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CT Density Changes with Rapid Onset Acute, Severe, Focal Cerebral Ischemia in Monkeys

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Abstract Computerized tomography (CT) is the most often used imaging modality in the evaluation of acute clinical stroke. However, the rapidity with which CT density changes occur after acute, severe, focal ischemia *cannot* be determined clinically. Even if the time of symptom onset is known, clinical stroke severity is highly variable. We studied the time course of CT density change after severe, rapid onset, acute, focal ischemia as documented by stable xenon CT cerebral blood flow (CBF) in monkeys. Eight monkeys (*Macaca mulatta*) were subjected to transorbital occlusion of the left posterior cerebral, anterior, middle, and internal carotid arteries to induce focal ischemia. CT density Hounsfield units (HU), CBF by stable xenon CT, arterial blood pressure, and blood gases were measured before occlusion, immediately after occlusion, at 30 min, and hourly for up to 6 h. Occlusion of the cerebral arteries decreased CBF to 8±5 ml/100 g/min within 15 min postocclusion. At 6 h, CBF was unchanged at 9±4 ml/100 g/min. CT density within the ischemic core fell from 42 to 38 HU immediately after occlusion ($P<0.05$), rose transiently, then fell at 2 h ($P<0.01$) and plateaued at 36±5 HU for a total decrease of 4–5 HU between 4 and 6 h poststroke. Changes in CT density lag severe focal ischemia by 2 h. Thus, when CT hypodensity is seen in acute stroke, it is likely 2 h old. It also provides an explanation for the phenomenon of clinical CT mismatch with clinical deficits and normal CT.

Keywords Acute stroke · Cerebral blood flow · Computerized tomography · Stable xenon

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Introduction

Presently, the only FDA-approved interventional therapy for acute ischemic stroke is recanalization by either tissue plasminogen activator (tPA) [1, 2] or thrombolectomy [3, 4]. Application of these therapies, however, requires rapid and accurate assessment of the etiology and severity of the stroke. The risk for symptomatic hemorrhagic transformation (HT) with recanalization of about 6.4 % with thrombolysis compared to 0.6 % with placebo [1] can go as high as 40 % (including asymptomatic HT) in patients treated by thrombolysis despite infarctions [2].

Magnetic resonance diffusion-weighted imaging (DWI) has proven effective in evaluating acute stroke [5, 6] and is more sensitive in detecting stroke with better inter-rater reliability than non-enhanced computerized tomography

(CT) [7, 8]. However, CT is the most accessible modality for rapid assessment of hemorrhage and infarction in acute stroke [9, 10] especially with the availability of quantitative, stable xenon CT cerebral blood flow (CBF) [11–14] and qualitative CT perfusion [15–18]. The combination of non-contrast CT (NCCT), CT angiography (CTA), and CTA source images combined compare favorably with diffusion-weighted MRI in detecting and predicting infarction [19]. However, primarily because of availability, no screening, rapidity, and ease, CT is the most frequently used imaging modality in the rapid assessment of acute stroke.

In clinical CT imaging of acute stroke, it is recognized that the degree of hypodensity is a function of both the severity and duration of the ischemia reflecting tissue water content [20, 21] and indicative of infarction [9, 15, 22–24]. However, when NCCT scan is obtained in an acute stroke patient, the images can only show whether or not the ischemia was sufficiently severe or prolonged to have caused an infarction at that point in time. The absence of CT change in a scan 6–8 h after symptom onset in verified time of onset ischemic stroke raises the question as to whether the patient could be safely recanalized. Based on the premise that CT hypodensity defines infarction, we sought to determine the rapidity with which CT hypodensity develops with acute, severe, ischemic stroke as documented by quantitative, stable xenon CT CBF. We also sought to determine whether our model of middle cerebral artery (MCA) stroke results in a progressively expanding volume of infarction core.

Methods

Animals and Surgical Procedures

Following a protocol approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh, eight rhesus monkeys (*Macaca mulatta*), five females and three males, weighing 8.5±3 kg, were purchased with complete health records and quarantined for a period of 30 to 90 days. After quarantine, the animals were housed in the Division of Laboratory Animal Resources of the University of Pittsburgh in a room on a 12-h dark–light cycle and under the care of the veterinary staff. The monkeys were fasted nothing per ostium for 6–8 h before the study.

On the day of the study, the monkeys were anesthetized with ketamine 10 mg/kg and atropine 1 mg, i.m., their tracheas intubated with cuffed endotracheal tubes, and a peripheral venous catheter (20 ga. Intracath) inserted for continuous i.v. fluid replacement (saline at 5 ml/kg/h). Femoral artery catheters were inserted via cutdown to monitor arterial pressure and for arterial blood gas sampling and analyses. Femoral vein catheters were inserted for fluid replacement and drug infusions.

Anesthesia was continued with fentanyl/diazepam (fentanyl 25 μg/kg bolus followed by a dose of 25 μg/kg/h plus diazepam 2–5 mg/h) during surgery and throughout the study. Initial EEG and bispectral index (BIS) readings were obtained (using an Aspect EEG monitor model, A-1000, Aspect Medical Systems, Inc., Boston, MA) and fentanyl infusion rate adjusted to maintain a BIS reading of 40 to 60. The monkeys were mechanically ventilated to maintain continuously monitored end-tidal CO2 at about 5–6 %. Physiologic parameters of arterial pressure and end-tidal CO_2 were continuously recorded using a portable bedside computerized data acquisition system (MP100WSP, Biopac Systems, Inc, Goleta, CA) at 20 Hz. Rectal temperature was continuously monitored and maintained at 37±0.5°C throughout the study. Physiological variables were maintained within normal limits throughout the study ranging between (mean±SD): mean arterial pressure, 93±11 to 109 ±7 mmHg; and end tidal CO_2, 30±3 to 37±12 mmHg without any significant trends in either variable.

Transorbital Occlusion of Cerebral Arteries

The left eye was enucleated, the optic foramen was enlarged superiorly and laterally, and the dura was incised. The subarachnoid space was dissected to expose the middle cerebral artery, the internal carotid artery, and the anterior cerebral artery. The posterior communicating artery was followed posteriorly to expose the posterior cerebral artery. The posterior cerebral artery (P2) and the anterior cerebral artery (A1) were cauterized. The middle cerebral artery (M1) was looped with 4–0 suture and a tourniquet formed by delivering both ends through a 23-gauge Intracath and the internal carotid artery looped with 4–0 silk for occlusion after the MCA is occluded in the CT scanner. The orbit was packed with gauze with the hub of the Intracath protruding beyond the orbit for occlusion of the MCA and ICA within a few seconds of each other to initiate the stroke while in the CT scanner.

Fig. 1 Stable xenon cerebral blood flow maps at four different axial levels in a nonhuman primate 4 h after transorbital occlusion of the left posterior cerebral artery (P2), middle cerebral artery, anterior cerebral and internal carotid artery to create a large, cortical and subcortical, well-defined, acute and severe stroke

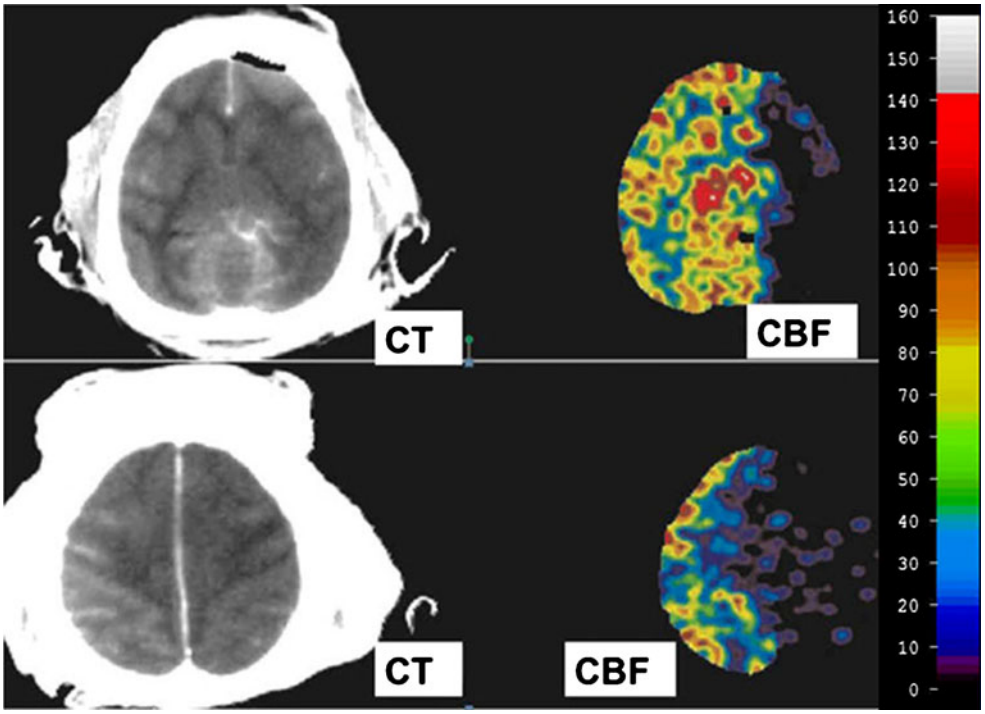

Fig. 2 Illustration of source computerized tomography (CT) (*left panel*) and stable xenon CT cerebral blood flow (CBF) map (*right panel*) 4 (*top*) and 2 h (*bottom*) after a rapid onset, acute severe stroke in two nonhuman primates after transorbital occlusion of the left posterior cerebral (P2), middle cerebral, internal carotid and anterior cerebral arteries. Note the hypodensity in the source CT corresponding to the area of the stroke in both monkeys

Stable Xenon Cerebral Blood Flow

A GE Lightspeed CT scanner equipped with the hardware and software for xenon/CT CBF studies (Diversified Diagnostics Products, Houston, TX) was used. Sixty-second cine series were obtained at 80 kVP and 190 mA. The scanner acquired four continguous 5-mm slices with a 1-s rotation time. The reconstructed field of view was 120 mm. The monkeys were placed supine in the scanner and their heads immobilized with towels, vacuum bags, and tape. Stable xenon CBF measurements were made by the administration of 33 % xenon in oxygen (XeScan, Praxair Pharmaceutical Gases, Danbury, CT) in oxygen for a period of 4.3 min with a minimum of 15 min between studies as previously described [25–27].

Axial CBF maps drawn parallel to the orbitomeatal line were made at four levels in 5-mm thick contiguous slices, at the level of the midbrain, the basal ganglia, the cerebral ventricles, and the cerebral cortex (Fig. 1). The level of the axial scan chosen was based upon the CBF maps showing

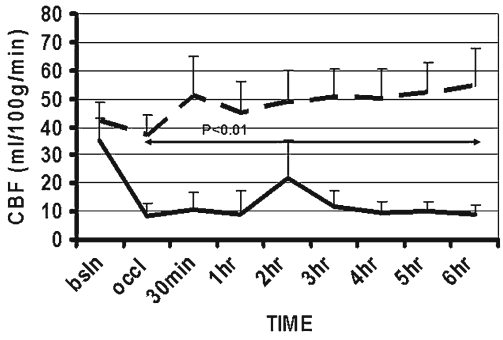

Fig. 3 Stable xenon CT cerebral blood flow (CBF) in the ipsilateral stroke volume defined by the black "zero flow" CBF regions on the map as illustrated in Figs. 1 and 2. Volumes of interest (VOI) of equal volume to the "core" volumes observed in the *ipsilateral* ischemic hemisphere were drawn on the *contralateral* hemisphere in eight nonhuman primates (*M. mulatta*) for up to 6 h after an acute severe stroke. Note that the data points are in between each of the time marks indicated on the *X*-axis. Differences in ischemic and normal CBF values of the ipsilateral and contralateral hemispheres, respectively, were significant ($P<0.01$) immediately after occlusion and for all subsequent points thereafter. Error flags=SD

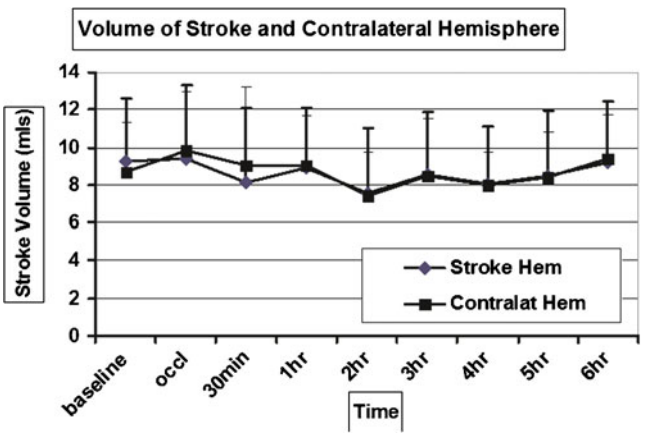

Fig. 4 Ischemic volumes (milliliters) and a mirror area on the contralateral hemisphere from which the CBF values were obtained in Fig. 3 in eight NHP before and after induction of a large focal ischemia showing that there was no significant change with time in the ischemic volume. No significant differences were observed between or within groups or between groups in ischemic pixel volume. Error flags=SD

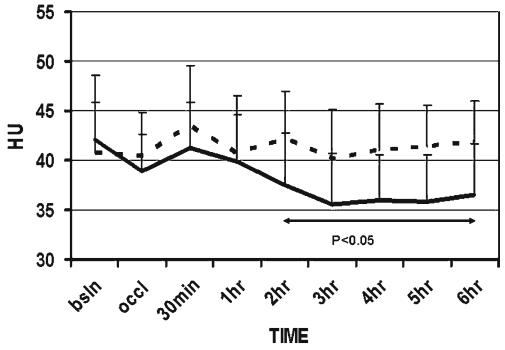

Fig. 5 CT density (Hounsfield units) in the area of the stroke as defined by the black regions of low CBF and in a mirror area for up to 6 h in eight NHP (*M. mulatta*). A significant difference ($P<0.05$) occurred immediately after occlusion, at 2 h ($P<0.01$) and thereafter between the stroke and mirror area on the contralateral hemisphere. Error flags=SD. See also Table 1

the largest area of CT-defined infarction in the 6-h scan which was either at the level of the basal ganglia or the cerebral ventricles, levels 1 or 2 (Fig.1). After selection of the level for analysis of the stroke, the volumes of interest (VOI) for the strokes were traced on the CBF areas of zero flow volume (black). However, in so doing, it included regions of greater than zero flow within the "black core" volumes of interest. The result is that CBF values averaged <10 ml/100 g/min flow as indicated by the quantitative CBF scale (Fig. 2, right panel CBF) which was simultaneously drawn on the CT image (Fig. 2, left panel CT). The <10 ml/100 g/min CBF rather than being set as a threshold was the mean of the CBF values obtained in the defined area of the stroke defined as "core." VOIs of equal size to the "core" VOI in the ischemic hemisphere were drawn to on the contralateral normal hemisphere for comparison. The volume of the VOI and the average CBF and Hounsfield units (HU) were obtained on both ischemic and contralateral hemispheres. Baseline CBF before occlusion was obtained based on the average CBF in the same regions drawn after the stroke. Both preocclusion baseline CBF scans were averaged to provide one baseline CBF map for both the ipsilateral and contralateral hemispheres. CT hypodensities were obtained within the regions of the stroke "core" with CBF values ranging less than <10 ml/100 g/min is below or at a level consistent with infarction by CT [28, 29].

Data and Statistical Analysis

The CBF, CT density (HU), and volume of CBF regions with CBF <10 ml/100 g/min were obtained before and after induction of focal ischemia and at 30 min and hourly for up to 6 h after occlusion. All values presented are mean±SD. The average values for each of these variables were obtained and at each time point and compared in time by repeated measures ANOVA (Prophet, AB Tech Corp) for each of the variables. A $P<0.05$ was considered statistically significant.

Results

The size and severity of the stroke produced in the MCA territory are shown by the 6 h postocclusion CBF maps (Figs. 1 and 2). The xenon blood flow maps show that within the ischemic core, there are regions or islands of perfusion. These regions could not be isolated in defining the core by visually hand-drawn voxels of interest (VOI) which necessarily includes these islands of perfusion. The result is that the CBF value within the "core" based on CBF is about ≤10 ml/100 g/min instead of zero flow.

Immediately after occlusion of the MCA and ICA, there was a sharp decrease in CBF in the ipsilateral hemisphere (Fig. 3) falling to 10–13 ml/100 g/min within 15 min after occlusion and remaining at that level throughout the 6 h of occlusion. The volume of the ischemic region was relatively constant ranging between 8 and 10 ml over the 6 h (Fig. 4). The volume of the VOI on the contralateral hemisphere was intentionally mirror matched to the volume in the ipsilateral hemisphere (Fig.3).

CT density changes showed a progressive decline with the onset of stroke reaching statistical significance immediately after occlusion ($P<0.05$) but transiently returning toward normal at 30 and 60 min postocclusion. Thereafter, there was a significant secondary decrease at 2 h which remained at that level for up to 6 h ($P<0.01$) (Fig. 5 and Table 1).

Discussion

Our findings in the monkey model of acute ischemic stroke reveal several important aspects of CT imaging in acute

Table 1 CT density (Hounsfield units) changes (mean±SD) in eight monkeys before and after occlusion of the PCA, MCA, and ICA

Hemisphere	Bsln	occ	30 min	1 h	2 h	3 h	4 h	5 h	6 h
Ischemic	42±7	39±4*	40±5	40±5	37±5*	36±5*	36±5*	36±5*	36±5*
Contralateral	41±5	41±4	42±6	41±6	42±5	41±5	41±5	41±4	41±4

*$P<0.01$ compared to corresponding mean in the contralateral hemisphere by paired repeated measures analysis

stroke that may be relevant to acute clinical stroke. First, within the volume of core with zero flow, we observed islands of perfused cortical tissue likely from leptomeningeal vessels creating variously perfused cortical regions within the volume of interest defined as "core" (Figs. 1 and 2). In patients enrolled in the DEFUSE study [30], 70 % of acute strokes had the "archipelago" pattern of flow, where islands of penumbra tissue were within the core volume, and in 30 %, the core was uncontaminated by penumbral tissue as historically depicted by a solid core surrounded by a penumbra [31]. The VOI we demarcated as core actually had an average flow of ≤10 ml/100 g/min. This is relevant to core volumes imaged by CT or CT perfusion or MRI (DWI and perfusion mismatch) because "core" volumes may contain penumbra or regions of higher flow. Therefore, it is not surprising that MRI DWI and PWI mismatch must approach 260 % before acceptable sensitivity and specificity levels can be achieved [32]. Voxel analysis of CT or MRI data could enable quantitative separation of core and penumbra volumes [33].

Second, in our model, acute, severe, ischemia with CBF values falling to ≤10 ml/100 g/min, a level associated with ischemic infarction [28, 29], decreased ($P<0.05$) CT density by 3 HU from 42±7 to 39±4 in about 15 min. CT density changes of 2 HU may be visible, but a 5-HU decrease is definitely visible [20]. CT density continued to decline with time reaching a significant ($P<0.01$) 5-HU decrease compared to the contralateral hemisphere at 2 h and beyond at 37±5 versus 42±5 ($P<0.01$). Thus, the time required for CT density to visibly change after an abrupt, severe ischemia to CBF values <10 min/100 g/min occurs in approximately 2 h. The magnitude of the change we observed is similar to the magnitude of changes in HU observed in acute ischemic stroke in patients with CT density decreasing by 1 to 2 HU within 6 h [21, 34]. However, because CT density changes reflect changes in brain tissue water content, prolongation of the duration of ischemia resulting in tissue necrosis and edema continues for days after stroke resulting in much higher water content [21, 34].

The delay between the change in CT density relative to the fall in CBF and thereby neurologic dysfunction is the basis for the clinical-CT mismatch hypothesis which predicts that a large mismatch between neurologic deficit (and the phenomenon of mismatch between clinical neurologic exam, i.e., NIH Stroke Scale and change in CT density) where a lack of change is associated with marked neurologic deficit as a basis for tPA administration. Analysis of several four major clinical trials on i.v. tPA therapy for clinical-CT mismatch using the Alberta Stroke Program Early CT Score (ASPECTS) showed that the magnitude of the mismatch did not identify patients who would benefit from i.v. tPA therapy [35]. However, the many problems associated with the use of the ASPECTS CT score including the percentage of patients showing recanalization with thrombolytic therapy obscure the conclusions.

Third, given the 2-h delay, early clinical CT hypodensity is indicative of a rapid onset, severe, acute, ischemic insult at CBF values below the critical level for infarction [28, 29] that is also associated with a higher risk for hemorrhagic transformation [17]. Conversely, if early CT changes are not visible several hours after symptom onset suggests that the severity of ischemia has not achieved a critical level.

Finally, the magnitude of the change in hypodensity is indicative of the severity of edema which relates to blood–brain barrier permeability and risk of hemorrhagic transformation. Acute ischemic stroke patients with CT hypodensity greater than 5 HU treated with tPA hemorrhaged with a positive predictive value of 86 % and a negative predictive value of 100 % [21], whereas CT density decrease of less than 4 HU fell within the non-hemorrhage group. A CT density change of 5 HU as observed in our study correlates with a 3.3 % increase in water content using a value of 1.5 HU/percent increase in water [20, 21, 36]. Clinically, symptomatic parenchymal hemorrhage occurs after recanalization after severe ischemia, i.e., CBF≤10 ml/100 g/min involving 20 to 80 % of the MCA territory [31].

Conclusions

Our results show that visible CT hypodensity lags an acute, severe, ischemic decrease in CBF by about 2 h. The results also show that our model of transorbital occlusion results in a well-defined fixed ischemic insult rather than a progressively expanding volume of core infarction.

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