Quantitative assessment of blood volume, blood flow, and permeability of the brain of clinically normal dogs by use of dynamic contrast-enhanced computed tomography

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Objective—To determine effects of regional variation, interobserver variability, and vessel selection on quantitative vascular variables derived by dynamic contrast-enhanced computed tomography (DCE-CT) of the brain of clinically normal dogs.

Animals—14 adult dogs with no evidence of CNS dysfunction.

Procedures—Dogs were randomly assigned to 4 groups, and DCE-CT was performed at the level of the frontal lobe, rostral portion of the parietal-temporal lobes, caudal portions of the parietal-temporal lobes, or occipital lobe–cerebellum for groups 1 to 4, respectively. Cerebral blood flow (CBF), cerebral blood volume (CBV), and permeability in gray and white matter for both a large and small artery were calculated and compared. Values among 3 observers and 4 regions of the brain were calculated and compared.

Results—Significant interobserver variability was detected for CBF and permeability in white matter. Values calculated for large and small arteries were correlated for CBV and CBF but not for permeability. Overall mean ± SD for CBF, CBV, and permeability in gray matter was 53.5 ± 27.7 mL/min/100 g, 2.9 ± 1.4 mL/100 g, and 1.4 ± 2.2 mL/min/100 g, respectively. Mean for CBF, CBV, and permeability in white matter was 44.2 ± 28.5 mL/min/100 g, 2.5 ± 1.5 mL/100 g, and 0.9 ± 0.7 mL/min/100 g, respectively. Values did not differ significantly among brain regions.

Conclusions and Clinical Relevance—Significant regional variations were not detected for quantitative vascular variables in the brain of clinically normal dogs. However, interobserver variability and vessel selection have an important role in variable estimation. (*Am J Vet Res* 2008;69:45–50)

Computed tomography and MRI are routinely performed in dogs to assist in the diagnosis of intracranial disorders. Although MRI is generally believed to provide superior delineation of soft tissues, compared with results for CT, both modalities are capable of defining regional anatomy and delineating mass lesions. With the administration of IV contrast agents (iodinated agents for CT and gadolinium agents for MRI), conspicuity of intracranial lesions improves. However, IV administration of contrast agents does not relay functional characteristics of brain lesions, nor does it provide a definitive diagnosis. Therefore, additional tests are required to properly diagnose and grade various pathologic conditions of the brain. These diagnostic tests usually include performing brain biopsies, which are costly, invasive, and associated with potentially serious morbidity and fatalities. Advances in imaging techniques have been targeted at the use of CT and MRI to generate functional data on brain lesions. These data can then be used to characterize various pathologic conditions of the brain and to provide diagnostic and prognostic information.[1]

Abbreviations

MRI	Magnetic resonance imaging
CT	Computed tomography
DCE	Dynamic contrast-enhanced
CBF	Cerebral blood flow
CBV	Cerebral blood volume
ROI	Region of interest

The development of novel software allows the generation of quantitative vascular variables from DCE-MRI[2,3] and DCE-CT[4] data. In this capacity, CT has certain advantages, including superior temporal resolution, more accessibility, less expense, and increased efficiency.[5] Furthermore, unlike MRI, the correlation between contrast agent concentration and signal intensity is linear with CT, thereby simplifying data processing.[6] Use of DCE-CT involves serial acquisition of images in the same anatomic location during IV administration of a contrast agent, which therefore allows observation and quantification of the first pass of iodinated contrast material through cerebral vasculature.[7] The basis for

Received June 4, 2007.
Accepted July 12, 2007.
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Supported in part by the Merck-Merial Scholarship Foundation
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DCE-CT is the central volume theory, which is defined by the following equation: CBF = CBV/MTT, where MTT is mean transit time. Deconvolution methods are used to extrapolate DCE-CT values for CBF, CBV, and permeability.[4,5] These values can be generated by use of dedicated, commercially available software, thereby adding functional information to the anatomic data acquired by traditional contrast-enhanced CT imaging. Measurements of contrast enhancement obtained from a regional input artery and venous output signal are used to assess the rate and degree of density change in brain tissue attributable to intravascular contrast. Quantitative measures of vascular function derived for DCE-CT have been used for diagnostic, prognostic, and treatment-planning purposes in humans. More specifically, DCE-CT has been used in humans to evaluate the extent of stroke, assess brain tumors, and monitor response to radiation therapy.[8-10]

The purpose of the study reported here was to establish reference values for the vascular variables CBF, CBV, and permeability in the brain of clinically normal dogs. Differences between gray and white matter were evaluated and used to determine whether vascular variables were uniform throughout the brain or were characterized by regional variations. Furthermore, variability of quantitative measures was evaluated by assessing the dependence of the vascular variables on arterial input selection and interobserver variability.

Materials and Methods

Animals—Dogs admitted to the Veterinary Medical Teaching Hospital at the University of California, Davis, and scheduled for contrast-enhanced CT to determine the cause of an extracranial disorder were evaluated for inclusion in the study. Inclusion criteria for each dog were no history of neurologic dysfunction, hypertension, or anemia and no abnormal results during neurologic examination.

Imaging procedures—Dogs were randomly allocated to 1 of 4 groups. For dogs of group 1, DCE-CT was performed on the frontal lobe. Similarly, DCE-CT was performed on the rostral portion of the parietal-temporal lobes, caudal portion of the parietal-temporal lobes, and occipital lobe–cerebellum of dogs in groups 2, 3, and 4, respectively. Osseous anatomic landmarks from which the CT scans were prescribed included the zygomatic process of the frontal bone for group 1, rostral aspect of the hypophyseal fossa for group 2, temporomandibular joint for group 3, and jugular process for group 4.

Anesthesia was induced in accordance with standard clinical protocols in all dogs. Anesthesia was maintained via inhaled isoflurane. Dogs were positioned in sternal recumbency within the CT scanner.[a] A preliminary exploratory view of the area of clinical interest and head was obtained. A precontrast image of the clinical area of interest was obtained. Then, the lateral preliminary exploratory view of the head was used to identify landmarks for the DCE-CT procedure. Nonionic, iodinated contrast medium[b] was injected (370 mg of I/kg at a rate of 2 mL/s) by use of an automated injection pump[c] via a catheter inserted in a cephalic or saphenous vein. The DCE-CT (continuous uninterrupted scanning of a single tissue slice) was performed at a rate of 1 image/s for 60 seconds starting immediately after the onset of the injection of contrast medium. This protocol allowed for the acquisition of at least 2 or 3 precontrast images prior to the arrival of the bolus of contrast medium and provided sufficient time for the entire bolus to pass through the cerebral circulation during acquisition of images. Technical settings used for the dynamic series were slice thickness of 3 mm, 120 kVp, 100 mA, acquisition time of 1 second, and a 512 × 512 matrix. The smallest field of view that included the entire head was used. Images were reconstructed by use of a soft tissue algorithm. After the dynamic series was obtained, postcontrast CT images of the clinical area of interest were acquired.

Image analysis—Data processing was performed by use of commercially available software[d] on a dedicated processing station.[e] Values for CBF, CBV, and permeability were calculated. To calculate these variables, ROIs were manually drawn for an extracranial input artery, an output vein, and 14 to 18 locations within the brain parenchyma of each dog. Brain ROIs included bilateral measures of dorsal, lateral, and deep gray matter; dorsal and lateral white matter; and, when applicable, cerebellum and brainstem. Major vessels and meninges were excluded from the brain parenchyma ROIs. Parametric maps were generated to provide the spatial distribution of gray and white matter for ROI selection.

Partial volume averaging can substantially alter arterial input function values when a small vessel is used.[5] Thus, it is recommended that a large artery be chosen for the input function. To evaluate the effect of vessel selection on estimation of variables, each DCE-CT data set was analyzed twice (once with a large input artery and once with a small input artery) by 1 observer (KLP). Depending on the location of the CT slice, the maxillary or lingual arteries were chosen as large vessels, whereas their initial branches were chosen as representative of small vessels. For these evaluations, selection of the jugular vein as the venous output function remained constant to specifically determine whether arterial selection could significantly alter hemodynamic values. In addition, the effect of interobserver variability on calculated values was assessed by having 3 observers (KLP, AGM, and REP) process the data for a large input artery and the jugular vein. Each observer manually drew ROIs in the dorsal gray, lateral gray, deep gray, dorsal white, and lateral white matter of all dogs.

Statistical analysis—All statistical analyses were performed by use of commercially available software.[f] Mean global values obtained by 1 observer for CBF, CBV, and permeability for gray and white matter were calculated and compared by use of a 2-tailed Student *t* test. Mean values for age and body weight for each group were compared by use of a single-factor ANOVA. Mean values for gray and white matter in the 4 anatomic locations were compared by use of a single-factor ANOVA. Values calculated by the 3 observers were compared by use of an ANOVA for repeated measures. Linear regression was performed to assess agreement between values

calculated for a small input artery and a large input artery. Values of $P \leq 0.05$ were considered significant for all statistical analyses.

Results

Fourteen dogs met the inclusion criteria. Groups 1 and 2 each consisted of 4 dogs, whereas groups 3 and 4 each consisted of 3 dogs. Various breeds were included, with no breed being overrepresented. There were 5 spayed females, 7 castrated males, and 2 sexually intact males. Mean ± SD age for all dogs was 10.6 ± 2.8 years, and mean body weight was 29.9 ± 10.8 kg. There were no significant differences in age and weight among groups.

Parametric maps of CBF, CBV, and permeability were drawn by use of DCE-CT data (**Figure 1**). The CBF, CBV, and permeability values were lower in the central brain parenchyma and higher in the periphery in the region of the meninges. Mean ± SD values for CBF, CBV, and permeability measured by 1 observer (KLP) were determined for groups 1 to 4 (**Tables 1–3**). Global mean ± SD values for all 4 groups (n = 14 dogs) calculated by 1 observer (KLP) for CBF, CBV, and permeability in gray matter were 53.5 ± 27.7 mL/min/100 g, 2.9 ± 1.4 mL/100 g, and 1.4 ± 2.2 mL/min/100 g, respectively. Global mean values for all 4 groups calculated by 1 observer (KLP) for CBF, CBV, and permeability in white matter were 44.2 ± 28.5 mL/min/100 g, 2.5 ± 1.5 mL/100 g, and 0.9 ± 0.7 mL/min/100 g, respectively. Although mean values for white matter were typically lower than mean values for gray matter, only CBV was significantly lower. There were no significant differences based on single-factor ANOVA assessment among groups for measurements in dorsal gray, lateral gray, deep gray, dorsal white, and lateral white matter, nor were there significant differences among dorsal, lat-

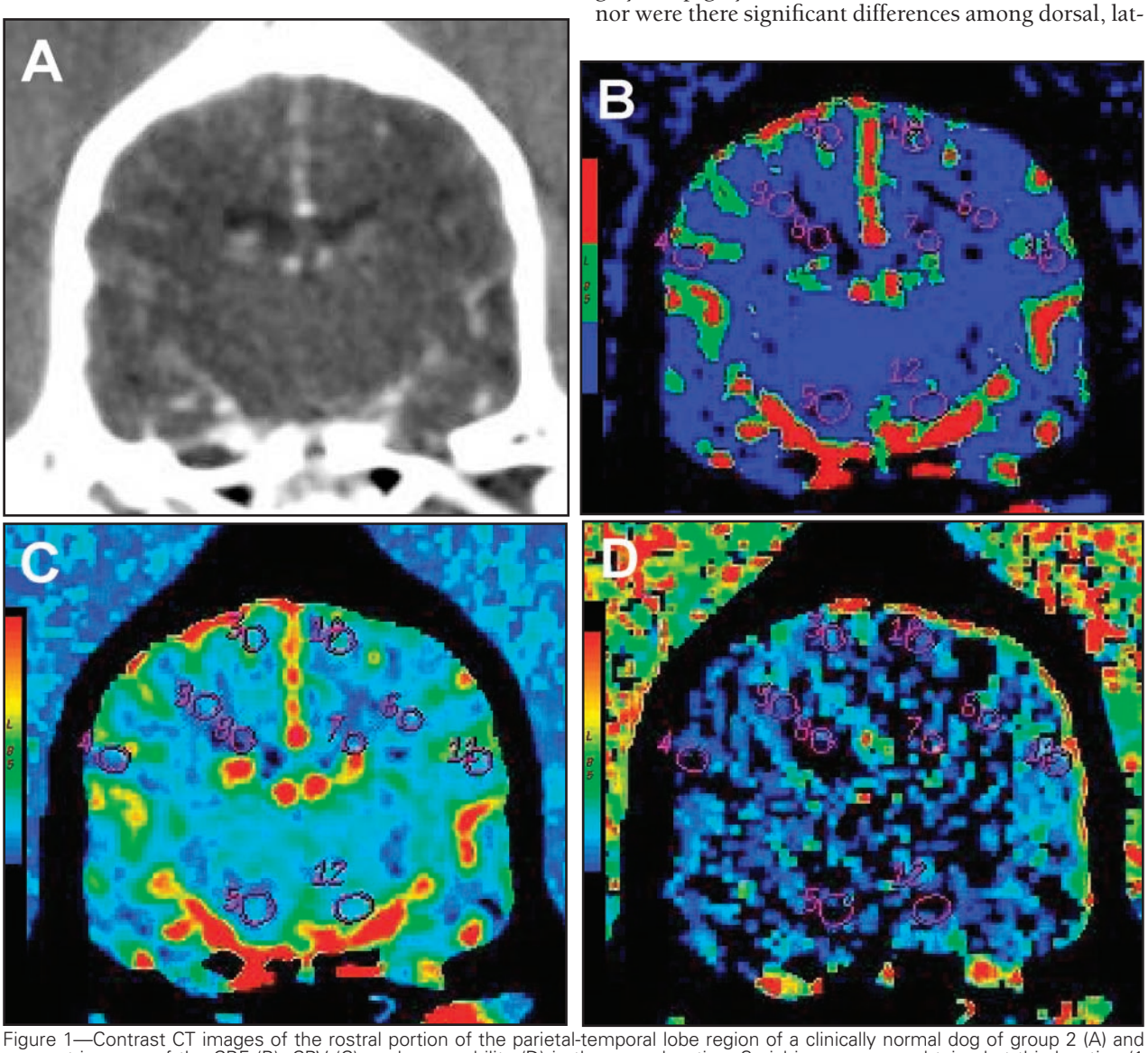

Figure 1—Contrast CT images of the rostral portion of the parietal-temporal lobe region of a clinically normal dog of group 2 (A) and parametric maps of the CBF (B), CBV (C), and permeability (D) in the same location. Serial images were obtained at this location (1 image/s for 60 seconds) during IV administration of contrast medium to generate parametric maps. In panels B through D, notice for the CBF that multiple ROIs (Nos. 1, 3, 4, 5, 6, 7, 8, 9, 11, and 12) are drawn bilaterally in the dorsal gray, lateral gray, deep gray, dorsal white, and lateral white matter. The color bars on the left indicate a range from 10 (blue) to 270 (red) mL/min/100 g for CBF in panel B, 0 (blue) to 10 (red) mL/100 g for CBV in panel C, and 0 (blue) to 10 (red) mL/100 g for permeability in panel D.

Table 1—Mean ± SD quantitative estimates of CBF for the various areas of gray and white matter evaluated in 14 clinically normal dogs.

Group*	Dorsal gray	Lateral gray	Deep gray	Dorsal white	Lateral white	Cerebellum	Brainstem
1	63.5 ± 14.9	64.8 ± 37.9	53.5 ± 35.2	59.4 ± 61.7	45.6 ± 13.6	ND	ND
2	43.4 ± 14.7	42.2 ± 26.9	49.3 ± 28.2	47.5 ± 23.1	43.1 ± 20.1	ND	ND
3	67.7 ± 45.0	67.9 ± 29.0	51.7 ± 22.1	52.7 ± 23.7	40.2 ± 13.7	ND	ND
4	38.6 ± 10.6	47.7 ± 18.0	ND	28.5 ± 6.7	24.5 ± 8.0	42.4 ± 40.7	37.8 ± 30.4

Values reported are No. of mL/min/100 g.
*Group 1, frontal lobe region (4 dogs); group 2, rostral portion of the parietal-temporal lobe region (4 dogs); group 3, caudal portion of the parietal-temporal lobe region (3 dogs); and group 4, occipital lobe and cerebellum region (3 dogs).
ND = Not determined.

Table 2—Mean ± SD quantitative estimates of CBV for the various areas of gray and white matter evaluated in 14 clinically normal dogs.

Group*	Dorsal gray	Lateral gray	Deep gray	Dorsal white	Lateral white	Cerebellum	Brainstem
1	3.6 ± 1.9	3.7 ± 1.8	3.1 ± 1.7	3.5 ± 2.8	2.5 ± 1.2	ND	ND
2	2.5 ± 0.7	2.3 ± 1.2	2.3 ± 1.4	2.4 ± 1.2	2.4 ± 0.9	ND	ND
3	3.5 ± 1.3	3.2 ± 1.0	2.7 ± 1.1	3.1 ± 1.4	2.2 ± 1.0	ND	ND
4	2.5 ± 1.1	2.9 ± 0.8	ND	1.5 ± 0.4	1.4 ± 0.5	1.8 ± 1.1	1.7 ± 0.7

Values reported are No. of mL/100 g.
See Table 1 for remainder of key.

Table 3—Mean ± SD quantitative estimates of cerebral vascular permeability for the various areas of gray and white matter evaluated in 14 clinically normal dogs.

Group*	Dorsal gray	Lateral gray	Deep gray	Dorsal white	Lateral white	Cerebellum	Brainstem
1	2.9 ± 4.1	2.5 ± 2.6	2.4 ± 4.2	1.0 ± 0.8	0.8 ± 0.8	ND	ND
2	0.6 ± 0.6	0.8 ± 0.5	0.7 ± 0.4	0.7 ± 0.7	0.8 ± 0.7	ND	ND
3	1.0 ± 0.8	0.7 ± 0.6	0.3 ± 0.4	1.2 ± 0.9	0.8 ± 1.0	ND	ND
4	1.2 ± 1.1	1.9 ± 2.0	ND	0.7 ± 0.6	1.4 ± 1.2	0.3 ± 0.2	1.1 ± 1.8

Values reported are No. of mL/min/100 g.
See Table 1 for remainder of key.

eral, and deep gray matter or between dorsal and lateral white matter.

Values for CBF obtained from a small input artery and a large input artery correlated well (r^2 = 0.91) and were described by the equation $CBF_{sa} = (0.954 \times CBF_{la}) + 2.03$, where CBF_{sa} is the CBF value for the small artery and CBF_{la} is the CBF value for the large artery (**Figure 2**). Similarly, there was good correlation (r^2 = 0.89) between the values for CBV obtained for a small input artery and a large input artery, which were described by the equation $CBV_{sa} = (0.920 \times CBV_{la}) + 0.21$, where CBV_{sa} is the CBV value for the small artery and CBV_{la} is the CBV value for the large artery. Correlation was poor (r^2 = 0.45) between the permeability values (described by the equation $permeability_{sa} = (0.544 \times permeability_{la}) + 0.41$, where $permeability_{sa}$ is the permeability value for the small artery and $permeability_{la}$ is the permeability value for the large artery) obtained by use of the small and large arteries.

When considering values for gray matter for all 14 dogs for each of 3 investigators (KLP, AGM, and REP), there were no significant differences among observers for CBF (P = 0.14), CBV (P = 0.96), or permeability (P = 0.10). When considering values for white matter for all 14 dogs for each of 3 investigators, there was no significant (P = 0.14) difference among observers for CBV. However, there were significant ($P < 0.001$) differences among observers for CBF and permeability. Mean ± SD values for CBF differed significantly between observers 1 and 2 (44.19 ± 28.5 mL/min/100 g and 33.37 ± 15.14 mL/min/100 g, respectively [P = 0.02]) and 2 and 3 (33.37 ± 15.14 mL/min/100 g and 55.77 ± 39.35 mL/min/100 g, respectively [$P < 0.001$]). Permeability differed significantly between observers 1 and 2 (0.86 ± 0.72 mL/min/100 g and 0.46 ± 0.39 mL/min/100 g, respectively [$P < 0.001$]) and between observers 1 and 3 (0.86 ± 0.72 mL/min/100 g and 0.55 ± 0.52 mL/min/100 g, respectively [P = 0.01]).

Discussion

Analysis of results of the study reported here indicated that it was possible to estimate CBF, CBV, and permeability in the brain of dogs by use of DCE-CT. Although our results were not compared with results for more invasive criterion-referenced techniques of direct perfusion measurements, the use of DCE-CT for estimating cerebrovascular variables has been validated in rabbits and a small group of dogs.[5,11] The values extracted from our study of clinically normal dogs closely resemble those reported in dogs, rabbits, and humans.[5,9,11-14] Moreover, our study clearly defined that CBF, CBV, and permeability were uniform throughout the brain of clinically normal dogs, regardless of the anatomic location being imaged.

One interesting fact was the lack of significant differences for CBF and permeability between the gray and white matter of the dogs in our study. Other investigators have found that white matter has significantly

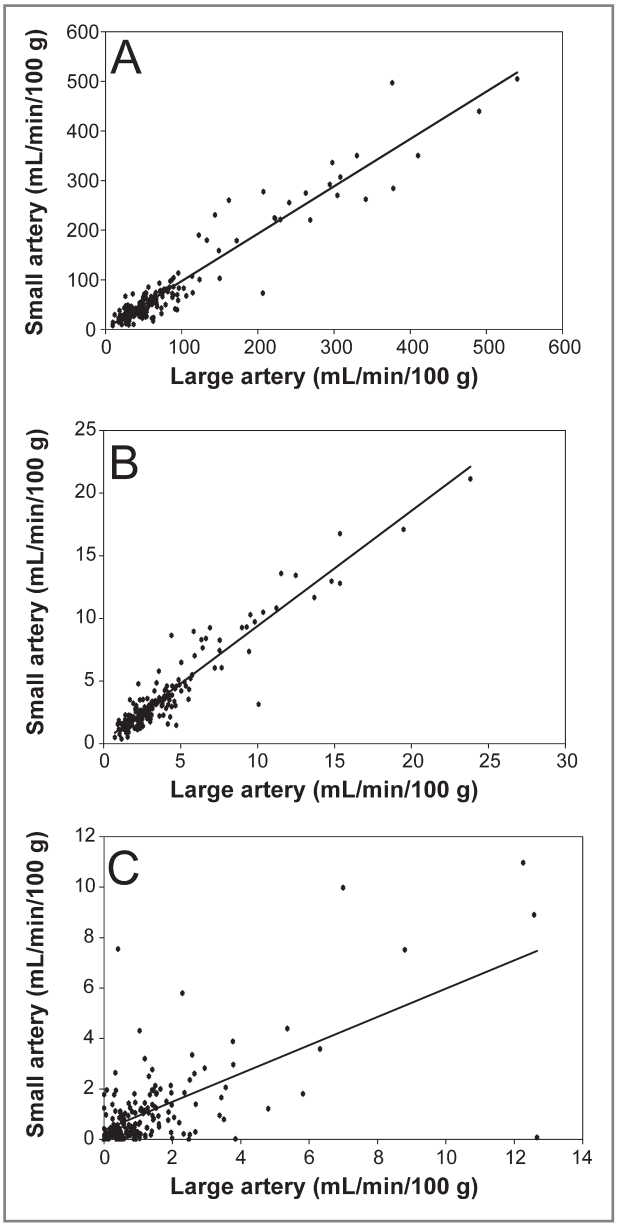

Figure 2—Values for CBF (A), CBV (B), and permeability (C) derived for a large artery plotted against those for a small artery for all 14 clinically normal dogs. Notice the line of best fit for each variable.

lower blood flow and blood volume than gray matter in dogs and humans.[11] Although we found that CBF, CBV, and permeability were consistently lower in white matter, only CBV was significantly lower in white matter than in gray matter. One possible explanation for this involves the precise location of the ROIs. In another study,[11] investigators evaluated the effect of small versus large ROIs and found that large regions encompassing a bulk of the gray or white matter in a given location did not yield significantly different results from small ROIs drawn in the same areas of gray and white matter. However, our white matter measurements were consistently higher than those reported for various species,[9,11,12] which suggested that perhaps gray matter was included in our regions. This is particularly likely given the relative difficulty associated with distinguishing gray matter from white matter on a CT image. Alternatively, the small number of dogs used in the study reported here may have precluded us from detecting significant differences.

In reality, most intracranial lesions do not respect boundaries of the gray and white matter. In humans, the quantitative variables measured for brain tumors and regions of infarction will often be compared with results for the same region on the contralateral side of the brain, which often contains both gray and white matter. For this reason, it may not be as important to distinguish between gray and white matter as it would be to define normal versus abnormal brain tissue. Although a range of values is cited in the literature, CBF reportedly decreases to 0 to 10 mL/min/100 g and CBV ranges from 0 to 1.5 mL/100 g in stroke patients.[9] In another study,[15] investigators defined infarction as a reduction in CBF of 34% or more, relative to results for the normal hemisphere. In a report[13] in which investigators evaluated 2 metastatic brain tumors, CBV and CBF were similar to values in contralateral brain tissue, whereas permeability was > 10 mL/min/100 g. Assuming dogs have similar alterations in quantitative measures obtained from diseased brain tissue, even the relatively high SD values for the data of the study reported here would not mask true intracranial disease.

Interobserver variability was highest when assessing the white matter but did not differ significantly when assessing gray matter. More specifically, CBF and permeability for white matter were lowest when measured by observer 2. Arguably, observer 2 may have drawn the most precise ROIs, which would result in values for CBF and permeability that most closely resemble those reported in the literature. This implies that careful selection of an ROI is necessary when exact differentiation of variables between gray and white matter is desired. Furthermore, this raises the question regarding whether a single observer should calculate values for all serial DCE-CT studies, thereby eliminating the confounding effect of interobserver variability when assessing changes in vascular variables in a single patient over time. Additional studies are warranted to clarify the effect of interobserver variability on the outcome of serial DCE-CT examinations.

The effect of the choice of the input artery on DCE-CT outcomes is variable.[11,12] The theoretic basis of this technique is the central volume principle, which relates CBF, CBV, and mean transit time in the following equation: CBF = CBV/MTT. The mathematic manipulation (deconvolution) of this equation to derive quantitative DCE-CT variables has been reported elsewhere[5,11] and is beyond the scope of our study. However, 1 main advantage of the deconvolutional method over other mathematic models is worth mentioning and involves the proposed independence of this technique from the shape of the arterial input function. Ideally, the supplying artery (ie, internal carotid artery) would be selected as the vascular input; however, this is often not possible because of the anatomic location of the region of clinical interest. In 1 study,[11] data for the values of CBF and CBV retrieved for the internal carotid artery were not significantly different from data obtained for noncarotid arteries. In contrast, investigators in another study[12]

found that the choice of arterial input had a profound effect on estimation of CBF and CBV when a slightly different deconvolutional technique was used.

Analysis of our results indicated that CBF and CBV were not influenced by the choice of arterial input function. Nevertheless, we did find that a significant effect was evident on the estimate of permeability, a variable that, to our knowledge, has not been evaluated. Mathematically, permeability is inversely related to the extraction fraction of contrast medium from the intravascular to the extravascular tissue. The extraction fraction is derived from a ratio of the arterial density to the tissue density over time.[1] It has been reported[14] that partial volume averaging can decrease the density measured from small vessels by as much as a factor of 4. Consequently, miscalculation of the extraction fraction is likely to happen with small vessels and result in direct effects on permeability. We suspect that the effect of vessel selection on permeability measurements was related to partial volume averaging in the smaller vessels and therefore recommend the use of large arteries for the calculation of quantitative DCE-CT variables.

In the study reported here, DCE-CT was used to estimate CBF, CBV, and permeability in the brains of 14 clinically normal dogs. Our measurements resembled those reported for various species. There was no significant variation in variables for gray and white matter between the frontal region, rostral portion of the parietal-temporal lobe, caudal portion of the parietal-temporal lobe, and occipital lobe–cerebellum. Interobserver variability and ROI precision may affect vascular variables, particularly those involving the white matter. Selection of the largest possible artery as the input function is warranted when measures of permeability are desired.

a. x/i Helical scanner, General Electric, Medical Systems Divisions, Milwaukee, Wis.
b. Isovue-370, Bracco Diagnostics Inc, Princeton, NJ.
c. MEDRAD Vistron CT, MEDRAD Inc, Indianola, Pa.
d. CT Perfusion 2, GE Medical Systems, Milwaukee, Wis.
e. GE Advantage workstation 4.2, GE Medical Systems, Milwaukee, Wis.
f. Microsoft Excel, Microsoft Corp, Redmond, Wash.

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