Quantitative Evaluation of C-Arm CT Cerebral Blood Volume in a Canine Model of Ischemic Stroke

**BACKGROUND AND PURPOSE:** Previous studies have shown the feasibility of assessing qualitative CBV measurements in the angiography suite by using FPD-CBCT systems. We have investigated the correlation of FPD-CBCT CBV lesion volumes to the infarct volume.

**MATERIALS AND METHODS:** Unilateral strokes were created in 7 adult dogs. MR imaging and FPD-CBCT data were obtained after MCA occlusion. FPD-CBCT CBV and ADC maps were generated for all subjects. The animals were sacrificed immediately following the last imaging study to measure infarct volume on histology. The reliability of FPD-CBCT-based lesion volume measurements was compared with those measured histologically by using regression and Bland-Altman analysis.

**RESULTS:** The best correlation \( R^2 = 0.72 \) between lesion volumes assessed with FPD-CBCT and histology was established with a threshold of mean healthy CBV \( -2.5 \times SD \). These results were inferior to the correlation of lesion volumes measured with ADC and histology \( R^2 = 0.99 \). Bland-Altman analysis showed that the agreement of ADC-derived lesion volumes with histology was superior to the agreement of FPD-CBCT-derived lesion volumes with histology.

**CONCLUSIONS:** We correlated FPD-CBCT measurements of CBV and MR ADC lesion volumes with histologically assessed infarct volume. As expected, ADC is a very accurate and precise method for determining the extent of infarction. FPD-CBCT CBV lesion volumes are correlated to the size of the infarct. Improvement of FPD-CBCT image quality provides an opportunity to establish quantitative CBV measurement in the angiography suite.

**ABBREVIATIONS:** CTP = CT perfusion; FPD-CBCT = flat panel detector conebeam CT; HU = Hounsfield units; NSA = number of signal-intensity averages; \( R^2 \) = coefficient of determination; RMSE = root-mean-square error; SD = standard deviation; \( t_{lesion} \) = lesion threshold; TOF = time-of-flight; TTC = 2,3,5-triphenyltetrazolium chloride; \( V_{lesion} \) = lesion volume

**ORIGINAL RESEARCH**

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**INTERVENTIONAL ORIGINAL RESEARCH**
studies showed that CBV maps assessed with FPD-CBCT correlated well with conventional CT protocols. Most important, observers were able to successfully detect reduced CBV in >80% of the cases in FPD-CBCT CBV in a qualitative fashion.

To enable discrimination between healthy tissue and ischemic core quantitatively, a threshold for infarction should be established. Previously reported studies in humans showed that ischemic core could be identified by absolute CBV or using a relative CBV threshold.14

We have investigated the feasibility of determining a CBV lesion threshold and calculating lesion volumes on the basis of CBV assessed with a FPD-CBCT system in a canine model of acute ischemic stroke. A CBV lesion threshold was identified by optimization of a linear regression model with respect to criterion standard lesion volume measurements obtained with histology. Volume measurements that showed the best agreement with histology were evaluated by using a Bland-Altman analysis. In addition, lesion volumes were determined from ADC maps derived from DWI.

Materials and Methods

Stroke Preparation

Experiments were approved by the Institutional Animal Care and Use Committee of the University of Massachusetts. Stroke was induced in 7 purpose-bred canines (beagles, mean weight of 10.0 kg) by injection of an autologous blood clot into the left or right, randomly selected, ICA under fluoroscopic guidance by using a 5F catheter, as previously described.15 Thrombin-induced autologous clot (4 National Institutes of Health unit/mL blood) was prepared in silicone tubing 1 day before the experiment. Mean diameter and length of clot for injection were 2.33 and 10.0 mm, respectively. To facilitate visualization of the clot under x-ray, we added barium sulfate into the blood/thrombin mixture at a concentration of 1.0 g per 10.0 mL of blood. During the procedure, animals were anesthetized by intramuscular injection of acepromazine (0.06 mg/kg), glycopyrrolate (0.01 mg/kg), and thiopental (15.0 mg/kg). Anesthesia was maintained during the entire procedure by mechanical ventilation of 2%–3% isoflurane in a 1:1 oxygen and air mixture. Physiologic monitoring, including heart rate, blood pressure, arterial oxygen saturation, temperature, end-tidal CO₂, blood glucose, and blood gases, was performed and recorded every 15 minutes during the procedure.

After injection, clot location was confirmed with conventional angiography and the animal was transferred to the MR imaging scanner for sequential perfusion imaging and DWI. At 4 hours following stroke onset, the animals were returned to the angiography suite for FPD-CBCT imaging. Animals were euthanized after completion of all data acquisitions with an overdose of sodium pentobarbital. Histology was performed on coronal brain sections by TTC staining.16,17 Infarct volumes were determined by a section-by-section manual segmentation of the infarct areas and multiplication with section thickness. Infarction was also confirmed qualitatively by analyzing sections stained with Fluoro-Jade C.

Image Acquisition

MR imaging data were obtained before stroke induction and 240 minutes after clot injection. FPD-CBCT data were acquired within 10 minutes of the last DWI.

MR imaging was performed on a 3T whole-body MR imaging scanner (Achieva; Philips Healthcare, Best, the Netherlands) by using an 8-channel knee coil. We used multislice Dual-SE sequence (TR/TE1/TE2 = 2630/15/80 ms, flip angle α = 90°, NSA = 2, FOV = 110.0 × 140.0 mm², acquired pixel size = 0.4 × 0.4 mm², 54 sections with thickness = 2.0 mm, no section gap), a spin-echo EPI DWI sequence (TR/TE = 2580.776 ms, flip angle α = 90°, NSA = 6, turbo = 29, FOV = 130.0 × 130.0 mm², acquired pixel size = 0.9 × 0.9 mm², 75 sections with thickness = 3.0 mm, no section gap), a 3D TOF sequence (TR/TE = 19.9/3.6 ms, flip angle α = 20°, NSA = 1, FOV = 130.0 × 130.0 mm², acquired pixel size = 0.2 × 0.2 mm², 100 sections with thickness = 1.0 mm, section gap = −0.5 mm), and a fast-field echo EPI perfusion sequence (TR/TE = 1500.0/20.1 ms, flip angle α = 40°, NSA = 1, FOV = 110.0 × 110.0 mm², acquired pixel size = 0.3 × 0.3 mm², 12 sections with thickness = 3.0 mm, section gap = 1.0 mm).

FPD-CBCT data were obtained on an x-ray angiography C-arm system (Allura Xper FD20; Philips Healthcare) with a cerebral soft-tissue protocol. Before all acquisitions, a system-specific air calibration of the C-arm system was performed. FPD-CBCT data (FOV = 251.5 × 194.5 × 251.5 mm³, voxel size = 0.98 mm³) were reconstructed from 600 x-ray images generated during a 20-second rotational motion of the x-ray source over approximately 200°. The first dataset was obtained without contrast. The second dataset was acquired with administration of contrast (iodamido 51%, Iopamiron; Bracco, Milan, Italy) intravenously with a power injector (Mark V ProVis; Medrad, Indiana, Pennsylvania) at an infusion rate of 2.0 mL/s for a total of 80.0 mL. Acquisitions were started after a delay of 25 seconds in order for the contrast agent to reach a steady state in the parenchyma.12

Image Processing and Data Analysis

ADC maps were generated with software available on the MR imaging console and analyzed by using Matlab (MathWorks; Natick, Massachusetts). Voxels with ADC values below 0.53 × 10⁻³ mm²/s were identified as lesion voxels and were automatically segmented.18 Subsequently, total lesion volumes were calculated.

In 3 cases, registration of the baseline run FPD-CBCT data to the contrast run was necessary because of subject motion between scans. In the remaining cases, baseline data were aligned with contrast-enhanced data without additional registration. 3D rigid registration was performed with elastix (http://elastix.isi.uu.nl)19 by using a stochastic gradient descent optimization routine and a mutual information similarity measure. Results of the registrations were all successful on visual inspection.

For all datasets, brain volumes were semiautomatically segmented from the T2-weighted Dual-SE data by an experienced observer (M.M.) using a region-growing algorithm. Subsequently, the ventricles, sinuses, and large veins were segmented by using the same technique from the proton-density-weighted Dual-SE data. Brain masks without these structures were generated by subtracting them from brain segmentations, and these masks were registered to the FPD-CBCT data. CBV expressed in milliliters per 100 g, defined as

\[
CBV = \frac{\Delta HU_{\text{brain}}}{\Delta HU_{\text{blood}}} \times V_{\text{oxel}} \times N \times h
\]

was calculated for all voxels within the brain mask with in-house-developed software by using the Insight Segmentation and Registration Toolkit (http://www.itk.org).20 \(\Delta HU_{\text{brain}}\) and \(\Delta HU_{\text{blood}}\) represent the difference in Hounsfield units at baseline and at steady-state contrast injection of brain tissue and blood, respectively. \(\Delta HU_{\text{brain}}\) was calculated by voxelwise subtraction of the baseline from the contrast injection.
anisotropic diffusion filter (conductance representations of the CBV values) were created. To reduce noise, a Pseudo-to-large vessel hematocrit values. CBV maps (ie, voxelwise reconstructed data before subtraction.

For all subjects, mean CBV values 0.625, and 5 iterations) was applied to baseline and contrast reconstructed data. Here, CBV values are visualized by a color scale, in which red and blue indicate high and low CBV, respectively. Mean healthy and ischemic CBV values for all subjects measured in the VOIs were 4.23 mL/100 g (range, 3.60–12.53 mL). Ischemic regions for all subjects were visualized and identified by FPD-CBCT CBV. Figure 2C gives representative FPD-CBCT-assessed CBV data overlaid on the non-contrast-enhanced CBCT data. Here, CBV values are visualized by a color scale, in which red and blue indicate high and low CBV, respectively.

Healthy and ischemic regions were localized by using histology data. Lesion volumes (Vlesion) in milliliters were determined by applying various lesion thresholds (tlesion) to the masked CBV data. Lesion thresholds were based on healthy CBV values measured in the normal hemisphere of the brain. Because the CBV values are subject to image noise and values may differ for different brain tissue types, CBV values measured in a VOI will result in a distribution of values. We, therefore, propose using mean CBV in a healthy VOI offset by a multiple of the σ in that VOI.

In this equation, k represents the multiplicative factor.
mean difference (SD) for CBV-histology and ADC-histology agreement were 2.18 (2.94) and 0.02 (0.64) mL, respectively.

**Discussion**

Recently performed research has made great advances in the assessment of qualitative CBV measurements in the angiography suite.

In this study, we have investigated the feasibility of using an FPD-CBCT system for the quantitative assessment of CBV with the objective of measuring lesion volume after stroke. Calculation of CBV values with FPD-CBCT required high-resolution pre- and postcontrast FPD-CBCT scans. Each of these acquisitions produces a patient radiation dose of approximately 50 mGy, which corresponds to that in a conventional head CT. To establish complete steady-state saturation with contrast through all brain parenchyma, we used a relatively high contrast load. Optimization of the infusion rate and total contrast volume is required before this technique can be implemented in clinical routine. CBV was assessed in a canine model of ischemic stroke. Mean CBV values were measured in bilateral VOIs in ischemic and healthy tissue. Overall mean normal CBV was 4.23 ± 1.01 mL/100 g, which is higher than the values reported by Ahmed et al, who found a mean CBV of 2.30 mL/100 g.

For all subjects, CBV measured in the ischemic regions was significantly lower than CBV in healthy regions. Lesion volumes were determined by 5 thresholds, which were chosen to be \( k \) times the SDs below the mean normal CBV, where \( k \) varied between 1.0 and 3.0. Subsequently, lesion volumes calculated with CBV and ADC were compared with volumes measured with histology. The experiments showed that the best agreement \( (R^2 = 0.72) \) was obtained when a lesion threshold of 2.5 was used. In a previously reported study, a lesion threshold of 55% of the normal CBV value was proposed for humans. In our experiments, this would correspond to a \( k \)-value of 1.8.

The results imply that on the basis of FPD-CBCT CBV, lesion volumes can be predicted with moderate reliability. The correlation was inferior to that obtained with ADC lesion volume measurements \( (R^2 = 0.99) \). The Bland-Altman analysis showed that the CBV lesion volume measurements contain a positive bias of 2.18 mL, which implies that on average, lesion volumes by CBV are underestimated and the SD (2.94 mL) of CBV lesion measurements is relatively large. Lesion volumes obtained with ADC showed excellent agreement with histology, a mean difference and SD of 0.02 mL and 0.64 mL, respectively.

The differences in healthy CBV values compared with those reported by Peterson et al, who found CBV of 2.9 ± 1.4

| Subject | CBV (SD) mL/100 g | CBV (SD) mL/100 g |
|---------|------------------|------------------|
| 1       | 4.42 (2.33)      | 0.80 (0.92)      |
| 2       | 3.77 (1.68)      | 0.43 (1.80)      |
| 3       | 3.17 (1.10)      | 1.05 (0.50)      |
| 4       | 4.47 (1.53)      | 0.85 (0.48)      |
| 5       | 6.28 (2.29)      | 3.46 (1.52)      |
| 6       | 3.60 (0.68)      | 0.63 (0.55)      |
| 7       | 3.91 (0.97)      | 0.78 (0.44)      |

* Values were calculated for selected volumes of interest of 0.12 mL.

left and right graphs, respectively. Mean difference (SD) for CBV-histology and ADC-histology agreement were 2.18 (2.94) and 0.02 (0.64) mL, respectively.
and 2.5 ± 1.5 mL/100 g in gray and white matter by using CTP, respectively.\textsuperscript{23} may be a result of nonlinearities of the FPD-CBCT system. In a study previously presented, we have characterized the noise of a FPD-CBCT system by using a water phantom.\textsuperscript{24} The root-mean-square deviation from the theoretic value of water was 9.4 HU with a mean SD of 19.1 HU. These results show that in order for FPD-CBCT CBV to be used quantitatively, CBCT image quality should be improved by reducing detector noise and photon scatter.

The results show that though an ischemic lesion can be identified qualitatively with FPD-CBCT CBV, quantitative lesion volume measurements in FPD-CBCT CBV are currently inferior to measurements performed with ADC, which showed better agreement with histology. The reliability of FPD-CBCT CBV is mainly limited by imaging physics.

**Conclusions**

We can conclude that FPD-CBCT CBV has great potential for in situ assessment of cerebral hemodynamic changes, which may benefit patient triage. Although healthy and infarcted tissue were qualitatively distinguishable by intrasubject analysis of FPD-CBCT, imaging quality should be further improved to generate quantitative CBV maps. Reliability of FPD-CBCT CBV could be improved by reducing image noise and photon scatter.

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