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Effect of delayed acquisition times on Gadolinium-enhanced MRI of the presumably normal canine brain.

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Running header (45 characters): Delayed MRI contrast enhancement.

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A delay in imaging following intravenous contrast medium administration has been recommended to reduce misdiagnoses. However, the normal variation of contrast enhancement in dogs following a delay has not been characterized. Contrast enhanced MR imaging of 22 dogs was assessed, in terms of identification of normal anatomic structures, to investigate the variation associated with 10 minute delay between contrast medium administration and imaging. All dogs had a normal brain MR imaging study and unremarkable CSF. Specific ROIs were assessed both objectively, using computer software, and subjectively using three observers. Mean contrast enhancement greater than 10% was seen in the pituitary gland, choroid plexus, meninges, temporal muscle, trigeminal nerve and the trigeminal nerve root. Structures with an active blood-brain-barrier had minimal contrast enhancement (<6%). Enhancing structures had significantly more contrast enhancement at t=1min versus t=10min, except in temporal muscle, the trigeminal nerve and the trigeminal nerve root. Inter-observer agreement was moderate to good in favor of the initial post contrast T1w sequence. The observers found either no difference or poor agreement in identification of the non-vascular structures. Intra-observer agreement was very good with all vascular structures and most non-vascular structures. A degree of meningeal enhancement was a consistent finding. The initial acquisition had higher enhancement characteristics and observer agreement for some structures; however, contrast-to-noise was comparable in the delayed phase or not significantly different. We provide baseline references and suggest that the initial T1w post contrast sequence is preferable but not essential should a delayed post contrast T1w sequence be performed.
Introduction:

Intravenous gadolinium chelates are used commonly in magnetic resonance (MR) imaging studies to improve contrast of normal and abnormal structures. Contrast enhancement results from alteration of the T1 and T2 relaxation time of hydrogen nuclei in the immediate vicinity of the gadolinium chelate. Enhancement on T1w images appears as increasing signal intensity of tissues with higher concentrations of the gadolinium molecule. Contrast media have significant use in brain imaging as the normal blood brain barrier (BBB) prevents gadolinium extravasation. Therefore lesions affecting the BBB often have increased intensity after gadolinium administration. The dose related, time-dependent and pulse technique differences in contrast enhancement have been quantified. Mean peak signal enhancement varies depending on the tissue or lesion. Some intracranial lesions have no enhancement immediately following contrast medium administration. A delay period following administration has, therefore, been recommended to allow gadolinium to accumulate in pathologic tissues. The majority of animals are anaesthetised during MR imaging and a delay following contrast medium administration is not typical. Our aim was to characterize the difference in post contrast T1-weighted images of the normal brain when allowing a 10 min delay between administration of contrast medium and image acquisition.

Materials & Methods:

Dogs undergoing a brain MR imaging examination between December 2009 and April 2010 but without haematologic, serum chemistry and cerebrospinal fluid (CSF) abnormalities were evaluated. Dogs were not included if there were signs of a cranial nerve deficit or intracranial lesions were present on the MR image, if a delayed phase scan was unobtainable due to anaesthetic reasons, or if noticeable movement occurred between the transverse sequences. Twenty-two dogs were identified. Age ranged from 8 months to 10 years, with a mean of 4.4 years. Five of 12 males were intact and three of 10 females were entire. The majority were mix breed dogs (N=4), Labrador
retrievers (N=3), Dalmatians (N=2), Jack Russell terriers (N=2), Shih-Tzus (N=2) and Boxers (N=2).

Dogs were anaesthetised for imaging using IV propofol (Propoflo; Abbott Laboratories, Berkshire) and maintained on isoflurane (Isoflo, Abbott Laboratories, Berkshire) in oxygen. Gadopentetate dimeglumine (Gd-DTPA) (Magnevist, Bayer plc, Newbury, Berkshire) was used as a contrast medium at 0.2mg/kg.

All images were acquired while the patient was in dorsal recumbency using a 1.5 Tesla unit (Siemens Magnetom Esenza, Siemens AG, Erlangen, Germany) with a human head/neck coil. T2w sagittal, dorsal and transverse; FLAIR transverse; T2* transverse and T1w transverse sequences were acquired in all dogs. T1-weighted transverse sequences were repeated immediately following contrast medium administration and again 10 minutes later (TR = 455-674ms, TE = 13). Standard slice thickness was either 3mm or 4mm for transverse plane images depending on patient size.

Enhancement characteristics of both contrast T1w sequences were assessed objectively using ROIs and subjectively involving three observers (RN, MS & GH) who were unaware of the timing of contrast medium administration.

For objective assessment, both sequences were analysed using a DICOM image viewer (OsiriX version 3.7; OsiriX Imaging Software). Regions of interest (ROIs) were selected to include the following structures: pituitary gland, choroid plexus of the lateral ventricles, meninges, temporal muscle, thalamus, cerebral cortex, white matter, hippocampus, trigeminal nerve and root, the piriform lobe and external air space (Figure 1). For identifying the different tissues of the brain, the ROIs were generated using the T2 transverse series and then extrapolated to all three T1-weighted sequences using point based registration. The ROI assigned to the external airspace, within the field of view, was used to determine signal noise measurements. For each ROI the mean signal intensity and standard deviation were recorded as arbitrary units.

Based on the ROIs measurements the signal-to-noise ratio (SNR), the contrast-to-noise ratio
(CNR) and the enhancement percentage (E%), were calculated as follows:

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\text{SNR} = \frac{\text{SI}_{\text{tissue}}}{\text{SD}_{\text{air}}}
\]

\[
\text{CNR} = \frac{\text{SI}_{\text{tissue}} - \text{SI}_{\text{wm}}}{\text{SD}_{\text{air}}}
\]

\[
\%\text{ enhancement} = \frac{\text{SI}_{\text{post}} - \text{SI}_{\text{baseline}}}{\text{SI}_{\text{baseline}}}
\]

\text{SI}_{\text{post}} - \text{mean tissue signal intensity at specified time after contrast administration; SI}_{\text{baseline}} - \text{mean tissue signal intensity before contrast; SD}_{\text{air}} - \text{standard deviation of background signal (average if comparing pre and post sequences); SI}_{\text{tissue}} - \text{mean signal intensity of tissue to contrast with SI}_{\text{wm}} - \text{mean signal intensity of white matter.}

For subjective assessment two board certified radiologists and one final year radiology resident were given all three T1w series for each of the 22 dogs. The pre contrast T1w image was given as a known control; however, the two post contrast T1w series were randomized (Figure 2). Each observer was asked to choose the series with the best visualization of the aforementioned structures or state there was no difference. To calculate intra-observer variability, the same assessment was repeated 2 weeks later, but with patient order and the T1w post contrast series layout randomized. At no time was the DICOM header or metadata information available to observers.

All data is shown as mean ± standard deviation. Respective data for SNR, CNR and E% of both post contrast series were analysed using 2-tailed Student paired t tests. Where one or both pairs of comparison data were not distributed normally a non-parametric sign rank (Wilcoxon matched pairs) test was used. Results of relevant differences in SNR, CNR and E% were tabulated with
calculation of standard deviations and P values. A P value of <0.05 was considered statistically significant. For inter and intra rater assessment Gwet's alternative coefficient (AC1) was used and significance defined by the agreement measures for categorical data.

Results:

There was no significant difference between baseline SNR and either the initial or delayed post contrast series for white matter, thalamus, and piriform lobe. The cerebral cortex and hippocampus were characterized by a significant difference between the baseline and the initial SNR, but not the delayed post contrast series (Figure 3). Mean enhancement percentages greater than 10% were seen in pituitary gland, choroid plexus, meninges, temporal muscle, trigeminal nerve and trigeminal nerve root. For both the 1 and 10 minute scans respectively, trigeminal nerve showed the most enhancement (57.5±11.4%, 53.7±13.9%), followed by the pituitary (54.9±19.6%, 38.4±19.9%), meninges (32.9±14.6%, 24.2±12.7%), choroid plexus (29.7±10.1%, 22.5±8.5%) temporal muscle (20.8±5.8%, 19.8±4.8%) and trigeminal nerve root (13.0±6.9%, 14.6±10.9%) (Figure 4). These structures all showed significantly more contrast enhancement at t=1min versus t=10min (p<0.05), except the temporal muscle, trigeminal nerve and trigeminal nerve root. The other structures had minimal enhancement (mean enhancement percentage <6%).

For CNR calculations, the white matter ROI was used as, in retrospect, it had the least enhancement percentage following contrast medium administration for both the 1 and 10 minute delayed series; 1.6±1.1% and 1.1±1.5% respectively. For structures with an enhancement percentage above 10%, the increase in CNR for the 1 and 10 minute scans respectively were: pituitary (30.3±12.1 & 20.7±11.6), choroid plexus (12.0±5.3 & 9.0±3.9), meninges (11.0±5.5 & 7.8±4.3), muscle (7.0±2.8 & 6.9±2.3), trigeminal nerve (24.2±7.2 & 22.7±8.2), trigeminal nerve root (4.4±2.4 & 5.3±4.4) (Figure 5).
Inter-observer agreement was moderate to substantial in favor of the initial post contrast sequence for the pituitary, choroid plexus and the meninges. Inter-observer agreement was substantial to almost perfect for hippocampus, thalamus and piriform lobe in favor of no difference being observed between both post contrast sequences. Inter-observer agreement was poor for the muscle, cerebral cortex, white matter, trigeminal nerve and the trigeminal nerve root. Intra-observer agreement was substantial to almost perfect in favor of the initial post contrast sequence for the pituitary, choroid plexus and meninges and, for observer 1, white matter. Observer 1 had substantial agreement for muscle in favor of the delayed post contrast images whereas the other two observers had almost perfect agreement for no difference between post contrast images. All other remaining tissues either had substantial-almost perfect agreement in favor of no difference between post contrast sequences or only slight agreement with no favoring between post contrast sequences.

Discussion:

All forebrain structures had minimal contrast enhancement (<6%) which is due to the highly selective blood brain barrier (BBB). Inter and intra-observer agreement for identifying these structures was either poor or highly favoring no difference between the post contrast series. When assessing the conspicuity of white matter, however, Observer 1 had high intra-observer agreement favoring the initial and delayed contrast series equally rather than no difference. We do not know why this observer's agreement was high as the SNR and enhancement characteristics were comparable to that of the most adjacent structures e.g. thalamus, which had poor inter and intra-observer agreement or leniency towards no difference. We conclude, however, that the overall equal leniency towards both post contrast sequences is clinically comparable to the other two observers finding no difference between them. The CNR for forebrain structures had a substantial increase for both post contrast phases; however, based on the relatively low enhancement values and low
agreement it is likely that these changes are not detectable and ultimately not clinically relevant.

Gadolinium uptake will be detected in structures with high vascularity e.g. pituitary gland; lateral, 3rd and 4th ventricles of the brain, choroid plexus and venous sinuses of the cranial dura mater,14 or where there is increased vascular permeability.17

The pituitary gland had a large degree of contrast enhancement for both the initial and delayed contrast sequences. The vascular supply to the pituitary gland is supplied directly from the internal carotid artery via the caudal hypophyseal artery to the neurohypophysis, and indirectly by the portal pituitary system.18 Both vascular phases appear separately leading to a distinct pituitary flush from the neurohypophysis followed by homogenous contrast enhancement. Using dynamic MR and CT imaging the entire pituitary gland exhibits peak homogenous contrast enhancement at 60-90 seconds following contrast medium administration before gradually returning to the baseline.18,19 We imaged the pituitary gland during this 60-90 second window and again approximately 10 minutes later, revealing a larger increase in CNR for the initial series. The difference in CNR between the two post contrast phases was supported by the high intra and inter-observer agreement favoring the initial post contrast series. The delayed series still had a mean increase of 474% in CNR from the baseline.

The choroid plexus had similar enhancement characteristics to the pituitary gland. There is similarity of anatomy of microvascular structures between the rat, dog and human identifying the arterial supply via the choroidal arteries, which originate from the internal carotid artery.20,21 As the choroid plexus is intrinsically highly vascular, there was an expected increase in contrast enhancement following contrast medium administration. Like the pituitary gland, the reduction in contrast enhancement in the delayed phase was supported by the high intra and inter-observer agreement favoring the initial post contrast series. This was observed despite only a 28.7% difference in CNR between the two post contrast series.

Meningeal enhancement in veterinary neuroimaging is described as meningeal disease22,23
however, human neuroimaging publications describe a small amount of meningeal contrast enhancement as a normal finding as a result of normal vascularity.\textsuperscript{24-26} We found a small amount of enhancement, appearing as short thin meningeal segments, in all 22 dogs (Figure 6). CNR was higher for the initial phase than the delayed phase, despite only differing by 24.3%. This was supported by substantial inter and intra-observer agreement in favor of the initial post contrast series.

Conspicuity of meningeal enhancement can be heightened by increasing the volume of injected contrast medium, reducing the slice thickness, selecting an optimal plane of section, using post contrast FLAIR sequences or by using fat suppressed spin echo sequences.\textsuperscript{25,27-29} With regards to post contrast FLAIR sequences the degree of enhancement can be variable as the effects of gadolinium lead to increased T1w signal, but decreased T2w; both of which contribute to FLAIR images. Enhancement in FLAIR images may ultimately depend on the concentration of gadolinium within specific tissue.\textsuperscript{27,29}

Others have found that canine paraspinal muscle enhancement reached approximately 6% at 1 minute, 22% at 4 minutes, 16% by 10 minutes and then slowly declined over 45 minutes.\textsuperscript{30} We found similar enhancement percentages but no significant difference between the initial and delayed series. The selection of image slice to determine muscle enhancement was not based on anatomic location but rather the slice having the largest cross sectional area of muscle without enhancing vasculature. For this reason, the specific acquisition time may vary more than for other ROIs, which were determined by the slice that best represented the anatomy. It is likely that this variability was responsible for the similar enhancement characteristics between both post contrast series. Muscle has a relatively small extracellular space, which does not allow the same sequestration of contrast medium as for other tissues.\textsuperscript{17} The permeability of the capillary endothelial cells in muscle occurs via tight junctions and intracellular gaps; however, the transfer of contrast medium is largely unidirectional.\textsuperscript{30,31,32} This would explain the lower enhancement characteristics and longer contrast washout of muscle
compared to the other vascular structures in our study. Based on objective analysis of temporal muscle enhancement, there was no significant difference in the enhancement percentage and CNR. Intra-observer agreement was almost perfect; however, the initial post contrast series was favored by one observer because enhancing vessels within muscle was more distinct in the initial post contrast series. The other 2 observers felt the muscle was not different between the two series.

Trigeminal nerve enhancement is a normal finding in canine patients without clinical signs of trigeminal nerve disease.\textsuperscript{33,34} The proposed mechanism for the enhancement is an incomplete blood-nerve barrier.\textsuperscript{35,36} Trigeminal nerve enhancement was identified in all 22 dogs. We found more enhancement of the trigeminal nerve than in the pituitary gland; this is contradictory to prior work (REF). The lower E\% of the pituitary gland is likely a reflection of the higher baseline SNR of the pituitary gland on T1w images (Figure 2A) due to signal from arginine vasopressin.\textsuperscript{35} The difference in CNR for the trigeminal nerve between both post contrast series was not significantly different. This is supported by the poor inter-observer agreement. Overall intra-observer agreement was lowest for the trigeminal nerve with observers 1 & 2 having fair agreement. Observer 3 had moderate agreement; however, this was in favor of no difference between the post contrast series.

The trigeminal nerve root was the only ROI with higher mean enhancement in the delayed phase. The enhancement percentage and CNR for each post contrast series was; however, not significantly different. Subjective assessment supported this finding through poor inter and intra-observer agreement or leniency towards no difference between the the post contrast series. For consistency the CNR was based on the enhancement properties of white matter; no other structures from the brain stem were assessed for contrast enhancement. Therefore, the larger enhancement percentage and CNR between the trigeminal nerve root and forebrain may reflect the difference in vascularity or higher dependency on the basilar artery for brain stem vascular supply; particularly the trigeminal nerve root.\textsuperscript{37}
We did not have histologic confirmation of brain normality but the MR images and CSF analysis were normal. Micro-motion or positional relaxation between the two post contrast series may have led to ROI registration errors. Also, we cannot guarantee that each slice chosen to represent each ROI occurred at the same time as the number of slices and starting position of each slice varied between patients. This may reflect the larger distribution of enhancement data.

In conclusion, there was variable enhancement of intrinsically vascular permeable tissues and some changes in enhancement were noted following an approximate 10 minute delay in acquisition. Although the initial acquisition had higher enhancement characteristics and observer agreement for some structures, CNR were comparable in the delayed phase or not significantly different. In addition, other structures had either comparable enhancement characteristics or low inter and intra-observer agreement between the two post contrast phases. With many intracranial structures and lesions having variable contrast enhancement, or lack thereof, when using an immediate post contrast sequence, performing a delayed post contrast sequence may allow for improved lesion conspicuity. We provide baseline references and suggest that the initial T1w post contrast sequence is preferable but not essential should a delayed post contrast T1w sequence be performed.
Figure 1) Transverse T2w images of the head. A; Temporal muscle, hippocampus, cerebral cortex and trigeminal nerve root. B; Pituitary gland. C; Thalamus and trigeminal nerve. D; White matter, meninges, choroid plexus and piriform lobe. Note; External air ROI is not shown in these images.

Figure 2) Three transverse T1w images of the same patient at the same level. A is the pre contrast image. B is the immediate post contrast image. C is the delayed post contrast image. Note the signal intensity of the pituitary gland in each image (arrowheads).

Figure 3) Signal-to-Noise Ratio for each T1w series: Pre-contrast (grey), initial post contrast (white) and delayed post contrast (striped). Asterisk denotes no significant difference (p>0.05) between each T1w series.

Figure 4) Enhancement percentage for each post contrast series: Initial and delayed. Asterisk denotes no significant difference (p>0.05).

Figure 5) Contrast-to-noise ratio (difference) for each post contrast series: Initial (striped) and delayed (white). Asterisk denotes no significant difference (p>0.05).

Figure 6) T1w transverse digital subtraction image using the pre-contrast image and the initial post-contrast image. Note the thin meningeal contrast enhancement (arrow).


29. Falzone C, Rossi F, Calistri M, Tranquillo M, Baroni M. Contrast-enhanced fluid-attenuated


