Neurological deterioration and computed tomography perfusion changes with increased time to peak in lacunar stroke

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Abstract:
OBJECTIVES: Lacunar strokes can have fluctuations and progression in the acute period leading to poor outcomes. Our study sought to evaluate if, in lacunar strokes, neurological deterioration (ND) was associated with blood pressure (BP) variations, stroke size, or increased time to peak (TTP) on admission computed tomography perfusion (CTP).

METHODS: Patients with lacunar stroke who had magnetic resonance imaging and CTP performed were enrolled in the study. ND was defined as ≥1-point worsening on a modified National Institutes of Health Stroke Scale (NIHSS) score or the Medical Research Council scale compared to baseline assessment. The difference in BP between the day of admission and the day of ND was calculated. Multivariate logistic regression analysis, adjusted for pertinent clinical and imaging covariates, was performed to determine predictors of ND.

RESULTS: Among 409 patients screened, 49 were eligible for the study. There was no difference in age, gender, race, medical history, admission BP, and the modified NIHSS score between patients with and without ND. In unadjusted analysis, patients with ND tended to have increased TTP in the stroke area compared to the control (12 [63%] vs. 11 [37%], \(P = 0.07\)). On multivariate analysis adjusted for covariates, presence of an increased TTP on CTP was a predictor of ND (odds ratio [95% confidence interval] = 4.80 [1.15–20.10], \(P = 0.03\)).

CONCLUSION: The presence of an increased TTP on CTP corresponding to the stroke lesion on diffusion-weighted imaging is a predictor of ND in patients with lacunar stroke. Larger studies are needed to confirm our findings.

Keywords: Computed tomography perfusion, ischemic stroke, neurological deterioration, time to peak

Introduction

Neurological deterioration (ND) is not uncommon in acute ischemic stroke (AIS). The rates of ND vary with the location and mechanism of stroke, with up to 42% reported in total anterior circulation infarction.¹ About 20%–30% of patients with lacunar stroke syndrome have ND in the first few hours or days of stroke.²

Lacunar strokes are due to the occlusion of small, penetrating arteries with poor collaterals. It commonly presents with motor, sensory, or coordination symptoms without visual deficits and cortical signs such as aphasia and neglect. In the acute period, neurological fluctuations with the progression of motor deficits are more likely to occur in lacunar strokes due to small...
vessel disease than other stroke etiologies.\[^3\] This is also associated with increased morbidity with poor discharge and long-term outcomes.\[^2,4\] Although lacunar strokes have a more favorable outcome compared to other stroke subtypes, about 18%–33% of patients at 1 year and 42% at 3 years are dependent.\[^8\] It is also associated with approximately 8% risk of recurrent stroke at 1-year, and dementia in 11% at 2–3 years.\[^4\] Therefore, it is important to understand factors associated with ND in lacunar strokes.

Although ND has been attributed to progressive hypoperfusion and extension of infarct in strokes related to large artery disease or cardioembolism, the association of perfusion deficit with ND in lacunar stroke due to small vessel disease is poorly understood.\[^5\] In one study, perilesional hyperperfusion was associated with stroke in the striato-capsular area but it was not associated with clinical outcome at 90 days.\[^6\] Hemodynamic factors such as blood pressure (BP) variations, poor collaterals, the extension of the thrombus, increase in stroke size, inflammation, and imbalance in excitatory and inhibitory neurotransmitters are possible mechanisms proposed for ND.\[^7-10\]

In this study, we sought to evaluate if ND in lacunar strokes was associated with BP variations, stroke size, or increased time to peak (TTP) on admission computed tomography perfusion (CTP) and patient outcomes.

**Methods**

**Data source and study design**

This is a retrospective observational study of consecutive AIS patients admitted to a tertiary comprehensive stroke center from March 1, 2015, to June 30, 2016. The Institutional Review Board approved the study.

**Study population**

Patients with AIS were included in the study if they had: (1) restricted diffusion lesion on diffusion-weighted imaging (DWI); (2) evaluable CTP imaging to assess perfusion changes corresponding to the stroke lesion on DWI; and (3) lacunar stroke due to small vessel disease based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.\[^11\] TOAST classification was adjudicated by one investigator (NN). Patients with nonlacunar ischemic stroke, with lacunar appearing stroke but stroke size >20 mm, and those without magnetic resonance imaging (MRI) or CTP were excluded. Patients included in the study were chart reviewed to abstract the clinical and discharge data elements needed: (1) demographics (age, gender, race); (2) medical history (hypertension, diabetes mellitus, hyperlipidemia, stroke, atrial fibrillation, coronary artery disease, congestive heart failure, peripheral vascular disease); (3) social history (smoking and alcohol use); (4) vital signs including systolic BP (SBP), diastolic BP (DBP), and mean arterial BP (MAP); (5) admission National Institutes of Health Stroke Scale (NIHSS) score; (6) supportive treatment received such as intravenous fluids and keeping head of patient bed flat; (7) treatment with alteplase and antiplatelet medications; (8) time from stroke onset or last known well to CTP and MRI; and (9) discharge disposition (to home, home with home health services, inpatient rehabilitation or skilled nursing facility).

The NIHSS is an assessment tool that includes relevant components of the neurological examination to quantify the severity of neurological deficits in acute stroke patients. The score ranges from 0 to 42. Stroke severity based on the NIHSS score is graded as mild (0–4), moderate (5–14), moderate to severe (15–24), and severe (≥25). Patients with a lacunar stroke usually have mild-to-moderate stroke severity. A modified NIHSS score was calculated based on the symptoms associated with the five lacunar syndromes (pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, and dysarthria clumsy hand syndrome) and it included NIHSS components for motor arm and leg, sensory, facial droop, and ataxia. A detailed chart review was performed to determine if a patient had ND during hospitalization compared to admission neurological assessment. The ND was defined as ≥1-point worsening on the modified NIHSS or ≥1-point worsening on the Medical Research Council scale for strength compared to baseline assessment. For this study analysis, patients were categorized into two groups— with and without ND.

All BP readings during the hospitalization were abstracted. The BPs recorded in each 24 hours were averaged. To assess if a change in BP was associated with ND, patients with a decrease in SBP ≥10 mmHg, decrease in DBP ≥5 mmHg, and a decrease in MAP ≥5 mmHg between the day of admission and the day of ND were identified in the two groups.

**Imaging protocol**

MRI images were obtained from 1.5T Avanto or 3T Verio Siemens scanners. Stroke protocol MRI included DWI, fluid-attenuated inversion recovery imaging, and susceptibility-weighted imaging sequences. Typical parameters for DWI were TR/TE = 4100/102 or 7300/80 or 8200/89 with b = 0 and 1000 s/mm², 4–5 mm thickness.

The standard multimodal CT protocol included noncontrast CT, CT angiography, and CTP, which were performed with a 320–detector row scanner (Toshiba Aquilion One; Toshiba Medical Imaging, Tokyo, Japan).

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The CTP was performed with the following protocol: temporally, the acquisition started 6 s after an injection of 50 ml of nonionic iodinated contrast material (Omnipaque 350; GE Healthcare, Chicago IL, USA) into an antecubital vein, at a rate of 5 ml/s, and lasted for 60 s. It consisted of three phases resulting in 21-time frames (80 KV, 300 mA). Spatially, one gantry rotation resulted in 320 axial sections with a thickness of 0.5 mm, which covered 160 mm on the z-axis. The field of view was 220 mm × 220 mm, and the matrix was 512 × 512. The CTP data were postprocessed using commercial software (Vitrea; Vital Images Minnetonka, Minnesota, USA). The CTP postprocessing was operated by a CT technologist. First, the 320 sections (0.5 mm) were merged into 32 sections (5 mm) to simplify the following analyses. Then, one algorithm, standard singular value decomposition, was selected to generate perfusion maps. Standard singular value decomposition was used to generate cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and TTP.

Imaging assessment
A neuroradiologist (MA) evaluated all DWI and CTP images. The investigator was provided with a brief history of the patient’s symptoms and was blinded to all other patient details. DWI images were reviewed to document the anatomical location of the stroke and measure the stroke lesion size. CTP images were reviewed to assess for any increase in TTP, and/or change in CBV corresponding to the stroke lesion noted on DWI.

Statistical analysis
Categorical variables were reported as percentages and continuous variables were reported as mean with standard deviation or median with interquartile range. Chi-squared test was performed for categorical variables and univariate regression analysis was performed on continuous variables to assess significance between two groups. Multivariate logistic regression analysis was performed to evaluate predictors of ND adjusting for covariates that included clinical (age, gender, race, total modified NIHSS, decrease in SBP and DBP, treatment with antiplatelets) and imaging (stroke size on DWI, and the presence of increased TTP corresponding to the stroke lesion) variables. The receiver operating characteristic (ROC) curve was generated to assess the prognostic accuracy for the model.

Model goodness-of-fit was expressed as c-statistic. The alpha level for statistical significance was 0.05. Odds ratio (OR) and 95% confidence intervals (CI) were reported for the results of regression models. Statistical analysis was performed using SAS version 9.4 SAS Institute Inc., Cary, NC.

Results

Baseline clinical and imaging characteristics
Among 409 patients included in the study, 73 patients were diagnosed to have stroke due to small vessel disease based on the TOAST classification. Among them, 15 patients were excluded due to the lack of CTP, and nine patients were excluded for stroke size more than 20 mm. The final study population consisted of 49 patients; 30 patients without ND [Figure 1], and 19 patients with ND [Figure 2]. Among 19 patients with ND, 14 patients had ND on day 2 of hospitalization and five patients had ND on day 3 of hospitalization. There was no difference in age, sex, race, medical history, alcohol and tobacco use, between patients with and without ND [Table 1]. The total NIHSS score and the modified NIHSS score were not different between the two groups. More patients in the ND group were made to have head of bed flat (5 [26%] vs. 1 [3%], P = 0.03). It is possible that some of the treating physicians kept the patient’s head of bed flat if they noticed ND during routine patient care. Most of the patients received intravenous fluids in both groups. There was no difference in the admission (day 1) SBP, DBP, and MAP; treatment with alteplase and antiplatelets; and time from stroke onset to CTP and MRI; between patients with and without ND. More patients with ND were discharged to inpatient rehabilitation compared to those who did not have ND, but it was not statistically significant (P = 0.10). The low rates of thrombolytics (10%–11%) in our study was due to exclusion of patients due to delay in arrival to the hospital ([n = 39 [80%]) and rapidly improving or too mild symptoms to treat ([n = 5 [10%]).

Sixty-three percent of patients had stroke diameters <10 mm in both groups [Table 2]. Patients with ND tended to have increased TTP in the stroke area compared to the no ND group (12 [63%] vs. 11 [37%], P = 0.07) but was not statistically significant [Figure 3].

Figure 1: Diffusion-weighted imaging and computed tomography perfusion of a 71-year-old woman with right leg weakness and no neurological deterioration. Admission modified National Institutes of Health Stroke Scale was 1 for right leg weakness. Patient was treated with clopidogrel. diffusion-weighted imaging performed 28 h from last known well showed acute ischemic stroke in the left pons (a) with corresponding increased time to peak on Computed tomography perfusion (b) performed 32 h from last known well.
A change in CBV was noted in a total of eight patients and it was not different between the two groups.

**Predictors of neurological deterioration**

On multivariate analysis adjusted for covariates, presence of an increased TTP on CTP corresponding to the stroke lesion on DWI was a predictor of ND (OR [95% CI] = 4.80 [1.15–20.10], P = 0.03). Age, gender, race, decrease in SBP or DBP, modified NIHSS score, and the stroke lesion size were not associated with ND [Table 3]. Supplemental Figure 1 shows the ROC curve for the model.

**Discussion**

In our study, among patients with a lacunar stroke, the presence of an increased TTP on CTP corresponding to the stroke lesion on DWI was a predictor of ND. The stroke size on DWI or decrease in BPs between the day of admission and the day of ND was not associated with ND.

ND in lacunar stroke is poorly understood and there are no effective treatments for ND. Supportive treatments such as intravenous fluids, permissive hypertension, and maintaining patients head of bed flat are instituted in clinical practice without clear evidence if such interventions are helpful to reduce further ND or improve neurological function. In our study, there was no difference in the number of patients treated with intravenous fluids between the two groups, although all except one patient in the ND group were on fluids. More patients in the ND group were made to lie flat (likely following ND) compared to those without ND.

To evaluate if a decrease in BP was associated with ND, we analyzed patients with a decrease in SBP ≥10 mmHg, decrease in DBP ≥5 mmHg, and a decrease in MAP ≥5 mmHg between the day of admission and the day of ND in the two groups and found no significant difference. In one study, SBP was higher in patients with hypoperfusion on CTP. However, the perfusion patterns in the stroke area were independent of final infarct volume, suggesting mechanisms other than hypoperfusion in lacunar stroke. We took arbitrary cut-off values of 10 mmHg for SBP, and 5 mmHg for DBP and MAP to correlate BP variations with ND. It is possible that BP requirements to prevent ND are specific to each individual patient based on their baseline BP, impairment of cerebral autoregulation, and collateral flow and that the BP change in one patient that results in ND may not be extrapolated to other patients. For patients with stroke in the basal ganglia or internal capsule, we excluded patients with ipsilateral carotid stenosis or occlusion as it could be a potential cause of stroke and the study was focused on lacunar stroke likely due to small vessel disease.

In a systematic review that assessed the diagnostic accuracy of CTP to detect AIS, two-thirds of false-negative AIS were due to lacunar stroke. Among the CTP maps, the sensitivity for identifying lacunar stroke is higher for TTP (48.7%) in contrast to MTT (35.1%), while both have excellent specificity (>97%). The sensitivity of CTP maps to identify lacunar stroke also varies with the stroke location with limited sensitivity for those in the basal ganglia and thalami and higher sensitivity for those in the subcortical white matter. In a meta-analysis of CTP studies in posterior circulation...
stroke, CTP has superior diagnostic sensitivity and inferior diagnostic specificity compared to noncontrast CT head for diagnosis of posterior circulation stroke.\(^{[15]}\) Technical and clinical factors such as not covering the whole brain for CTP, using singular value decomposition for image processing, reduced cardiac output, and atrial fibrillation could influence the detection of ischemia on CTP maps.\(^{[16]}\) In our study, increased TTP was observed in 23 (47\%) patients, more among patients with ND than without ND (63\% vs. 37\%) and it was a predictor of ND on multivariate analysis. In one study with 26 patients, ND (defined as \(>3\) points worsening on NIHSS within 7 days of stroke) was associated with higher MTT and lower CBF on CTP obtained within 24 h of stroke.\(^{[3]}\) We did not assess for MTT, as TTP appeared to be more sensitive than MTT in identifying lacunar stroke based on a previous study.\(^{[14]}\) Not all patients with increased TTP on CTP have ND. However, it appears to be one of the factors that play a role in ND. Understanding other precipitating factors such as individual BP thresholds for ND and extension of

| Variable | Yes (n=19), n (% | No (n=30), n (%) | P |
|----------|----------------|----------------|---|
| Age (years), mean±SD | 65±13 | 62±15 | 0.50 |
| Sex (female) | 10 (53) | 15 (50) | 0.86 |
| Race | | | |
| White | 13 (68) | 20 (67) | 0.90 |
| Nonwhite | 6 (32) | 10 (33) | |
| Past medical history | | | |
| Hypertension | 16 (84) | 25 (83) | 0.94 |
| Diabetes mellitus | 11 (58) | 13 (43) | 0.32 |
| Hyperlipidemia | 7 (37) | 12 (40) | 0.83 |
| Stroke | 6 (32) | 6 (20) | 0.50 |
| Atrial fibrillation | 0 (0) | 2 (7) | 0.51 |
| Coronary artery disease | 2 (11) | 4 (13) | 1.00 |
| Congestive heart failure | 1 (5) | 1 (3) | 1.00 |
| Peripheral vascular disease | 0 | 1 (3) | 1.00 |
| Social history | | | |
| Tobacco use | 11 (58) | 13 (43) | 0.32 |
| Alcohol use | 7 (37) | 9 (30) | 0.62 |
| Admission vital signs (mmHg), mean±SD | | | |
| SBP | 151±16 | 151±19 | 0.96 |
| DBP | 80±14 | 81±15 | 0.70 |
| MAP | 103±13 | 104±15 | 0.91 |
| Change in BP from day of admission to ND | | | |
| Decrease in SBP ≥10 mmHg | 4 (21) | 10 (33) | 0.35 |
| Decrease in DBP ≥5 mmHg | 5 (26) | 7 (23) | 1.00 |
| Decrease in MAP ≥5 mmHg | 7 (37) | 11 (37) | 0.99 |
| Total NIHSS score, median (IQR) | 3 (1-5) | 3 (1-4) | 0.81 |
| Modified NIHSS score, median (IQR) | 2 (1-4) | 2 (0-3) | 0.54 |
| Head of bed flat | 5 (26) | 1 (3) | 0.03 |
| Intravenous fluids | 18 (95) | 25 (83) | 0.38 |
| Alteplase use | 2 (11) | 3 (10) | 1.00 |
| Antiplates | | | |
| Aspirin | 14 (74) | 28 (93) | 0.09 |
| Clopidogrel | 13 (68) | 15 (50) | 0.20 |
| Aspirin and clopidogrel | 8 (42) | 13 (43) | 0.93 |
| Last known well to CT perfusion time (h), median (IQR) | 15 (6-20) | 14 (5-32) | 0.79 |
| Last known well to brain MRI time (h), median (IQR) | 21 (15-27) | 22 (17-35) | 0.28 |
| Discharge disposition | | | |
| Home | 3 (16) | 11 (37) | 0.10 |
| Home with home health care services | 5 (26) | 9 (30) | |
| Acute inpatient rehabilitation | 10 (53) | 6 (20) | |
| Skilled nursing facility | 1 (5) | 4 (13) | |

SD: Standard deviation, IQR: Interquartile range, NIHSS: National Institutes of Health Stroke Scale, ND: Neurological deterioration, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial blood pressure, CT=Computed tomography, MRI=Magnetic resonance imaging

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stroke may help in anticipating and possibly preventing ND. Patients with hypoperfusion in the penetrating lenticulostriate arteries have unexplained early ND. The hypoperfusion can lead to the extension of the infarct from the noncore hypoperfused region resulting in ND particularly if it involves the corticospinal tract.\[7\]

In an observational study, dual antiplatelets improved outcomes of lacunar stroke patients who had ND.\[17\] We did not find a similar association in our study possibly due to the differences in the sample size and definition of ND between the two studies. The study by Berberich et al.,\[17\] had 458 patients with lacunar stroke compared to our study with only 49 patients. The inclusion of patients with CTP limited our sample size. Moreover, while we used a modified NIHSS to evaluate ND, Berberich et al.,\[17\] defined ND as an increase in ≥3 points in total NIHSS or ≥2 points for limb paresis.

Major strengths of the study include the confirmation of AIS with DWI, lacunar stroke due to small vessel disease defined based on TOAST criteria and stroke size ≤20 mm, and blinded assessment of CTP by a neuroradiologist who had limited information on patient symptoms. Our study is limited by the selection bias due to retrospective study design and small sample size. Besides, the limitations of varied CTP parameters for the detection of lacunar stroke and posterior circulation stroke as described above call for standardization of parameters of CTP use in the acute setting. However, it provides some promising results to test the association of ND with increased TTP on CTP using larger cohorts. Since it was a retrospective study, we used NIHSS score and neurological examination documented in the patient’s charts for the study. Although neurology residents and stroke fellows trained in NIHSS perform the assessment and documentation as part of routine patient care, bias from using data documented from multiple people is a limitation of the study. We did not perform follow-up MRI that would have been useful to assess for extension of the infarct that may have led to ND. Since the anatomical location of the infarct is of utmost importance that could predict ND, diffusion tensor imaging analysis to identify cortical spinal tract within the initial stroke lesion or the noncore hypoperfused region at risk of becoming a core would be helpful to correlate with ND.

### Table 2: Imaging characteristics

| Variable                                      | Yes (n=19) | No (n=30) | P  |
|-----------------------------------------------|------------|-----------|----|
| Stroke location (n)*                          |            |           |    |
| Putamen                                       | 2          | 1         | 0.55|
| Globus pallidus                               | 0          | 1         | 1.00|
| Internal capsule                              | 8          | 8         | 0.35|
| Caudate                                       | 1          | 0         | 0.39|
| Thalamus                                      | 3          | 11        | 0.19|
| Corona radiata                               | 7          | 10        | 1.00|
| Midbrain                                      | 1          | 1         | 1.00|
| Pons                                          | 3          | 8         | 0.49|
| Medulla                                       | 1          | 0         | 0.39|
| Stroke size (mm), median (IQR)                | 14 (8-15)  | 13 (10-17)| 0.43|
| Stroke size, ≤10 mm, n (%)                    | 12 (63)    | 19 (63)   | 0.99|
| Increase in time to peak in stroke area, n (%)| 12 (63)    | 11 (37)   | 0.07|
| Increase in cerebral blood volume in stroke area, n (%) | 3 (16)    | 1 (3)     | 0.28|
| Decrease in cerebral blood volume in stroke area, n (%) | 1 (5)      | 3 (10)    | 1.00|

*Some patients had stroke extending to adjoining locations listed. IQR: Interquartile range, ND: Neurological deterioration

### Table 3: Multivariate logistic regression analysis for predictors of neurological deterioration

| Variable                                      | OR (95% CI) | P  |
|-----------------------------------------------|-------------|----|
| Age                                           | 1.03 (0.98-1.08)| 0.27|
| Gender                                        | 1.29 (0.31-5.46)| 0.73|
| Race                                          | 0.31 (0.05-1.82)| 0.20|
| Decrease in SBP ≥10 mmHg                      | 0.35 (0.07-1.82)| 0.21|
| Decrease in DBP ≥5 mmHg                       | 1.97 (0.38-10.37)| 0.42|
| Modified NIHSS                                | 1.09 (0.79-1.49)| 0.61|
| Increase in TTP                               | 4.80 (1.15-20.10)| 0.03*|
| Stroke size                                   | 0.89 (0.75-1.06)| 0.18|
| Dual antiplatelets (aspirin and clopidogrel)  | 1.02 (0.25-4.15)| 0.98|

*P<0.05. Model c-statistic 0.758, Hosmer and Lemeshow Goodness-of-fit test 0.916. OR: Odds ratio, CI: Confidence interval, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, NIHSS: National Institutes of Health Stroke Scale, TTP: Time to peak

Conclusion

In this study, the presence of an increased TTP on CTP corresponding to the stroke lesion on DWI was a predictor of ND in patients with lacunar stroke. The findings of this study should be interpreted in the context of the study design and limited sample size. It could help in the identification of patients who might experience ND and needs close monitoring. Larger studies are needed to confirm these findings.
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Conflicts of interest

Nandakumar Nagaraja: is a consultant stroke adjudicator for the Women’s Health Initiative study.

Amreen Farooqui, Mehmet S Albayram, Varalakshmi Ballur Narayana Reddy: report no conflicts of interests.

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Supplemental Figure 1: Receiver operating characteristic curve for multivariate analysis model