Assessment of computed tomography perfusion RAPID estimated core volume accuracy in patients following thrombectomy

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Keywords
Cone-Beam Computed Tomography; Diffusion Magnetic Resonance Imaging; Perfusion Imaging; Stroke; Endovascular Procedures

Abstract
Background: Computed Tomography Perfusion (CTP) maps ischemic core volume (CV) and penumbra following a stroke; however, its accuracy in early symptom onset is not well studied. We compared the accuracy of CTP RAPID estimated CV with diffusion weighted imaging (DWI) infarct volume (IV) in patients following thrombectomy.

Methods: Charts of anterior circulation large vessel occlusion post-thrombectomy cases with thrombolysis in cerebral infarction (TICI) 2b/3 reperfusion from 2017 to 2019 were reviewed. CTP time was dichotomized as 0-3 hours and ≥ 3 hours from the last known normal (LKN) cognition. The volumetric difference (VD), defined as DWI IV minus CTP CV, core volume overestimation (CVO), defined as CTP CV minus DWI IV and Alberta stroke programme early CT score (ASPECTS) were calculated. Large CV was defined as ≥ 50 ml CV. Modified Rankin Score (mRS) at 90 days were reviewed. We performed independent sample t-test and Spearman correlation coefficient test.

Results: Total cases (n) were 61. In < 3 hours window from LKN (n = 27), the mean VD was 58.3 ± 0.1 ml (P = 0.990) and CVO (n = 11; 40.7%) was 39.6 ± 35.7 ml (P = 0.008). Mean large CV (n = 8) was 78.3 ± 25.4 ml with median ASPECTS of 8 [interquartile range (IQR) = 6.5-9.0] and median mRS at 90 days of 2 (IQR = 0.8-3.3). In ≥ 3 hours window from LKN (n = 34), CVO (n = 5) was uncommon and large CV had median mRS at 90 days of 5 (IQR = 4.0-6.0).

Conclusion: CTP more frequently overestimates CV in patients who are < 3 hours from LKN. The treated patients with large CV in < 3 hours and > 3 hours had good and poor functional outcomes, respectively.

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Introduction
Computed tomography perfusion (CTP) estimates ischemic core and penumbra volume for large vessel anterior circulation strokes based on cerebral blood flow (CBF), cerebral blood volume (CBV), Time-to-Maximum (Tmax), and mean transit time (MTT). Various CTP post-processing programs have been introduced to estimate ischemic core volume (CV) and tissue at risk of death, including CTP RAPID iSchemaView, which was used in major trials for determining the usefulness of mechanical thrombectomy (MT) in patients with anterior circulation large vessel occlusions (ACLVO) and extending the alteplase use window. The most accurate estimate of ischemic core lesion was found when CBF was < 30% using the RAPID software and when volumetric accuracy was verified by diffusion-weighted imaging (DWI) on magnetic resonance imaging (MRI).

The median time between CTP and MRI imaging studies in subjects with the most accurate CV estimation was 36 minutes. Studies have shown that CTP overestimates the ischemic CV when compared to DWI, hypothesizing that it falsely recognizes region of leukoaraiosis as ischemic CV. Therefore, this study aimed to investigate the accuracy of CTP estimated CV soon after symptom onset in patients with ACLVO by comparing with DWI infarct volume (IV).

Materials and Methods
This study was exempted by the University of Louisville Institutional Review Board (20.0416). This is a retrospective analysis of consecutive patients who underwent MT for ACLVO from 2017 to 2019. Patients with adequate baseline CTP and follow-up 36-hour brain MRI were included. To best estimate the accuracy of DWI IV after reperfusion, only patients who had adequate reperfusion, were included in the analysis. Adequate reperfusion was defined in this study as a thrombolysis in cerebral infarction (TICI) score 2b/3 (reperfusion > 50% of the affected territory) or higher. Patients with parenchymal hematoma, as graded per the European Cooperative Acute Stroke Study (ECASS II) classification were excluded. The following patient baseline characteristics were noted: age, sex, National Institutes of Health Stroke Scale (NIHSS) score at admission, last known normal (LKN) cognition to CTP time, LKN cognition to MRI time, LKN cognition to reperfusion time, and CTP to reperfusion time. The CTP RAPID estimated CV was defined as relative CBF < 30% of normal brain.

Results
There were 61 MT cases that met the criteria of adequate baseline CTP, 36-hour follow up brain MRI, and adequate reperfusion of TICI 2b/3. The mean ± stranded deviation (SD) of age of the subjects was 66 ± 13.9 years, among who 57.4% were male. The patients were dichotomized into two groups based on CTP time from LKN cognition. Group A included subjects with CTP time from LKN < 3 hours while group B included subjects with CTP time from LKN cognition ≥ 3 hours. The baseline characteristics and volumetric analysis for both groups are included in table 1.

Volumetric analysis
Less than 3 hours window from LKN cognition (Group A): 27 cases had CTP within 3 hours from LKN cognition with the median time of 74 minutes (IQR = 56.0-122.0). The mean CTP CV and DWI IV were 36.9 ± 33.4 and 52.1 ± 37.1 ml, respectively. In addition, the mean VD was 58.3 ± 0.1 ml, which was not statistically significant (P = 0.990). 11 (40.7%) cases had significant CVO as 39.6 ± 35.7 ml (P = 0.008). An example of CVO is illustrated in figure 1.

Greater than 3 hours window from LKN cognition (Group B): 34 cases had CTP > 3 hours from LKN cognition with the median time of 74 minutes [interquartile range (IQR) = 56.0-122.0]. The mean CTP CV and DWI IV were 36.9 ± 33.4 and 52.1 ± 37.1 ml, respectively. In addition, the mean VD was 58.3 ± 0.1 ml, which was not statistically significant (P = 0.990). 11 (40.7%) cases had significant CVO as 39.6 ± 35.7 ml (P = 0.008). An example of CVO is illustrated in figure 1.
Table 1. Patient characteristics, imaging timing, and volumetric assessment of patients with baseline computed tomography perfusion (CTP) at different time frames from symptom onset.

| Characteristics                              | LKN cognition to CTP (< 3 hours), Group A | LKN cognition to CTP (≥ 3 hours), Group B | P    |
|----------------------------------------------|------------------------------------------|-------------------------------------------|------|
| Patients (n)                                 | 27                                       | 34                                        |      |
| Age (year) (mean ± SD)                       | 62.9 ± 13.2                              | 68.4 ± 14.1                               |      |
| Sex (male) [n (%)]                           | 14 (42.4)                                | 21 (61.7)                                 |      |
| Imaging timing                               |                                          |                                           |      |
| Median Baseline NIHSS (IQR)                  | 17 (11.0-21.0)                           | 17 (12.3-20.8)                            | 0.401|
| Median CTP to MRI B time, mins (IQR)         | 74 (56.0-122.0)                          | 378 (245.0-521.3)                         | <0.001∗|
| Median LKN cognition to CTP time, mins (IQR) | 453 (322.0-646.0)                        | 419.5 (337.3-558.8)                       | 0.728|
| Median LKN cognition to groin time, mins (IQR)| 130 (110.0-186.0)                      | 430 (291.8-588.8)                         | <0.001∗|
| Median CTP to groin puncture time, mins (IQR)| 46 (36.5-70.0)                          | 55 (33.5-74.3)                            | 0.431|
| Volumetric assessment                        |                                          |                                           |      |
| CTP core volume (ml) (mean ± SD)             | 36.9 ± 33.4                              | 47.4 ± 28.8                               |      |
| DWI core volume (ml) (mean ± SD)             | 52.1 ± 37.1                              | 75.3 ± 69.5                               |      |
| VD (ml) (mean ± SD)                          | 58.3 ± 0.1                               | 61.8 ± 46.5                               |      |

LKN: Last known normal, CTP: Computed tomography perfusion, NIHSS: National Institutes of Health Stroke Scale, MRI B: Magnetic resonance imaging of brain, DWI: Diffusion-weighted imaging, SD: Standard deviation; VD: Volumetric difference

*P value <0.05.

Large core volume ASPECTS and functional outcome: In group A, eight cases had a large CV with a mean volume of 78.3 ± 25.4 ml and median ASPECTS of 8 (IQR = 6.5-9.0).

Figure 1. Head imaging of patient with symptom onset less than 3 hours showing core volume overestimation. Computed tomography (CT) scan of head at (A) nuclear level and (B) supranuclear level show hypodensity at left middle cerebral artery (MCA) territory [Alberta stroke programme early CT score (ASPECTS) of 8]. Magnetic resonance imaging (MRI) of head after 16 hours from thrombectomy shows (C,D) restricted diffusion in diffusion weighted imaging sequence and (E,F) hyperintensity in T2- fluid inversion recovery sequence at left MCA territory, and (G) computed tomography perfusion (CTP) RAPID iSchemaView shows volume with cerebral blood flow < 30% (core volume) of 82 ml.
The group A cases with large CV had a median NIHSS at admission of 17 (IQR = 15.0-18.0) and had favorable functional outcomes (defined as mRS ≤ 2 at 90 days) with median mRS at 90 days of 2 (IQR = 0.8-3.3).

In group B, five cases had a large CV with a mean volume of 116.8 ± 75.3 ml and median ASPECTS of 6 (IQR = 5.0-7.0). The group B cases with large CV had a median NIHSS at admission of 16 (IQR = 13.0-19.0) and had poor functional outcomes (defined as mRS > 2 at 90 days) with median mRS at 90 days of 5 (IQR = 4.0-6.0). Two of these patients died.

Effect of time from imaging to reperfusion: In group A, VD did not increase with the increased time from CTP imaging to the reperfusion (rho = 0.309, P = 0.117). While in group B, VD did increase with longer duration of time from CTP imaging to reperfusion (rho = 0.378, P = 0.028) (Figure 2).

Figure 2. Scatter plots of volumetric difference (VD) and computed tomography perfusion (CTP) to reperfusion time duration (A) within 3 hours window from symptom onset (rho = 0.309, P = 0.117), and (B) ≥ 3 hours window from symptom onset (rho = 0.378, P = 0.028).

Discussion
This study was specifically interested in testing the hypothesis that CTP RAPID estimated CV overestimates core volume. We compared baseline ischemic CV in two groups using a CTP-CBF threshold < 30% of normal brain, which demonstrated a volumetric agreement between CTP CV and follow up DWI lesion greater than three hours from symptom onset. Volumetric overestimation of the ischemic core by CTP scan was seen in more than one third of the patients within three hours from symptom onset. This study suggests there is not volumetric agreement when time of reperfusion from baseline CTP is less than three hours from symptom onset. Further, patients from this group with large CV (> 50 ml) had poor functional outcomes. A previous study showed that treated patients with initial large ischemic core (~70 ml) had poor functional outcomes. Similarly, this study depicted treated patients with large ischemic core (> 50 ml) beyond three hours of symptom onset also had poor functional outcome. It is important to recognize these patients early in symptom course because IV grows over time. Considering the current study and ones, it has been shown that patients with large CV (> 50 ml) had better functional outcomes when intervening at less than three hours from symptom onset when compared to those with intervention longer than three hours from LKN cognition. In addition to improving patient functional outcome, overestimation of CTP CV could have potential impacts on criteria surrounding interventional action in patients with acute stroke.

CTP RAPID estimated ischemic core and penumbra volume provide immediate information in decision making for acute revascularization treatment. In patient selection for MT in ACLVO, ASPECTS is dependable for symptom onset less than 6 hours. The use of CTP mismatch ratio and CV criteria has shown to be beneficial in an extended window from 6-24 hours. However, ASPECTS is accompanied by constraints, as it is affected by the quality of CT scan, motion artifact, intracranial metals, interrater reliability, cerebral small vessel disease, and structural dissimilarity. In such situation, automated perfusion reading of CTP stands to be valuable even for the ACLVO with early symptom onset. There were a higher number of good outcomes in trials that used CTP in the window of 6 hours from symptom onset (EXTEND-IA and SWIFT PRIME).
when compared with trials that primarily used non-contrast ASPECTS (REVASCAT, ESCAPE and MR CLEAN). This supports selective use of CTP RAPID imaging results in better outcome among treated patients.\textsuperscript{11-15} These studies showed the importance of and dependence on CTP RAPID imaging results.

In addition to being used in studies determining effective MT candidates, RAPID CTP estimation of CV is also utilized in determination of Alteplase time windows. It is currently recommended that the administration of Alteplase in patients with acute stroke be limited to within 4.5 hours from LKN cognition. \textsuperscript{16} Ma et al. found beneficial effects of Alteplase in an extended widow of up to 9 hours after onset of stroke, compared to placebo, in terms of good functional widow of up to 9 hours after onset of stroke, compared to placebo, in terms of good functional outcome (mRS = 0-1 at 90 days). The study above appeared to foresee the IV more readily in short time and is progressively used for patient selection for MT.\textsuperscript{19,20} Studies comparing accuracy between these two imaging modalities may have an impact in future patient care as it could change common practice surrounding management in patients with acute stroke.

Conclusion

CTP-CBF $< 30\%$ of normal brain volume overestimated the core volume in more than one third of the cases with symptom onset less than three hours after ACLVO. Within this time window, treated patients with overestimated core volume $\geq 50$ ml and favorable ASPECTS had good recovery. Volumetric agreement was noted on CTP CV after three hours of symptom onset with reliable prognostic data.

Conflict of Interests

The authors declare no conflict of interest in this study.

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References

1. Murphy BD, Fox AJ, Lee DH, Sahlas DJ, Black SE, Hogan MJ, et al. Identification of penumbra and infarct in acute ischemic stroke using computed tomography perfusion-derived blood flow and blood volume measurements. Stroke 2006; 37(7): 1771-7.
2. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med 2018; 378(8): 708-18.
3. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. Lancet 2016; 387(10029): 1723-31.
4. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med 2018; 378(1): 11-21.
5. Campbell BCV, Ma H, Ringleb PA, Parsons MW, Charilov L, Bendzus M, et al. Extending thrombolysis to 4.5-9 h and
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wake-up stroke using perfusion imaging: A systematic review and meta-analysis of individual patient data. Lancet 2019; 394(10193): 139-47.

6. Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, et al. User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. Neuroimage 2006; 31(3): 1116-28.

7. Yoo AJ, Verduzco LA, Schaefer PW, Hirsch JA, Rabinov JD, Gonzalez RG. MRI-based selection for intra-arterial stroke therapy: Value of pretreatment diffusion-weighted imaging lesion volume in selecting patients with acute stroke who will benefit from early recanalization. Stroke 2009; 40(6): 2046-54.

8. Wilson AT, Dey S, Evans JW, Najm M, Qiu W, Menon BK. Minds treating brains: understanding the interpretation of non-contrast CT ASPECTS in acute ischemic stroke. Expert Rev Cardiovasc Ther 2018; 16(2): 143-53.

9. d’Esterre CD, Boesen ME, Ahn SH, Pordeli P, Najm M, Minhas P, et al. Time-dependent computed tomographic perfusion thresholds for patients with acute ischemic stroke. Stroke 2015; 46(12): 3390-7.

10. Schroder J, Thomalla G. A critical review of alberta stroke program early CT score for evaluation of acute stroke imaging. Front Neurol 2016; 7: 245.

11. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015; 372(1): 11-20.

12. Jovin TG, Chamarro A, Cobo E, de Miguel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015; 372(24): 2296-306.

13. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA alone in stroke. N Engl J Med 2015; 372(24): 2285-95.

14. Campbell BC, Mitchell PJ, Kleinitz TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015; 372(11): 1009-18.

15. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015; 372(11): 1019-30.

16. Ma H, Campbell BCV, Parsons MW, Churilov L, Levi CR, Hsu C, et al. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. N Engl J Med 2019; 380(19): 1795-1803.

17. Lui YW, Tang ER, Allmendinger AM, Spektor V. Evaluation of CT perfusion in the setting of cerebral ischemia: Patterns and pitfalls. AJNR Am J Neuroradiol 2010; 31(9): 1552-63.

18. Copen WA, Dipoloy AR, Schaefer PW, Schwamm LH, Gonzalez RG, Wu O. Exposing hidden truncation-related errors in acute stroke perfusion imaging. AJNR Am J Neuroradiol 2015; 36(4): 638-45.

19. Lima PO, Furie KL., Silva GS, Lev MH, Camargo EC, Singhal AB, et al. The pattern of leptomeningeal collaterals on CT angiography is a strong predictor of long-term functional outcome in stroke patients with large vessel intracranial occlusion. Stroke 2010; 41(10): 2316-22.

20. Menon BK, d’Esterre CD, Qazi EM, Almekhlafi M, Hahn L, Demchuk AM, et al. Multiphase CT angiography: A new tool for the imaging triage of patients with acute ischemic stroke. Radiology 2015; 275(2): 510-20.