Modified CT perfusion contrast injection protocols for improved CBF quantification with lower temporal sampling

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Perfusion CT (PCT) has emerged as a widely recognized technique for assessing neurological blood flow disorders such as stroke. By acquiring sequential images of an anatomical location after the injection of contrast material, vital functional information about the physiology of the brain can be obtained. The anatomic coverage provided has typically been limited to the amount of coverage provided by a single gantry rotation [1, 2]. At present, only 2 cm to 4 cm slices can be obtained even with state-of-the-art multi-detector scanners. Such limited coverage has been shown to cause false negative findings, since the locations chosen to obtain the cross-sectional images in the brain may not be the area of physiological change due to stroke [1, 3, 4].

Simple solutions for increasing the anatomical coverage, such as performing two PCT scans consecutively, may not be feasible for all clinical scenarios. Obtaining multiple PCT scans increases the volume of contrast agent injected into the patient [1, 5] as well as the total scan time. Using a large amount of contrast agent for dual PCT scans may limit the amount that can be used for a succeeding CT angiography scan. Spending extra time for setting up two scans is not ideal in an emergency situation such as stroke detection. Reducing the frequency of sampling for CT perfusion offers potential benefits over traditional techniques by allowing for expanded anatomic coverage with a single contrast injection.

Jog Mode is an innovative technique for increasing the anatomical coverage of a brain perfusion scan while utilizing a single contrast bolus. The scanner table is toggled back and forth between different locations in the brain within a single study. This technique essentially doubles the coverage that can be provided by a conventional PCT protocol. Because of the time required for the table to move between two adjacent locations, the Jog Mode approach reduces the frequency of image sampling for each scan location to four seconds.

In addition to potentially increasing the anatomic coverage provided with a single contrast injection, reducing the frequency of temporal sampling can also be used to reduce the overall radiation dose applied to the patient. Previously published articles describe 30-50 second acquisitions [2, 3, 6]. At a sampling rate of one image per second, this can result in up to 50 exposures per anatomic location. Adverse effects have been reported for patients undergoing multiple perfusion studies at 120 kVp and 100 - 200 mAs [7].

Most of the recent literature recommends using 80 kVp and less than 150 mAs [3, 6], which represents an approximately 80% decrease in the radiation exposure associated with the adverse effects described in [7]. This radiation dose can be further reduced by a factor of three or four if the rate of temporal sampling is three or four seconds, respectively. For example, the entire radiation dose of a 48 second CT perfusion scan performed at 80 kVp and 100 mAs with a temporal sampling of 4 seconds (total of 12 scans at each location) will result in a similar CT dose index (CTDI) to that of a single traditional non-contrast brain scan performed at 140 kV and 500 mAs.

One major concern with reducing the frequency of sampling, however, is the potential effect that this could have on the quantitative accuracy of various PCT measurements. Roberts et al. [1] demonstrated that clinically relevant perfusion maps could be obtained by using an approach similar to the Jog Mode which resulted in toggling the table back and forth within a
single contrast injection. However, the imaging protocol they describe decreases their frequency to five seconds, which was found to cause a discrepancy between the quantitative cerebral blood flow (CBF) measurements and the reference standard values when used with 40 ml contrast agent [5].

The most likely reason for their failure to obtain quantitative CBF measurements with an infrequent temporal sampling relates to the underlying principles of deconvolution-based CT perfusion methods. Deconvolution analysis in CT perfusion uses the time-enhancement curve obtained through sequential scans as an indicator of change in contrast concentration to deduce quantitative perfusion values [8]. The time-enhancement curve for each voxel of brain tissue is deconvolved with the arterial input curve. The width of the resultant deconvolved curve corresponds to the Mean Transit Time (MTT) value of the tissue.

The area under the tissue curve for each brain voxel is divided by the area under a purely vascular voxel (usually in the superior sagittal sinus) to produce the Cerebral Blood Flow (CBV) value of the brain tissue voxel. The CBF is calculated by dividing the CBV and MTT values [9, 10]. Hence an incorrect representation of the tissue and/or arterial time-enhancement curve has a high possibility of producing inaccurate computations of perfusion values. One such case for a misrepresented curve would be with decreased sampling frequency. As the time interval between scans increases, sufficient samples of the curve might not be obtained, and important determinants of the curve shape such as the peak enhancement value could be missed. Deconvolution analysis of these incorrect curves could produce inaccurate quantitative perfusion values.

Wintermark et al. proposed increasing the volume of contrast injected into the patient to circumvent the loss of information due to a reduced sampling frequency [3]. Extending the injection protocol stretches the time-enhancement curve and allows for capturing more data points on the curve, even with a lower frequency of sampling. Thus, with increased amounts of injected contrast material, the chance of missing important information for calculating quantitative perfusion values is reduced (Figure 1). While Wintermark et al. [3] demonstrated the ability to obtain accurate clinical diagnosis from less frequently sampled PCT scans by using modified contrast injection schemes, they did not report the level of accuracy of quantitative perfusion values for such techniques.

The purpose of our study was to independently reproduce the results of Wintermark et al. while also providing information as to the degree to which quantitative perfusion maps obtained with four second sampling compare to values obtained with more frequent temporal sampling.

**Methods**

**Imaging protocol**

A perfusion CT series (80 kV; 150 mA, 75 ml non ionic contrast agent with a flow rate of 3-4 ml/s; delay 5 seconds, data acquisition 65 seconds) was obtained in 15 patients with a modified injection protocol. The amount of contrast injected to the patient was increased to 75 ml to widen the resulting enhancement curve. Four 10 cm thick slices were acquired at the suitable locations in the brain determined by the radiologist in charge. The scanning parameters resulted in a temporal sampling resolution of 1.3 seconds.

**Data processing**

The PCT data were analyzed using the CT Perfusion package in the Extended Brilliance Workspace Workstation (Philips Healthcare, Cleveland, OH, USA). When necessary, motion artifacts were corrected by registering the images. The MTT maps were calculated by closed-form (non-iterative) deconvolution using the arterial reference. The CBV values were calculated as the area under the time attenuation curves. Finally, the CBF values were obtained from the CBV and MTT values using the simple formula $\text{CBF} = \frac{\text{CBV}}{\text{MTT}}$ [5, 9, 10].

The control data were obtained by processing the scans at the normal temporal sampling resolution of 1.3 seconds. For each patient, a simulated “Jog Mode” scan was created by reducing the frequency of samples for the same
data to four seconds by sub-selecting one out of every three images.

Data analysis
A region of interest (ROI) was drawn over the entire brain for patients with no visible blood flow abnormalities, or over the entire normal hemisphere in the case of single-hemisphere infarct or ischemia, in order to obtain the quantitative values of CBV, CBF and MTT. The software automatically provided the average values of the pixels selected by the ROI for the mentioned values.

In general the ROI consisted of the normal cortical gray matter, normal white matter, the head of the caudate nucleus on each side and lentiform nuclei on each side [5]. Quantitative perfusion values were compared between functional maps of the same patient obtained with each of the two temporal sampling rates.

Statistical analysis
Bland-Altman analysis [11] was performed between the CBV, CBF and MTT measurements of the same patients for each of the temporal sampling rates. The Bland-Altman technique is useful for assessing the interchangeability of measurements obtained by two different methods. It compares the average of the two measurements with the difference between them. This allows for a direct comparison of bias and level of agreement between the two data sets. Average bias is assessed by comparing the mean of differences between the measurements with zero. A mean value closer to zero shows less overestimation or underestimation. Additionally, the mean ± 1.96 SD (standard deviation) shows the 95% limits of agreement between the two measurements. The limits of agreement may be used as a parameter to assess the clinical relevance between the measurements [11].

Results
The average CBF value for normal mixed tissue was 65.3 +/- 14.9 ml/100 g/min with the normal (1.3 s) sampling frequency and 64.3 +/- 16.6 ml/100 g/min with the decreased (4 s) sampling frequency. For all 15 cases, the perfusion maps acquired for the decreased sampling frequency were visually comparable to the perfusion maps of the normal sampling frequency (Figure 2). The results of the Bland-Altman analysis for CBV, CBF and MTT values are shown in Table 1 and Figures 3, 4 and 5 respectively.

Discussion
We restricted our ROIs to the normal mixed tissue of the brain since the standard values for such tissue already exist. This allows for a direct comparison of accuracy between our values and the standard values. Our results show that all the physiological values obtained with a less frequent temporal sampling are within the range of their respective standards. The CBF values for the reduced sampling frequency were 64.3 ± 16.6 ml/100g/min, which correlates well with the normal brain tissue CBF values of 54.7 ± 27 ml/100g/min for Xenon CT previously published by Wintermark et al. [4].

<table>
<thead>
<tr>
<th>Mean</th>
<th>Limits of agreement</th>
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<tbody>
<tr>
<td>CBV</td>
<td>0.18</td>
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<td></td>
<td>2.1</td>
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<tr>
<td></td>
<td>-1.8</td>
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<tr>
<td>CBF</td>
<td>-1</td>
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<tr>
<td></td>
<td>-25.9</td>
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<tr>
<td></td>
<td>23.9</td>
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<tr>
<td>MTT</td>
<td>0.4</td>
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<td></td>
<td>-2</td>
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<td></td>
<td>2.9</td>
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Table 1. Bland-Altman analysis of CBV, CBF and MTT measurements between normal and decreased temporal frequency. The units for CBV, CBF and MTT are ml, ml/100g/min and seconds respectively.
Figure 3. Bland-Altman analysis of CBF values for normal and increased temporal sampling measurements.

Figure 4. Bland-Altman analysis of CBV values for normal and increased temporal sampling measurements.

Figure 5. Bland-Altman analysis of MTT values for normal and increased temporal sampling measurements.

The Bland-Altman analysis also shows that the measurements with normal and decreased sampling frequencies are interchangeable. The mean value for CBF is 1.1 ml/100g/min and 95% limits of agreement as 23.97 ml/100g/min and -25.98 ml/100g/min. The mean value denotes that there is minimal bias between the two measurements.

In order to compare the clinical significance of our limits of agreement we performed Bland-Altman analysis on the data described in a comparison study between PCT and Xenon CT by Wintermark et al. [4]. Their CBF data for healthy parenchyma without arteries had a mean of -1.964 ml/100g/min and limits of agreement as 21.55 ml/100g/min and -25.48 ml/100g/min. The closeness of their mean to zero and their limits of agreement are comparable to our results. Since these data are generally accepted as showing the interchangeability between PCT and Xenon CT, we can also suggest that our modified injection protocol may be used interchangeably with an increased and normal temporal sampling.

Previous studies have suggested that MTT and CBV thresholds correlated well with clinical outcome for acute stroke patients [6, 12]. The largest of these studies [6] suggested that a relative MTT increase of 45% correlated with viable tissue at risk for infarct, while tissue with a CBV of less than 2.0 ml/100g correlated with unsalvageable, already infarcted tissue. Because inaccuracies in perfusion measurements due to under-sampling should theoretically affect the entire brain uniformly, it is suggested that the relative MTT thresholds to determine abnormal tissue should remain unaffected with reduced temporal sampling. However, since the 95% limit of agreement for CBV measurements was approximately 2.0 ml/100g, it is not recommended that the absolute CBV threshold of 2.0 ml/100g described by Wintermark et al. [6] should be used as a marker for infarcted tissue with reduced temporal sampling. Nevertheless, analysis of data from the multi-center trial of Wintermark et al. [6] also showed a strong correlation between infarcted tissue and a relative CBV threshold of 60% (personal communication), so it is possible that such a relative CBV threshold may be useful for identifying infarcted tissue. Further studies should be conducted to validate this statement.

There may be some concern that increasing the volume of contrast administered for a PCT study may limit the amount that can be used for a succeeding CTA study. It has been shown...
that a contrast volume of up to 150 ml rarely causes any major complications such as renal failure [13]. Even if an increased contrast volume of 75 ml is used for the CT perfusion scan, a typical CTA study can still be performed with 50-75 ml of contrast using modern, multi-slice CT [5].

Conclusion

Increasing the volume of injected contrast agent produced quantitative CBF values in the range of expected physiological values for perfusion scans obtained with four-second temporal sampling.

References


