; PI, pulsatility index; PSV, peak systolic velocity; RI, resistive index; SD, standard deviation; Sm, systolic mean velocity; Sm/Dm, ratio of systolic to diastolic mean velocity; Vm, mean velocity.

glaucoma in human patients than RI.[30] The higher sensitivity of Sm/Dm in our study might have been because of the difference in calculation methods of each TCD vascular resistance variable. All of these indices are calculated using systolic and diastolic components of arterial waveforms. However, RI and PI are calculated by the use of instantaneous velocities (ie, PSV and EDV), whereas Sm/Dm is determined on the basis of mean velocities. Given that the initial alterations of cerebral blood flow in intracranial hypertension are mainly associated with decreases in diastolic flow,[15,16] the changes in diastolic mean velocities of cerebral arterial waveforms could have been more prominent than the changes in diastolic instantaneous velocities in dogs with suspected intracranial hypertension in our study.

Interestingly, no significant differences in TCD variables were observed between dogs in groups I (no structural diseases) and II (intracranial structural diseases without intracranial hypertension). According to the volume-pressure curve, intracranial pressure remains relatively stable against the increase in the intracranial volume when the intracranial volume is mildly increased from the normal volume (ie, the brain has an autoregulatory compensation mechanism). Consequently, the cerebral perfusion pressure initially is maintained despite the mild increase in the intracranial volume.[3] In human patients with hydrocephalus, mildly to moderately increased intracranial pressure (ie, 20 mmHg) did not cause significant changes in cerebral perfusion and PI.[31] Considering this compensatory mechanism, the lack of significant differences in the TCD variables between groups I and II might have been because the intracranial structural diseases in group II only caused mild or no increase in the intracranial pressure. Therefore, the possibility that a mild increase in the intracranial pressure cannot be detected by the TCD vascular resistance variables should be considered.

The combination of MRI findings including effacement of cerebral sulci, brain herniation, compression of CSF space, and brain shifting is useful and reliable for the diagnosis of intracranial hypertension in dogs and therefore was used as a diagnostic criterion for intracranial hypertension in our study.[9,24] However, each MRI finding indicative of intracranial hypertension is nonspecific. To determine the relationship between TCD vascular resistance variables and each MRI finding, multiple linear regression analysis was performed. This statistical analysis showed that only effacement of the cerebral sulci was a predictor of high TCD vascular resistance (data not shown). In our study, TCD vascular resistance variables may be changed more by the influence of the forebrain swelling than local structural influence.

In our study, despite the association between MRI findings indicative of intracranial hypertension and TCD variables, no differences in TCD variables were found between dogs with and without neurologic abnormalities suggestive of intracranial hypertension. Neurologic examination findings can be clues to the diagnosis of intracranial structural diseases and intracranial hypertension in dogs. However, importantly, intracranial structural diseases and intracranial hypertension can cause no abnormalities in the neurologic examination when they are relatively mild or when the brain's compensatory mechanism is preserved. Neurologic examination was normal in 23.5–27.3% dogs with intracranial structural diseases.[32] Additionally, a previous study showed that 13% of dogs with transtentorial herniation and foramen magnum herniation on MRI had normal mentation status.[7] In our study, 9 dogs (9/13, 69%) in group III had normal findings on neurologic examination. This higher proportion of the dogs exhibiting normal findings on neurologic examination in group III than that in the previous study[7] could have been because dogs with obvious neurologic abnormalities suggestive of severe intracranial hypertension[8] were excluded in our study. Considering the association

between TCD variables and MRI findings in our study, it is possible that TCD can be a more sensitive and easier-to-use tool for detecting intracranial hypertension than neurologic examination.

Mannitol administration used in some dogs could have affected the TCD variables in our study. Because of ethical concerns, we performed TCD only after treatment with mannitol. In our hospital, we routinely start administration of mannitol soon after detection of MRI findings indicative of intracranial hypertension. Previous studies in human patients with intracranial hypertension have shown that PI was decreased by 20% after mannitol administration by the increase in diastolic flow velocity associated with the decrease in intracranial pressure.[33,34] Therefore, in our study, it is possible that the worsening of the TCD vascular resistance variables associated with intracranial hypertension could have been blunted by mannitol administration.

In addition to TCD, various noninvasive methods for assessment of intracranial pressure have been applied to dogs.[7,9,24,35,36] The combination of MRI findings is useful and reliable for the diagnosis of intracranial hypertension in dogs.[9,24] In a recent study, the combination of these MRI findings yielded a sensitivity of 72% and a specificity of 96% for the diagnosis of intracranial hypertension in dogs.[9] However, MRI is unsuitable for repetitive, bedside, and quantitative evaluation of intracranial pressure. Considering its higher availability than that of MRI, TCD should be promising for noninvasive monitoring of intracranial pressure. Finite element analysis and simulated biomechanical response behavior of brain tissue is another promising method of noninvasively assessing intracranial pressure. This method simulates deformation and biomechanical response behavior of brains at various levels of decreasing cerebral perfusion pressure and increasing intracranial pressure after the construction of patient-specific 3-dimensional models of brains from MRI data.[35] Although it can be a good tool to estimate intracranial pressure, this method is complicated and cumbersome to use in clinical settings.

Meanwhile, optic nerve sheath diameter assessment using ultrasound examination seems promising considering the relationship between optic nerve sheath diameter and intracranial pressure in dogs with experimental intracranial hypertension.[36] Based on a study that showed a moderately positive correlation between optic nerve sheath diameter measured using T2-weighted MRI and body weight ($r = 0.71–0.76$),[24] clinical studies enrolling dogs of various breeds with a wide range of body weights might be necessary for clinical application. Interestingly, the relationships between intracranial pressure and both optic nerve sheath diameter and TCD vascular resistance variable seem different in experimental studies. One study showed that the relationship of intracranial pressure to optic nerve sheath diameter was slightly nonlinear with optic nerve sheath diameter increased more in the early stages of intracranial hypertension.[36] On the other hand, another study demonstrated that the relationship between TCD vascular resistance variables and intracranial pressure was linear in dogs.[20] This discrepancy might be due to different effects of intracranial pressure on cerebral blood flow and optic nerve sheath size. Therefore, the combination of TCD and optic nerve sheath diameter may be a more reliable tool to noninvasively detect intracranial hypertension.

Our study had several limitations. First, intracranial pressure was not directly measured in our study. Ideally, diagnosis of intracranial hypertension would be made by direct intracranial pressure measurements, but doing so was not acceptable in our study because it requires invasive techniques. Increased intracranial pressure causes a shift of intracranial structures such as brain herniation and compression of the CSF space, which are observed on MRI.[12] Therefore, we classified the dogs by the MRI findings of suspected intracranial hypertension.[9,24] Secondly, the study population was restricted to dogs with clinical conditions for which general anesthesia was acceptable, and dogs with severe intracranial hypertension that precluded isoflurane general anesthesia were excluded from the study. We exclusively enrolled dogs that underwent MRI under isoflurane general anesthesia to: (1) obtain MRI findings of suspected intracranial hypertension and (2) abolish the effect on TCD variables of differences among protocols that used anesthesia, sedation, or no sedation. However, it is clinically relevant that our study demonstrated that in dogs, TCD variables can be altered even in relatively mild intracranial hypertension where the brain's compensatory mechanisms are preserved. Thirdly, ours was a cross-sectional study, and thus, it cannot show a causal relationship between changes in TCD variables and intracranial hypertension. Because TCD can be performed noninvasively and repeatedly, it may be possible to confirm causality by serially monitoring dogs with intracranial hypertension using TCD. Fourthly, the repeatability of TCD was only shown in normal laboratory dogs. Although it takes a relatively short amount of time (about 2–3 minutes) to perform TCD in dogs, prolongation of anesthesia time by approximately 30 minutes for a repeatability study was deemed unethical in patients with intracranial diseases. Repeatability of TCD might be different between dogs with clinical disease and normal laboratory dogs. Lastly, sample sizes were small, and Doppler waveforms of the basilar artery could not be obtained in 3 dogs. This problem also can occur in humans, especially in older women because of hyperostosis of the skull.[14] To improve the ability of detecting Doppler signals, the use of ultrasound contrast agents may be useful.[37] However, it will be necessary to study the influence of the use of contrast agents on TCD variables.

In conclusion, our findings indicate that TCD can be clinically useful for the diagnosis of suspected intracranial hypertension. Additional studies involving dogs with a more severe clinical disease and studies in conscious dogs are needed to establish the usefulness of TCD as a routine clinical diagnostic test for intracranial hypertension.

Footnotes

[a] APERTO Eterna; Hitachi Medical Corporation, Tokyo, Japan
[b] Life Scope BSM-5192; Nihon Kohden Corporation, Tokyo, Japan
[c] Toshiba Aplio XG; Toshiba Medical Systems Corporation, Tochigi, Japan
[d] PVT-745BTV; Toshiba Medical Systems Corporation, Tochigi, Japan
[e] JMP Pro, 12.0.1; SAS Institute Inc., Cary, NC
[f] IBM SPSS Statistic, version 22; IBM Corporation, Armonk, NY

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Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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