JVIN Journal of Vascular and Interventional Neurology
OFFICIAL JOURNAL OF THE ZEENAT QURESHI STROKE INSTITUTE

Mean transit time on Aquilion ONE and its utilization in patients undergoing acute stroke intervention

Haitham Dababneh, MD[1*], **Asif Bashir, MD**[1*], **Waldo R Guerrero, MD**[2*], **Kelvin Wilson, MD**[3*], **Mohammed Hussain, MD**[1], **Sara Misthal, MD**[4], **Walter Morgan, MD**[5], **Keith Peters, MD**[6], **Jawad F Kirmani, MD**[1], and **J Mocco, MD MS**[7]

[1] *JFK New Jersey Neuroscience Institute at Seton Hall University, Edison, NJ, USA*

[2] *University of Texas Health Science Center, Houston, TX, USA*

[3] *Neurosurgery, University of Florida, Gainesville, FL, USA*

[4] *Hahnemann University Hospital, Drexel University, Philadelphia, PA, USA*

[5] *Neurology, University of Florida, Gainesville, FL, USA*

[6] *Radiology, University of Florida, Gainesville, FL, USA*

[7] *Neurosurgery, Vanderbilt University, Nashville, TN, USA*

Abstract

Background—Neuroimaging techniques have been beneficial in identifying patients with salvageable penumbra. We sought to validate the mean transit time (MTT) map on computed tomography perfusion (CTP) imaging utilizing an Aquilion ONE computed tomography (CT) scanner running a singular value decomposition plus algorithm in patients with acute large vessel ischemic stroke who underwent endovascular therapy.

Methods—We conducted a retrospective analysis of consecutive patients presenting to the emergency room who met the following criteria: 1) had a large vessel acute ischemic stroke; 2) had a high-quality whole-brain CTP; 3) treated with endovascular therapy; and 4) received a follow-up MRI with diffusion-weighted imaging (DWI) within 48 h. A blinded neurologist, neuroradiologist, and neurosurgeon utilized the Vitrea software to process the images independently using an infarct perimeter method.

Results—Twelve patients met the inclusion criteria. A comparison was made between the volumes of infarct core (IC) utilizing MTT and DWI after accounting for other co-founding factors (i.e., recanalization rate, time between CT and MRI, time to achieve recanalization, and IV t-PA administration). MTT was redefined as capillary MTT (cMTT) which represented evolving capillary flow influenced by hypoxia induced vasodilation/vasoconstriction. We divided the patients into two groups based on the degree of reperfusion: A) patients with a TICI score of IIb or III and B) patients with a TICI score of I or IIa. We compared the two groups and found that the rate of reperfusion significantly affected the volume of the infarct on MTT when compared with a follow-up MRI (p value < 0.04). Furthermore, we found a strong positive correlation $R^2 = 0.6$ between the average MTT infarct volume and the final DWI MR volumes. In addition, the averaged MTT IC volumes were 84% of the final averaged DWI IC volumes.

Conclusion—Although further studies are required to validate this retrospective study, preliminary data suggest that cMTT maps can be a valuable and accurate tool in the assessment of patients with acute stroke who may benefit from aggressive endovascular therapy.

Keywords

Acute ischemic stroke; computed tomography perfusion; endovascular intervention; thrombectomy; thrombolysis; thromboaspiration; diffusion-weighted imaging

Published December, 2014.

***Correspondence to:** H Dababneh, Haitham82@gmail.com

Introduction

Every year 795,000 people experience a new or recurrent stroke in the US. Approximately 610,000 of these are first attacks and 185,000 are recurrent attacks [1]. The Centers for Disease Control and Prevention have noted that aside from being the leading cause of serious long-term disability, the estimated total costs of acute and long-term management following a stroke has an estimated $54 billion impetus every year in the US [1,2]. The financial dividend includes cost of health care services, medications, and missed days of work. As mentioned above, approximately 795,000 strokes occur every year of which an estimated 80%–85% represent the ischemic stroke subtype. In order to optimize patient outcome, timely recognition and prompt intervention to rescue the "at-risk tissue" or the penumbra during an ischemic stroke is essential. In addition to obtaining a proper history and physical exam, imaging modalities play an essential role in augmenting the diagnostic value and formulating subsequent treatment strategies for strokes. The utility of performing computed tomography (CT) during an acute phase of the stroke has been augmented by additional modalities such as CT angiography and CT perfusion. In fact, the application of this combined approach has been coined as "multimodal CT imaging" that incorporates non-contrast and contrast-enhanced CT, CT angiography, and CT perfusion. A multimodal CT imaging approach is increasingly being recognized as a valuable means of identification of patients that may benefit from either intravenous or endovascular intervention or both as opposed to none contrast computed tomography (NCCT) alone [3]. This approach also permits adequate and more accurate assessment of sites of vascular occlusion, infarct core (IC), salvageable brain tissue, and the degree of collateral circulation [4].

We published a small case series in 2011 involving 3 patients presenting to a University teaching hospital with AIS who underwent multimodal CT imaging utilizing an Aquilion ONE (Toshiba Medical Systems, Otawara, Japan) 320-dectector row CT scanner that uses a singular value decomposition lus (SVD+) algorithm to generate perfusion maps [5]. The SVD+ algorithm is a tracer delay-insensitive SVD deconvolution algorithm. As such, it automatically compensates for delays in the contrast arrival time. A key feature of Aquilion ONE is the ability to permit acquisition of whole brain imaging using precise isophasic and physiological uniformity. By implementing such uniformity, Aquilion ONE delineates regions with increased or decreased mean transit time (MTT) of blood traversing through the capillaries that supply regions affected by the ischemic insult. Commonly, perfusion algorithms do not compensate for delays in contrast timing. They combine two effects in the MTT map: 1) capillary flow (i.e., the effects of vasodilation or vasoconstriction of the vessels) and 2) time of contrast arrival. In contrast, delay-insensitive algorithms such as the SVD+ algorithm separate these effects into two maps. The delay of contrast arrival is represented in the time-to-peak (TTP) map and the MTT map represents the effects of capillary flow. Following this principle, we have sought to refine the concept of MTT to reflect a more dynamic capillary flow function that is influenced by physiological factors associated with an ischemic event. Such an MTT or capillary MTT (cMTT) highlights the flow of blood in regions of ischemic penumbra or the IC determined by the degree of vasodilatation or vasoconstriction of the capillaries caused by hypoxic processes. Areas of increased cMTT within increased time to peak regions represent ischemic penumbra. Areas of diminished cMTT within increased time to peak regions would indicate IC. Although the aforementioned pilot case series was limited by small sample size, there was a consistent overlap between the IC volumes measured on MTT with volumes on follow-up diffusion-weighted imaging (DWI) [5]. In our current retrospective analysis of patients who presented with AIS, we primarily aimed to compare and correlate the ischemic penumbra/IC size represented on the cMTT map using Aquilion ONE with DWI MRI volumes in patients who underwent endovascular reperfusion. We chose to observe the image findings of patients who underwent endovascular treatment since it will stop the expansion of theIC. The endovascular approach utilized a combination of intra-arterial thrombolysis, mechanical thrombectomy, thromboaspiration, and/or angioplasty and stenting.

Materials and Methods

Patient selection

We conducted a retrospective analysis of consecutive patients presenting to the emergency room of a university hospital who met the following criteria: 1) had a large vessel acute ischemic stroke; 2) had a high-quality whole-brain CTP; 3) received endovascular therapy; and 4) had a follow-up MRI with DWI within 48 h. A blinded neurologist, neuroradiologist, and neurosurgeon utilized the Vitrea *fX* software (Vital Images, Minnetonka, MN, USA) to process images independently. At-risk territory was defined by the area of delayed perfusion on the TTP map. The IC volume on the MTT map, as determined by values less than 3 s within at-risk territory,

was measured on each slice. The total IC volumes were calculated by taking the sum of the IC on individual slices multiplied by the thickness of each slice. Unpaired t-test was applied to the data sets to assess statistical significance between IC on MTT and the area of limited restriction on follow-up DWI. It should be noted that the IC identification using either imaging modality (MRI or CT perfusion) was processed independently of each other, ensuring that the reviewers were blinded to the results of either imaging method.

MRI Image Acquisition

MR imaging was performed on either a 1.5 or 3 T (Siemens, Forchheim, Germany) whole-body scanner with echo planar capabilities. Diffusion-weighted images were obtained using single-shot, spin echo planar imaging with sampling of the entire diffusion tensor. Two 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 s/mm2 and the low b-value was 0 s/mm^2. A repetition time of 7300 mS was used. The echo time for each scan was 89 mS. Other parameters were field of view (FoV) read of 200 mm, image matrix of 1.5 × 1.5 voxels, slice thickness of 4 mm with 1-mm gap, and 2 signals averaging. Isotropic DWI images were reviewed.

CT Perfusion Acquisition

The CTP study was performed using an Aquilion ONE 320-detector CT system. Image acquisition was performed as a dynamic contrast material-enhanced scan. Each gantry rotation represented a single time-point and captured images of the entire brain with a 0.5 mm section thickness, 512 × 512 matrix, 240-mm axial field of view, and 160-mm scan length. 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 s prior to the start of the dynamic scan. The scanning protocol was as follows: first scan at 7 s, followed by continuous intermittent scans at 2-s intervals beginning at 11 s. The initial scan (80-kVp tube voltage, 310-mA tube current) was acquired prior to any contrast arrival and constitutes a non-contrast anatomical map used for bone subtraction with all subsequent image volumes. Scans were performed during initial contrast material bolus arrival using an 80-kVp tube voltage and a 150-mA tube current. During the expected period of arterial peak between 18 and 28 s, tube current was increased to an 80-kVp tube voltage and a 300-mA tube current. Arterial phase scanning ceased at 36 s. During the venous phase, intermittent scans were performed every 5 s starting at 40 s and ending at 60 s using an 80-kVp tube voltage and a 150-mA tube current. The scanning speed was 0.75 s/rotation, and the total scanning time was 60 s. Volume CT dose index ($CTDI_{vol}$) and dose length product (DLP) [6] 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 $mSv•mGy^{-1}•cm^{-111}$ [7]. CTP data were analyzed using Vitrea *fX* version 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 conspicuity 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 analogous to the block-circulant 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 the patients in this study were imaged using the same acquisition CT perfusion protocol and thus the reported dose was equivalent. The cumulative $CTDI_{vol}$ for the 19 intermittent gantry rotations was 202.5 mGy for each patient. Cumulative DLP was 3244 mGy•cm. The effective dose for each patient was estimated to be 6.8 mSv.

A total of 485 patients presented to our emergency department at the university teaching hospital center with an acute stroke between January 2010 and May 2011. Of the patients presenting to the hospital, 28 underwent acute endovascular treatment, 12 of whom met the inclusion criteria. Refer to Tables 1 and 2 for patient demographics and stroke patterns. A comparison was made between the volumes of IC utilizing SVD+ cMTT maps and DWI MR sequences (Figure 1) after accounting for other confounding factors (i.e., recanalization rate, time between CT and MRI, time to achieve recanalization, and IV t-PA administration). Capillary

Table 1. Patient demographics

Subject	Age	Race	Gender	DM	CAD	HTN	Afib	HLD	NIHSS	t-PA	Anticoagulation	Lupus/vasculitis
1	82	AA	F	Y	Y	Y	Y	N	25	N	Y	N
2	47	W	M	N	N	Y	N	N	26	N	N	N
3	78	W	F	N	N	Y	N	N	13	N	Y	N
4	19	W	F	N	N	N	N	N	22	Y	N	Lupus
5	73	W	M	N	N	Y	Y	N	15	Y	N	N
6	73	W	M	N	N	Y	N	Y	12	Y	Y	N
7	41	W	M	N	N	Y	N	N	n/a	N	N	N
8	19	H	F	N	N	N	N	N	15	Y	N	Vasculitis
9	84	W	F	N	Y	Y	N	Y	16	N	N	N
10	42	W	F	N	N	N	N	N	n/a	Y	N	N
11	65	W	F	N	N	N	N	N	16	Y	N	N
12	68	W	F	N	N	Y	N	Y	n/a	Y	N	N

Y: yes; N: no; AA: African American; W: White; H: Hispanic; M: male; F: female.

Table 2. Patient stroke information

Subject	Time CT to MRI (h/min)	Stroke pattern	Reperfusion	MTT infarct volume (cm^3)	MRI infarct volume (cm^3)
1	33:49	L M1	P	1.2	90.0385
2	10:43	L M1	C	113.15	106.195
3	17:08	L ICA	C	20.6	17.18
4	11:09	L M1	P	2.4	99.185
5	24:00	L M1	C	5.05	9.24
6	7:38	L P1	P	30.75	57
7	39:48	L M2	P	2.7	124.035
8	18:33	R CCA	C	4.55	5.76
9	27:53	L M1	C	16.05	37.425
10	28:07	R M1	C	74.2	12.33
11	24:49	L M2	P	1.1	26.46
12	6:55	L M1	C	15	21.13

L M1: left middle cerebral artery M1; L ICA: left internal carotid artery; L P1: left posterior cerebral artery P1; R CCA: right common carotid artery; P: partial reperfusion; C: complete reperfusion.

flow evolution as dictated by hypoxic mediated vasoconstriction/vasodilation was objectified by cMTT. We divided the patients into two groups based on the degree of reperfusion: A) patients with a TICI score of IIb or III and B) patients with a TICI score of I or IIa. We compared the two groups and found that the rate of reperfusion significantly affected the volume of the infarct on follow-up MRI (p value < 0.04). Furthermore, we found a strong positive correlation (R^2 = 0.6) between the cMTT infarct volume and the DWI MR volume for patients within group A. No such correlation was seen in group B (Figure 2). We noted that averaged cMTT IC volumes were 84% of averaged DWI IC volumes in group A. A comparison between cMTT and DWI IC volumes was demonstrated in groups A and B using bar graphs (Figures 3 and 4)

Discussion

Interpretation of perfusion imaging helps distinguish between tissue that is irreversibly damaged and tissue that is at risk but potentially salvageable through prompt intervention and establishing revascularization. One such element of the CT perfusion scan is MTT, which provides a measure to monitor clearance of intravascular contrast agents through computational algorithms [8,9]. Current perfusion algorithms quantify the severity of tissue hypoperfusion in terms of metrics that attempt to capture various aspects of delayed contrast passage through affected brain regions [10]. The ability of Aquilion ONE perfusion maps to detect and accurately display alterations in MTT (i.e., IC or penumbra) is a product of the SVD+ algorithm. SVD+ is a delay insensitive algorithm that uses calculations to account for delayed blood flow through the collaterals. In addition, it minimizes noise and performs calculations with fast computation ensuring delay insensitivity of MTT to give a representation of the degree of ischemia. The algorithm uses the principle of deconvolution guaranteeing that the contrast traversing through the arteries (arterial density curve) is negated from the contrast reaching the capillaries, and the resultant brain tissue that is supplied (tissue density curve) is systematically “deconvoluted” to give rise to the impulse residue function. In fact, it has recently been reported that commercial software packages using delay-sensitive deconvolution algorithms can overestimate penumbra— hence, final infarct volume— and thus, penumbra estimated with delay-insensitive software may better correlate with final infarct volume [11,12]. The benefits of the delay-insensitive algorithm eliminate potentially erroneous prolonged MTT times [13]. Other sources of delay may be attributed to abnormal vasculature or collateral vasculature. The cMTT provides a representation of the IC and the ischemic

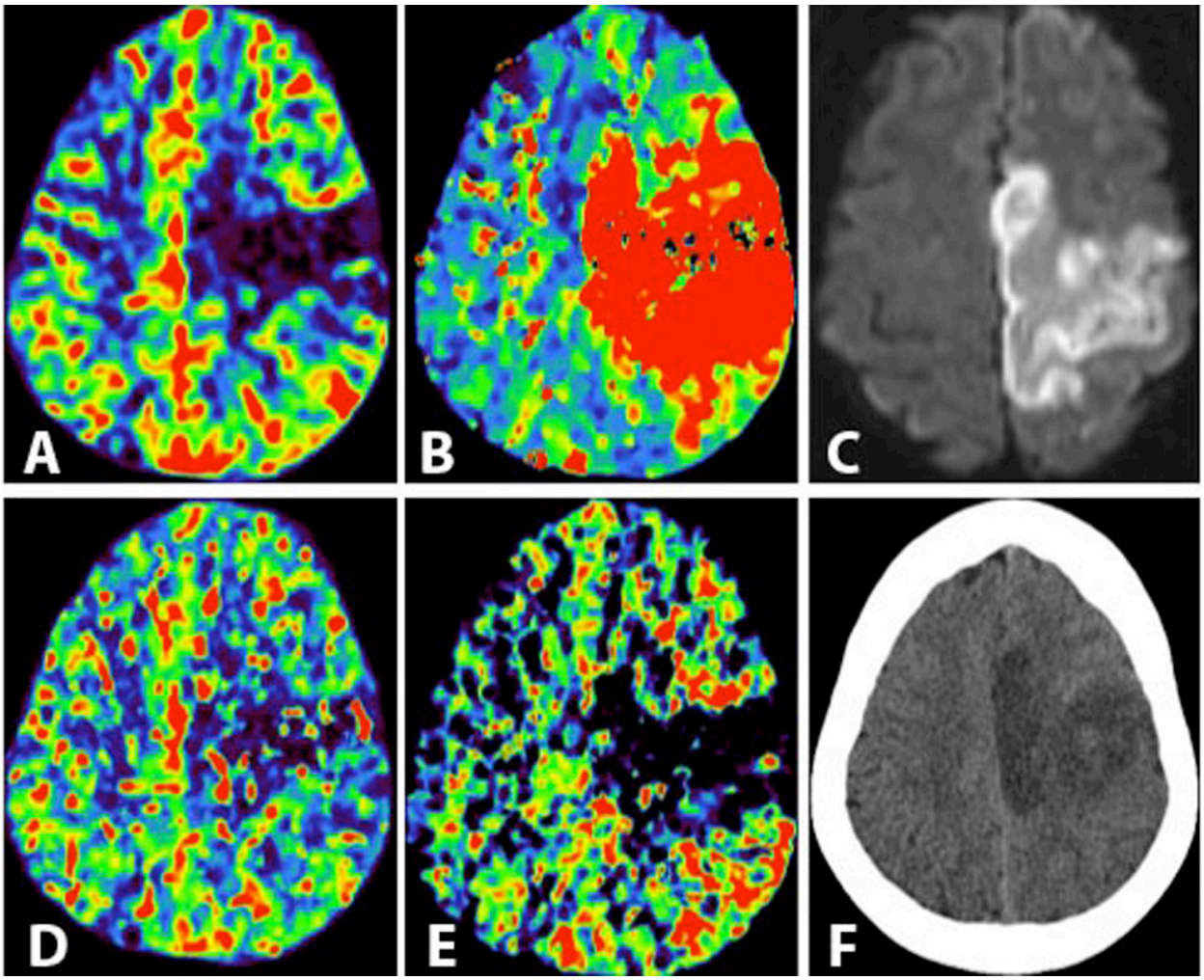

Figure 1. CTP map demonstrating decreased CBV in the left MCA territory (a) and increased TTP in the entire left MCA and distal part of the ACA (b). Follow-up diffusion-weighted MRI (c) 18 h later showing the final infarct in the left MCA and ACA territory matching the area of decreased MTT on initial imaging. MTT maps reveal an area of decreased MTT potentially representing the IC and larger area of increased MTT showing ischemic penumbra (e); for comparison CBF is shown in (d). Follow-up noncontrast CT scan three days later showing the infarcted brain tissue (f).

penumbra that will aid in the accurate clinical decision making of AIS.

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 [14]. Inversely, in the IC there is capillary lumen obstruction resulting in a relative vasoconstriction [15]. Acute ischemia leads to constriction of cerebral pericytes secondary to increased levels of oxidative and nitrosative stress [16]. In addition, ischemia-related damage to the basement membrane and to endothelial cells leads to disruptions of the blood–brain barrier and the development of vasogenic edema [17]. Since time is inversely proportional to velocity, an increased blood flow velocity secondary to capillary vasoconstriction would correspond to a decreased cMTT that ultimately corresponds to the final core infarct. Inversely, a decreased blood flow velocity secondary to capillary vasodilation would correspond to an overall increased cMTT, thus correlating with the area of potentially salvageable tissue or the penumbra. It is these cells that are contained within the realm of the ischemic region of dysfunctional yet potentially salvageable tissue that form the target of thrombolytic therapy [18–20]. This

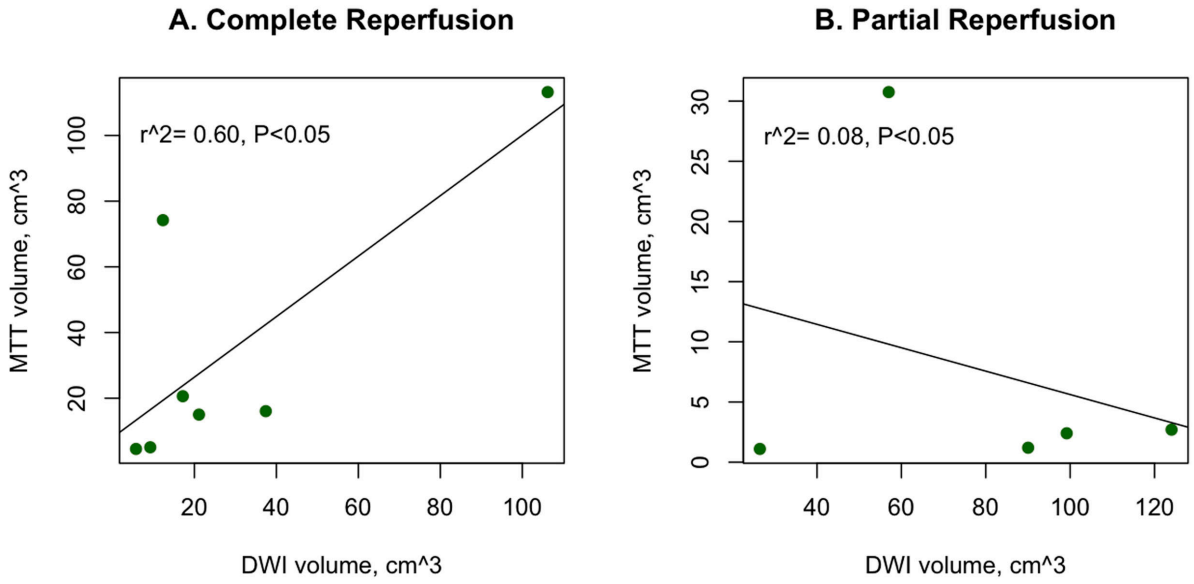

Figure 2. Strong positive correlation in group a, and no evidence of any correlation in group B. (a) Complete reperfusion and (b) Partial reperfusion.

demonstrates how the concept of MTT can be refined to reflect the dynamic functionality of capillaries that respond to changes mediated by hypoxia. This more localized cMTT determines the penumbra and core infracted volume. Therefore, since capillary dysfunction is a feature reflected by cMTT, the value of diagnostic modalities directly demonstrated by capillary dysfunction such as stenosis or occlusions may become important in acute stroke management [10].

For the intents and purposes of our study, we chose to select the subgroup of patients who underwent endovascular treatment since the clinical outcome of enhanced reperfusion achieved through endovascular treatment serves to prevent the expansion of the IC. The deceleration of the IC conversion from the penumbra was observed more effectively with statistical significance ($p < 0.04$) in patients who underwent endovascular treatment to yield TICI scores of 2b and 3 as opposed to the subgroup attaining TICI scores of 1 and 2a. In fact, the subgroup of patients attaining TICI scores of 2b and 3 showed average IC volumes on the cMTT that were 84 % of the area represented on averaged DWI MRI imaging. Furthermore, we observed a strong positive correlation ($R^2 = 0.6$) between the average cMTT infarct volume and the final DWI MR volumes. We were able to observe how the formation of ischemic core from the penumbra was attenuated in the subgroup of patients who achieved a higher degree of endovascular mediated reperfusion (objectified by TICI scores of 2b and 3). In turn, the ischemic penumbra, as represented by capillary mediated vasoconstriction of vessels supplying the hypoxic tissue yielded a lower cMTT (by virtue of increased flow velocity of blood in the constricted capillary) that was represented on Aquilion ONE and comparable with the DWI MRI representation.

Our study has significant limitations. First and foremost, it is retrospective in nature, and as such is subject to the potential restrictions and biases inherent in a retrospective design. Additionally, the threshold for MTT objectifying IC was set at 3 s as a means of establishing and benchmarking a baseline value through which flow dynamics in patients after stroke and revascularization could be compared. CT perfusion data that were obtained by using Aquilion ONE are static and do not reflect the degree of penumbra conversion to IC during the various different time frames. As a result, final IC volume indices may have increased secondary to a considerable time elapse between (8 h or more) the acquisition of CT perfusion and DWI MRI. This bias would be minimized in a prospective study that ensures that the acquisition times for DWI volume and MTT are done in tandem without significant time delays.

In conclusion, the utility of CTP in detection of large ischemic infarcts has shown to yield a higher sensitivity

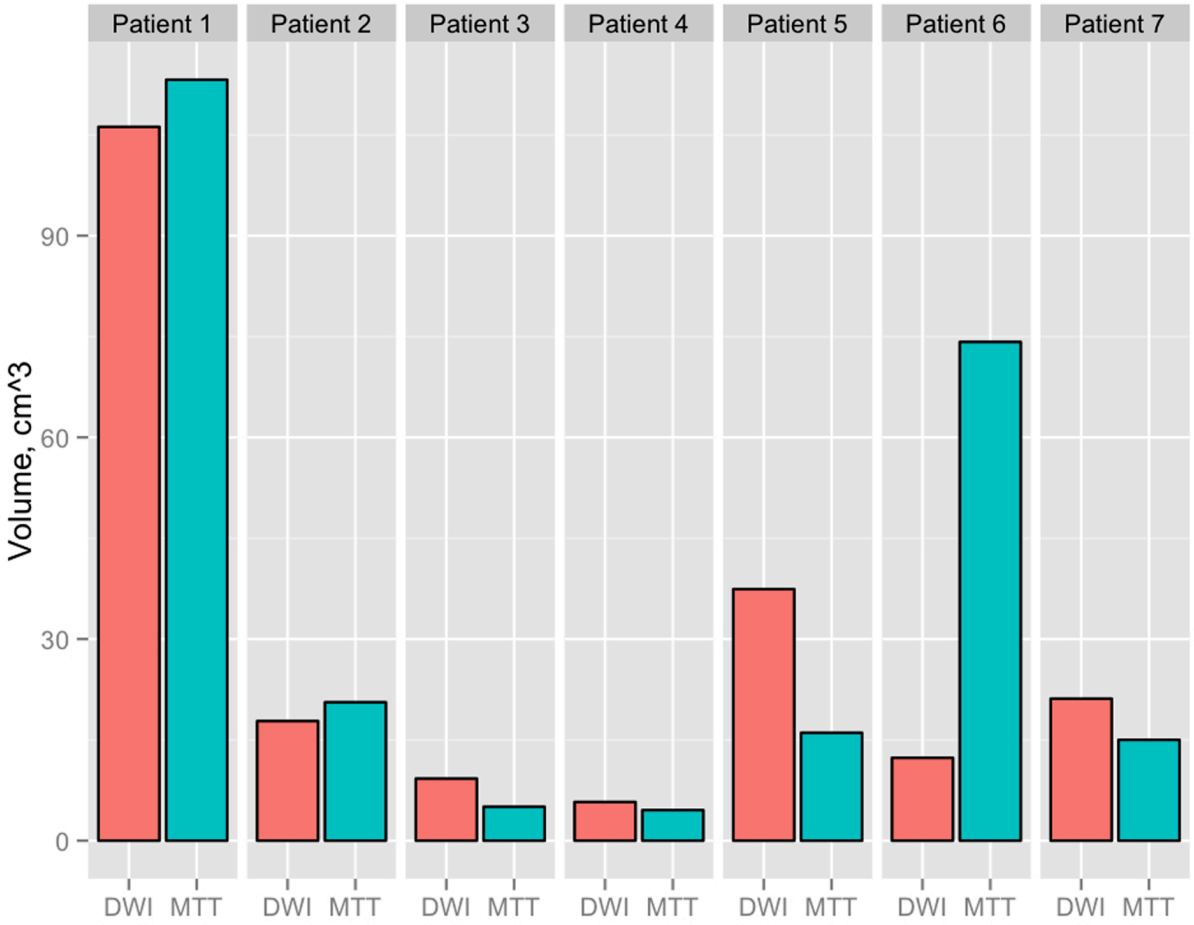

Figure 3. A comparison between cMTT IC volume and diffusion-weighted MRI IC in group A.

and specificity (100% and 92% respectively) compared with those for NCCT (93% and 67%, respectively) [21]. Additionally, CTP images have also shown to be a more accurate means of detecting ischemic stroke in patients presenting with symptoms within 12 h when compared with conventional noncontrast CT images [22]. Aquilion ONE utilizes a 320-dectector row CT scanner with a SVD+ algorithm to generate perfusion maps with remarkable isophasic and physiological uniformity to acquire whole-brain imaging. Using such a delay-insensitive algorithm, Aquilion ONE delineates areas outlined by increased cMTT in regions that represent the ischemic penumbra with those with diminished cMTT indicating IC. In turn, the IC and penumbra are a function of capillary vasoconstriction/vasodilatatory mechanisms secondary to tissue hypoxia. After achieving a higher degree of reperfusion objectified by TICI scores of 2a and 3 in patients with AIS undergoing endovascular mediated reperfusion, our study demonstrates that there was a consistent overlap between the IC volume measured on cMTT and final infarct volume on follow-up diffusion-weighted imaging on the MRI. Although further studies are required to validate this retrospective analysis, preliminary data suggest that a cMTT map may be a valuable and accurate tool in the assessment of patients with acute ischemic stroke who may benefit from aggressive endovascular therapy.

Disclosure

Dr. Mocco disclosures are: Consultant: Lazarus Effect, Medina Medical, Pulsar Vascular, Reverse Medical, Edge Therapeutics; Investor: Blockade Medical, Medina Medical; Advisory Board: Codman Neurovascular; NIH Funding: NIH 1U01NS086492-01; NIH 1R01NS078828-01A1. Dr. Peters is a speaker bureau for Toshiba.

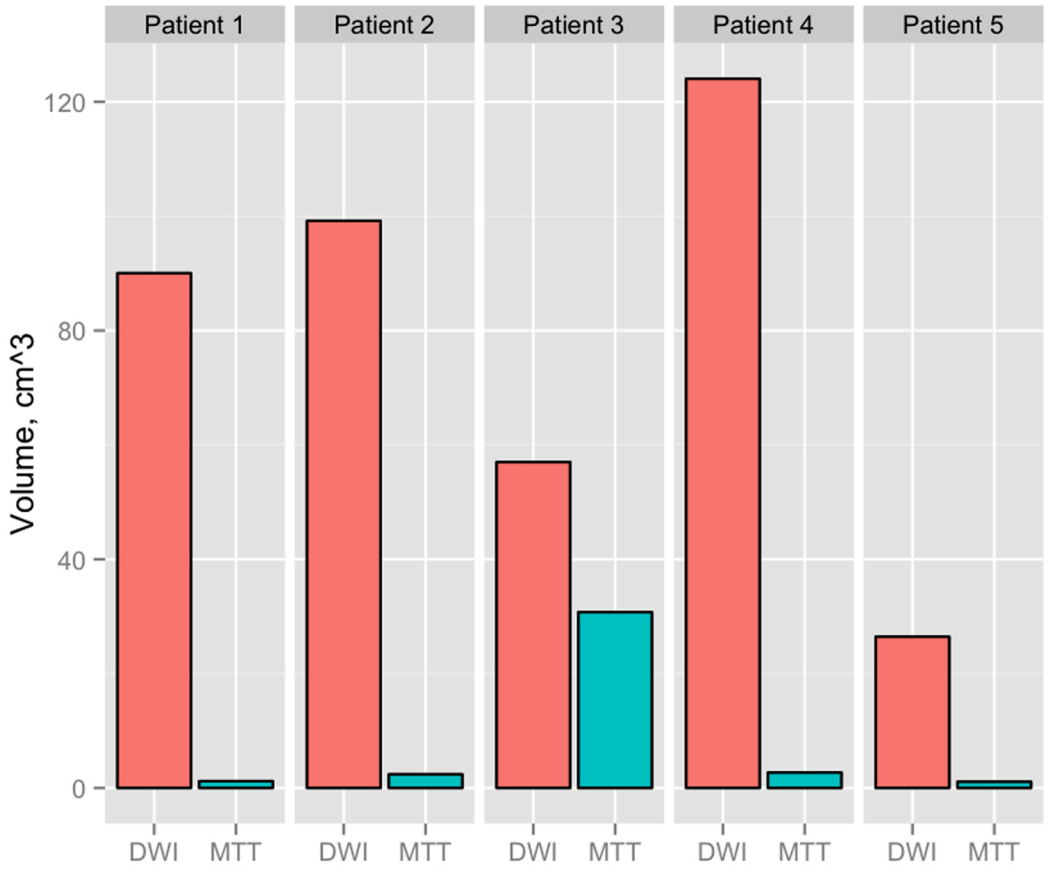

Figure 4. A comparison between cMTT IC volume and diffusion-weighted MRI IC in group B.

[80]

Acknowledgment

The authors thank Dr. Erin Angel (Toshiba America Medical Systems, USA), who provided support with regard to the technical terminology.

References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation* 2012;125:e2–e220.
2. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation* 2011;123:933–944.
3. Kloska SP, Nabavi DG, Gaus C, Nam EM, Klotz E, Ringelstein EB, et al. Acute stroke assessment with CT: do we need multimodal evaluation? *Radiology* 2004;233:79–86.
4. Tan JC, Dillon WP, Liu S, Adler F, Smith WS, Wintermark M. Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. *Ann Neurol* 2007;61:533–543.
5. Dababneh H, Guerrero W, Wilson K, Hoh BL, Mocco JD, Bennett J, et al. Observation of Mean Transit Time (Mtt) Perfusion Maps on a 320-Detector Row Ct Scanner and its Potential Application in Acute Ischemic Stroke. *J Neurol Neurophysiol* 2011;2:117.
6. Commission IE. *Medical electrical equipment: part 2-44—particular requirements for the basic safety and essential performance of x-ray equipment for computed tomography* (3.0) Geneva, Switzerlandinternational Electrotechnical Commission2009;60601-2-44
7. McCollough C, Dianna C, Edyvean S, Geise R, Gould B, Keat N, et al. The measurement, reporting, and management of radiation dose in CT: report of AAPM task group 23 of the Diagnostic Imaging Council CT Committee 2008. in *American Association of Physicists in Medicine (AAPM)* 2008;96
8. Mouridsen K, Friston K, Hjort N, Gyldensted L, Ostergaard L, Kiebel S. Bayesian estimation of cerebral perfusion using a physiological model of microvasculature. *Neuroimage* 2006;33:570–579.
9. Mouridsen K, Christensen S, Jespersen SN. Reliable estimation of capillary transit time distributions at voxel-level using DSC-MRI 3915. in *Proceedings of the International Society for Magnetic Resonance in Medicines 19th Annual Meeting and Exhibition* Montréal: Canada2011:3915.
10. Ostergaard L, Jespersen SN, Mouridsen K, Mikkelsen IK, Jonsdottir KY, Tietze A, et al. The role of the cerebral capillaries in acute ischemic stroke: the extended penumbra model. *J Cereb Blood Flow Metab* 2013

11. Konstas AA, Lev MH. CT perfusion imaging of acute stroke: the need for arrival time, delay insensitive, and standardized postprocessing algorithms? *Radiology* 2010;254:22–25.
12. Wintermark M, Flanders AE, Velthuis B, Meuli R, van Leeuwen M, Goldsher D, et al. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. *Stroke* 2006;37:979–985.
13. Angel E. SVD+ Dynamic Volume CT: Delay insensitive Brain Perfusion Analysis., in White Paper Toshiba America Medical Systems I (ed). 2010
14. Moncada S, Radomski MW, Palmer RM. Endothelium-derived relaxing factor. Identification as nitric oxide and role in the control of vascular tone and platelet function. *Biochem Pharmacol* 1988;37:2495–2501.
15. Mori E, del Zoppo GJ, Chambers JD, Copeland BR, Arfors KE. Inhibition of polymorphonuclear leukocyte adherence suppresses no-reflow after focal cerebral ischemia in baboons. *Stroke* 1992;23:712–718.
16. Peppiatt CM, Howarth C, Mobbs P, Attwell D. Bidirectional control of CNS capillary diameter by pericytes. *Nature* 2006;443:700–704.
17. Kwon I, Kim EH, del Zoppo GJ, Heo JH. Ultrastructural and temporal changes of the microvascular basement membrane and astrocyte interface following focal cerebral ischemia. *J Neurosci Res* 2009;87:668–676.
18. Ebinger M, De Silva DA, Christensen S, Parsons MW, Markus R, Donnan GA, et al. Imaging the penumbra - strategies to detect tissue at risk after ischemic stroke. *J Clin Neurosci* 2009;16:178–187.
19. Hakim AM. Ischemic penumbra: the therapeutic window. *Neurology* 1998;51:S44–46.
20. Warach S, Latour LL. Evidence of reperfusion injury, exacerbated by thrombolytic therapy, in human focal brain ischemia using a novel imaging marker of early blood-brain barrier disruption. *Stroke* 2004;35:2659–2661.
21. Ezzeddine MA, Lev MH, McDonald CT, Rordorf G, Oliveira-Filho J, Aksoy FG, et al. CT angiography with whole brain perfused blood volume imaging: added clinical value in the assessment of acute stroke. *Stroke* 2002;33:959–966.
22. Wintermark M, Fischbein NJ, Smith WS, Ko NU, Quist M, Dillon WP. Accuracy of dynamic perfusion CT with deconvolution in detecting acute hemispheric stroke. *AJNR Am J Neuroradiol* 2005;26:104–112.