Observation of Mean Transit Time (Mtt) Perfusion Maps on a 320-Detector Row Ct Scanner and its Potential Application in Acute Ischemic Stroke

Haitham Dababneh1, Waldo Guerrero1, Kelvin Wilson2, Brian L. Hoh2, J Duffy Mocco2, Jeffery Bennett3 and Michael F. Waters1*4

1Departments of Neurology, University of Florida, College of Medicine, Gainesville, FL 32610
2Neurosurgery, University of Florida, College of Medicine, Gainesville, FL 32610
3Radiology, University of Florida, College of Medicine, Gainesville, FL 32610
4Neuroscience, University of Florida, College of Medicine, Gainesville, FL 32610

Abstract

Background and Purpose: We present three patients with acute ischemic stroke who underwent computed tomography perfusion (CTP) imaging utilizing an Aquilion ONE (Toshiba Medical Systems, Nasu, Japan) 320-detector row CT scanner using a Singular Value Decomposition Plus (SVD+) algorithm to generate perfusion maps. These MTT maps may prove to be a sensitive and specific predictor of ischemic penumbra (IP) and infarct core (IC).

Methods: Patients, who presented with an acute ischemic stroke, received high quality whole-brain CTP scans and a follow up MRI or non-contrast CT (NCCT) scan, and underwent successful pharmacological and/or interventional reperfusion procedures were selected for evaluation. A neuroradiologist utilizing Vitrea FX 3.1 software reviewed images, and the IC volumes were calculated.

Results: A comparison was made between the volumes of infarct core utilizing SVD+ MTT maps and DWI MR sequences or a sub-acute NCCT. There was a correlation between the infarct core volume measured on MTT and final infarct volume on follow up imaging. However due to limitations associated with a small sample size, a statistical correlation cannot be definitively calculated from this data set.

Conclusions: Utilization of the SVD+ MTT map may allow for a more accurate assessment of the infarct core and surrounding salvageable tissue as compared to cerebral blood flow/cerebral blood volume (CBF/CBV) mismatch though further studies are required to validate this observation.

Keywords: Mean transit time; Ischemic penumbra; Infarct core; CT Perfusion; Singular Value Decomposition plus; Deconvolution; Interventional endovascular procedures

Introduction

Ischemic penumbra (IP) was first proposed by Astrup in 1981 [1] referencing regions of brain tissue where blood flow is sufficiently reduced to result in hypoxia and dysfunction of physiologic function, but not severe enough to cause irreversible damage and necrosis in an acute ischemic stroke [2,3]. Identifying the mismatch between IC and IP allows the possibility of identifying patients who may have a higher likelihood of benefitting from aggressive interventional therapies. The current medical standard for rescue of the IP is intravenously administered tissue plasminogen activator within 4.5 hours of symptom onset. Select studies have suggested that systemic thrombolysis is safe up to 9 hours postictus [4,8]. Further, new advances in interventional procedures such as Penumbra and Merci have expanded the time window for acute stroke treatment. Recently, CTP has become more available in emergency rooms for assessment of technically adequate quality, and 3) had successful pharmacological uniformity. It utilizes whole head volumetric coverage and delay insensitive SVD+ brain perfusion software allowing for more accurate and complete analysis of cerebral perfusion. MTT maps have become more reactive to flow changes with the introduction of the SVD+ perfusion algorithm. We have observed that areas of decreased mean transit time on MTT maps correlate with areas of restricted diffusion on MR imaging.

Materials and Methods

We selected three acute, large vessel stroke patients presenting to the emergency department between the dates of November 2010 and May 2011 who: 1) experienced a unilateral large vessel stroke, 2) underwent both whole-brain CTP as part of our acute stroke protocol and a follow up MRI or NCCT scan as a part of their standard work up all of technically adequate quality, and 3) had successful pharmacological...
and/or intervensional reperfusion procedures. None of the patients had evidence of hemorrhage on initial or follow-up non-contrast CT. (Table 1) provides detailed summaries of patient demographics. Images were reviewed by a neuroradiologist utilizing Vitrea FX 3.1 (Vital, Toshiba America Medical System) software including CTP, MRI, and NCCT. 5mm slices were evaluated. The time to peak (TTP) was first used to identify areas of brain tissue with delayed perfusion. In our experience, the average value of MTT in the presumed infarct core is less than 3 seconds. This value was chosen to select the presumed infarct core area on each slice within the corresponding area of increased TTP. Vitrea FX 3.1 calculated the area for each slice based on our selection of decreased MTT. The MTT volume was calculated by adding all the areas multiplied by the thickness of each slice. For comparison to final infarct, areas with hyperintense signal on diffusion weighted MRI were selected. The area for each slice was measured, then the total volume of diffusion abnormality was calculated by adding all the areas multiplied by the total thickness of each slice. For the NCCT, the neuroradiologist chose the region of hypodensity believed to represent the infarct core. Then the area of hypodensity was calculated and the total volume was obtained by calculating the area of each slice multiplied by its thickness.

Mr image acquisition

MR imaging was performed on either a 1.5 or 3 Tesla (Siemens, USA) whole-body scanner with echo planar capabilities. Diffusion weighted images were obtained using single-shot, spin echo echoplanar imaging with sampling of the entire diffusion tensor. Three high b-value images corresponding to diffusion measurements in different gradient directions were acquired. Double inversion pulses were used to help reduce eddy current effects. The high b-value was 1000 sec/mm² and the low b-value was 0 sec/mm². A repetition time of 7300mS was used. The echo time for each scan was 89mS. Other parameters were FoV (field of view) read of 200mm, image matrix of 1.5x1.5 voxels, slice thickness of 4 mm with 1mm gap, and 2 signals averaging. Isotropic DWI images were reviewed.

Ct perfusion acquisition

The CTP study was performed using the Aquilion ONE. Image acquisition was performed as a dynamic contrast material enhanced scan covering the entire brain with 0.5mm section thickness, 512x512 matrix, and 160mm axial field of view. Omnipaque (50 ml, Iohexol 350, GE healthcare, Shanghai, China) was injected by a power injector at a flow rate of 5 mL/s. Contrast material was injected 7 seconds prior to the start of the dynamic scan. The scanning protocol was: first scan at 7 seconds, followed by continuous intermittent scans at 2-second intervals beginning at 11 seconds. Scans were performed before contrast material bolus arrival (80 kV tube voltage, 150 mA tube current). During the expected period of arterial peak between 18-28 seconds, tube current was increased (80 kV tube voltage, 300 mA tube current). Arterial phase scanning ceased at 36 seconds. During the venous phase, intermittent scans were performed every 5 seconds starting at 40 seconds and ending at 60 seconds (80 kV tube voltage, 150 mA tube current). The scanning speed was 1 second per rotation, and total scanning time was 60 seconds. CT dose index (CTDI) and dose length product (DLP) [15] data were collected from the console for each scan. Effective dose was estimated for each patient by multiplying the DLP by a region specific dose conversion factor for adult head of 0.0021 mSv•mGy•cm⁻¹ [16]. Computed tomography perfusion data were analysed using Vitrea FX 3.1. A region of interest (ROI) of the arterial input function (AIF) was automatically applied on a single branch of the insular segment of the middle cerebral artery (MCA) at the side contralateral to the affected hemisphere. An ROI of the venous output function was also established on the superior sagittal sinus. To minimize the specificity of vasculature, vascular-pixel elimination (VPE) was applied to dynamic CT images before smoothing and subsequent deconvolution analysis. The MTT was calculated after determination of residue function using the delay-compensated SVD+ which is theoretically delay-insensitive and equal to the block-circular SVD method. CBV values were obtained by dividing the area under the curve of the brain tissue by the area under the curve of the venous output function after automatic pixel-by-pixel determination of the start point and discard of the second bolus. Subsequently, CBF values were calculated by dividing the CBV by the MTT in accordance to the central volume principle.

Results

All patients in this study were imaged using the same acquisition protocol and thus the reported dose was equivalent. CTDI for each of the 19 intermittent gantry rotations was 16mGy leading to a cumulative CTDI of 239.7mGy for each patient. Effective dose for each patient was estimated to be 8mSv.

Imaging of patient 1 revealed a left M1 segmental thrombosis. Whole brain perfusion studies revealed an increased TTP in the entire left MCA distribution. MTT was also elevated in the majority of the left MCA territory indicating a large area of potential ischemic penumbra (Figure 1). Re-canalization of the left MCA thrombus was established with Penumbra retrieval device (Penumbra Inc., Alameda, CA, USA). Patient underwent a NCCT of the head 6 days later, which revealed infarct in the area of decreased MTT on initial perfusion studies (Figure 2).

Imaging of patient 2 demonstrated an abrupt cut-off of the right P1 segment of the PCA. Patient received systemic thrombolysis. Follow-up brain MRI (Figure 3A) showed a right PCA infarct, which matched the area of decreased MTT on CT perfusion (Figure 3B).

Imaging of patient 3 revealed an intraluminal clot in the right MCA. MTT was principally increased in the right MCA territory consistent

| Patient | Age | Gender | Onset to imaging | Admission NIHSS | t-PA | Mechanical recanalization | Recanalization at 24 hours |
|---------|-----|--------|------------------|----------------|------|--------------------------|--------------------------|
| 1       | 65  | F      | Unknown          | 20             | No   | Yes                      | Complete                 |
| 2       | 76  | M      | <2 hours         | 7              | Yes  | No                       | Partial                  |
| 3       | 18  | F      | <1 hour          | 15             | Yes  | Yes                      | Complete                 |

Table 1: Summary of patient information.

| Patient | MTT value (seconds) | MTT infarct core volume (cm³) | CT infarct core volume (cm³) | HU | MRI infarct core volume (cm³) | MTT infarct volume as % of final |
|---------|---------------------|-------------------------------|-----------------------------|----|-----------------------------|----------------------------------|
| 1       | 2.91                | 16.75                         | 16.31                       | 19.97 | N/A                         | 102                             |
| 2       | 2.78                | 32.7                          | 36.17                       | 22.16 | 41.2                        | 79                              |
| 3       | 2.49                | 4.55                          | N/A                         | 5.76  | 79                          | 79                              |

Table 2: Comparison of MTT infarct volume with follow up imaging.
with ischemic penumbra, though there was a smaller area of decreased MTT suggestive of infarct core. Patient received systemic thrombolysis and re-canalization with Penumbra retrieval device. Follow up MRI examination (Figure 4A) revealed a correlation between the area of decreased MTT on the perfusion study and DWI hyperintensity on MR imaging (Figure 4B).

The mean MTT value for infarcted tissue was 2.72 seconds. For patient 1, the volume of infarct on MTT was 102% of the volume of infarct on follow-up NCCT. Images for patient 2 demonstrated a volume of infarct on MTT that was approximately 90% of the total infarct volume observed on follow-up CT and 79% as detected on diffusion weighted MRI. Similarly, patient 3 had a volume of infarct on MTT which was 79% of the infarcted volume observed on follow-up diffusion weighed MRI. The mean MTT lesion volume was 18 cm³. Using CT for patient 1 and diffusion MRI for patients 2 and 3, the mean infarct volume on follow-up imaging was determined to be 21 cm³. Thus, the MTT infarct core volume represented 85% of the final infarct volume on follow-up imaging (Table 2 & Graph 1).

Discussion

To our knowledge, studies assessing the efficacy of MTT maps in determination of IC or IP on Aquilion ONE utilizing SVD+ perfusion algorithm have not been published. We have observed that with this technology, MTT maps appear to identify both IC and IP in the evaluation of acute large vessel strokes. However, this observation requires further validation. When evaluating imaging studies in these cases it was noted that the area of final infarct on follow-up corresponded to decreased MTT on the acute CTP study, whereas areas immediately surrounding the presumed infarct core demonstrated increased MTT. The areas delineated by increased MTT may represent the ischemic penumbra. There was consistent overlap between the infarct core volume measured on MTT and final infarct volume on follow up imaging. However, due to small sample size, a statistical correlation could not be definitively calculated.

Graph 1: Comparison of infarct core volume measured on MTT vs follow up imaging in our three patients.
In the evaluation of patients with acute stroke, discriminating IC from IP is of critical importance for differentiating patients who may benefit from revascularization from those who are at high risk for hemorrhagic complications or may not benefit from aggressive intervention. The ischemic penumbra is the area surrounding the infarct core that is physiologically stunned, but potentially salvageable whereas tissue within the infarct core displays necrosis of neuronal and glial elements secondary to severe hypoperfusion at <10-12 ml/100g/ min. Tissue within the surrounding ischemic penumbra while still hypoperfused at approximately 50-60 ml/100 g/min, remains viable if reperfused [17]. The salvagability of tissue in the ischemic penumbra is secondary to the preservation of autoregulatory mechanisms i.e. vasodilatation and collateral flow. When this vasodilatation occurs there is a decrease in velocity across the capillary bed [18]. Inversely, in the infarct core there is capillary lumen obstruction resulting in a relative vasoconstruction [19]. Cells within the ischemic region of dysfunctional yet potentially salvageable tissue are the target of thrombolytic therapy [20-22].

According to literature describing previous MDCT scanners, MTT maps were found to be a more reliable predictor of ischemia than CBF because the MTT values of normal gray and white matter are not significantly different as they are for CBF [14]. However, Wintermark et al, reported that CBF is more specific than MTT in ischemic stroke because MTT values can be prolonged in TIA as well as stroke [23]. Furthermore, various other reports have stated that although MTT is the most sensitive marker for early ischemic lesion, it cannot differentiate between infarct core and ischemic penumbra [24]. Currently the most widely accepted technique for the evaluation of IC and IP on CTP is assessment of CBF/CBV mismatch, where penumbra is defined as the area of decreased CBF but relatively preserved CBV [13,14].

The ability of the MTT maps to detect and accurately display alterations in MTT (i.e. infarct core or penumbra) is both a product of the Aquilion ONE itself and the deconvolution SVD+ algorithm it utilizes to calculate the perfusion maps. SVD+ is a delay insensitive algorithm that uses calculations to account for delayed blood flow, minimize noise, and perform calculations with fast computation, thus ensuring delay insensitivity of MTT. With a single arterial input, each part of the brain will have a different delay due to its distance from the arterial input. This delay using the standard SVD algorithms can potentially display normal brain as having prolonged MTT values at points far from the input [25]. Other sources of delay may be abnormal vasculature or collateral vasculature. This results in MTT maps displaying delayed flow as opposed to reduced travel time through brain tissue. With SVD+, the sensitivity of the MTT map to ischemia is visible in the TTP and delay maps whereas the MTT map is reserved for the capillary velocity [22]. The sensitivity to delayed flow is measured in the TTP and delay maps, thus ensuring that MTT actually represents the capillary velocity [22].

This pilot study demonstrates that MTT maps on the Aquilion ONE 320 detector row CT scanner using SVD+ algorithm software may be useful in differentiating IC from IP. This study is limited by several factors including: 1) CTP and follow-up scans were separated in time and thus susceptible to dynamic changes in the vascular response to ischemia. This may have altered the size of the IC more substantially than what was seen on follow up imaging. The time lag between initial and follow up imaging may have accounted for the volume difference between average MTT and average final infarct volume. This may be overcome in a prospective study in which patients receive an MRI immediately following CTP. 2) Small sample size with an insufficient quantity of patients to statistically support our observation. 3) Definition of IC has yet to be systematically delineated and proven. Based on our observations, an MTT of less than 3 seconds was selected as an indication of IC. In this study, the approximate value for infarct core on MTT was 2.72. This cannot be ideally defined in this study and would require a prospective study to further validate. 4) Resolution of CT images limits exact delineation of IC borders. This can be seen with patient 2 above; infarct core on MTT is judged to be slightly larger than on follow up NCCT.

Conclusion

We believe that the MTT maps produced by the Aquilion ONE 320 detector row CT scanner and calculated with SVD+ algorithm may be a sensitive and specific marker for capillary velocity in acute stroke. Thus, in IC where capillary velocity is increased there is a corresponding decrease in the MTT. In IP where capillary velocity is decreased the MTT is increased. If this observation holds true in further studies, MTT maps generated in this fashion may prove to be a valuable imaging modality in differentiating between penumbra and infarct core, potentially allowing for greater extension of the thrombolytic treatment window in instances when the IC remains relatively small in the presence of a large IP. This would be particularly valuable in identifying salvageable brain tissue in patients with unknown time of symptom onset where brain physiology may be more valuable criteria than the clock in treatment decision making.

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