Does computed tomography permeability predict hemorrhagic transformation after ischemic stroke?

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AIM: To use perfusion-derived permeability-surface area product maps to predict hemorrhagic transformation following thrombolytic treatment for acute ischemic stroke.

METHODS: We retrospectively analyzed our prospectively kept acute stroke database over five consecutive months for patients with symptoms of acute ischemic stroke (AIS) who had computed tomography (CT) perfusion (CTP) done at arrival. Patients included in the analyses also had to have a follow-up CT. The permeability-surface area product maps (PS) was calculated for the side of the ischemia and/or infarction and for the contralateral unaffected side at the same level. The cerebral blood flow map was used to delineate the ischemic territory. Next, a region of interest was drawn at the centre of this territory on the PS parametric map. Finally, a mirror region of interest was created on the contralateral side at the same level. The relative permeability-surface area product maps (rPS) provided an internal control and was calculated as the ratio of the PS on the side of the AIS to the PS on the contralateral side. A student t-test was performed after log conversion of rPS between patients with and without hemorrhagic transformation. Log conversion was used to convert the data into normal distribution to use t-test. For the group of patients who experienced intracranial bleed, a student t-test was performed between those with only petechial hemorrhage and those with more severe parenchymal hematoma with subarachnoid haemorrhage.

RESULTS: Of 84 patients with AIS and CTP at admission, only 42 patients had a follow-up CT. The rPS...
The aim is to restore blood flow and reperfuse ischemic brain tissue at risk of disastrous progression towards irreversible infarction. Although it is well established that this therapy has made significant reduction in the irreversible infarction. Although it is well established that this therapy has made significant reduction in the irreversible infarction.

The primary purpose of this study is to assess whether PS can predict hemorrhagic transformation on follow-up scans in patients with acute ischemic stroke and, if so, whether the severity of the hemorrhagic event can be anticipated.

**MATERIALS AND METHODS**

**Patient selection**

A retrospective review of a prospectively maintained acute stroke database at a tertiary care centre was performed on patients with symptoms of AIS during five consecutive months and in whom a CTP had been performed upon hospital arrival (Table 1). All patients with symptoms lasting less than 6 h were evaluated by the on-call neurologist and/or stroke neurologist and underwent routine stroke imaging protocol. Patients were treated according to standard institutional protocols, including intravenous or intra-arterial thrombolysis. This study was approved under an umbrella retrospective review of CT perfusion methodology by the institutional ethics committee.

During the study time period, 84 patients with symptoms of AIS received a CTP examination at admission. If tPA was then administered, a follow-up unenhanced CT was performed at 24 h. If tPA was deemed not clinically indicated, a follow-up CT was ordered at the radiologist’s discretion. A follow-up CT was performed at 24 h. If tPA was deemed not clinically indicated, a follow-up CT was ordered at the radiologist’s discretion.
Table 1  Characteristics of patients who presented with acute ischemic stroke

| Patients (n = 42) | Age (years) | Sex (M/F) | IV tPA | Mechanical | No tPA | Onset to CT (min) | Onset to therapy |
|------------------|-------------|-----------|--------|------------|--------|------------------|-----------------|
| No hemorrhage (27; 64.3%) | 70.1 ± 12.57 | 12/15 | 24 (88.9%) | 0 | 3 (11.1%) | 127 | 168 |
| Hemorrhage (15; 35.7%) | 69.9 ± 13.6 | 7/8 | 14 (92.9%) | 5 (33.3%) | 1 (6.7%) | 111 | 143 |
| P value | 0.89 | 0.83 | 0.7 | 0.07 | | | |

CT: Computed tomography; tPA: Tissue plasminogen activator; M: Male; F: Female.

RESULTS

The demographic information on our patients is summarized in Table 1. The average PS for the affected
hemisphere in those who experienced any hemorrhagic transformation was not significantly ($P = 0.26$) higher (Mean + std: 3.06 + 1.81) compared to those who did not (2.47 + 1.75; Table 2). The average PS in the contralateral normal side was also not significantly different ($P = 0.18$) between those with hemorrhagic transformation (1.79 + 1.10) and those without (2.3 + 1.35; Table 2). The rPS derived using the normal side as the internal control was significantly higher ($P = 0.003$) in cases of hemorrhagic transformation (1.71 + 1.64) compared to those who did not have any (1.07 + 1.30; Table 2).

Using the overall mean rPS of 1.3 as a cutoff, values above the threshold showed an increased likelihood of subsequent hemorrhagic transformation. The sensitivity of using this score to predict hemorrhagic transformation was 71.4, the specificity was 78.6, with a positive predictive value of 62.5 and negative predictive value of 84.6. The accuracy was determined at 76.2. The odds ratio of an event occurring with such an rPS was 9.2.

Of the 15 cases of hemorrhagic transformation, there was no statistically significant difference ($P = 0.35$) in the rPS between those with petechial or the more severe hemorrhagic events (Table 3).

**DISCUSSION**

This retrospective study supports previous reports that showed a significant correlation between the measure of neurovascular injury (PS) and the propensity of patients to experience ipsilateral intracranial hemorrhage. In contrast to other studies, we did not find significantly increased permeability in the contralateral unaffected hemisphere. We postulate that because the average time from onset of symptoms to CT was well under 6 h, the inflammatory mediators and free radical products had not yet taken action on a global scale. Yang et al$^{[13]}$ showed also that the blood-brain barrier permeability was in the normal ranges for several hours after permanent middle cerebral artery occlusion and that BBB disruption occurs with late reperfusion. This is a global process and underscores the importance of using the

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**Table 2** The permeability surface area product based on the computed tomography perfusion at the time of hospital presentation

| Patients ($n = 42$) | Permeability surface area product | Relative permeability |
|---------------------|---------------------------------|----------------------|
|                      | Normal side | Affected side | $P$ value | Normal side | Affected side | $P$ value |
| No hemorrhage (27; 64.3%) | 2.32 ± 1.38 | 2.34 ± 1.65 | 0.49 | 1.04 ± 0.53 |
| Hemorrhage (15; 35.7%) | 1.84 ± 1.06 | 3.21 ± 1.88 | 0.002 | 1.83 ± 0.78 |
| $P$ value | 0.18 | 0.26 | 0.003 |

**Table 3** Petechial and catastrophic bleeds among patients who experienced intracranial hemorrhage

| Patients ($n = 15$) | Permeability surface area product | Relative permeability |
|---------------------|---------------------------------|----------------------|
|                      | Normal side | Affected side | $P$ value | Normal side | Affected side | $P$ value |
| Petechial hemorrhage (8; 53.3%) | 2.03 ± 1.30 | 3.70 ± 2.28 | 0.02 | 1.78 ± 0.66 |
| Hematoma + SAH (7; 46.7%) | 1.61 ± 0.75 | 2.66 ± 1.23 | 0.06 | 1.89 ± 0.94 |
| $P$ value | 0.92 | 0.74 | 0.35 |

SAH: Subarachnoid haemorrhage.
contralateral PS as control. Although PS has been shown here and elsewhere to be useful in predicting subsequent intracranial hemorrhage with relatively high specificity and sensitivity, it does not differentiate between mild petechial and the more severe parenchymal hemorrhagic events. A hemorrhagic event can range quite widely in the severity spectrum and can appear minor and asymptomatic with trivial hemorrhagic petechiae to large parenchymal hematoma with space-occupying effect. These imaging characteristics have been used as an indirect marker to predict the clinical outcome. A post hoc analysis of the ECASS II data shows that only parenchymal hemorrhage affecting greater than 30% of the infarct and associated with mass effect leads to an early clinical deterioration and worsened long-term outcome, like death. Thus, in practical terms, although the PS is quite good at evaluating the degree of blood-brain barrier damage that predisposes patients to further injury, it does not give clinicians a sense of who may proceed to catastrophic complication.

Ideally, a method would exist to, first, identify those who will develop symptomatic complications and to halt thrombolytic therapy in these patients. Second, the method would identify those who will develop only asymptomatic complications so that clinicians can extend thrombolytic therapy in this group, with the ultimate goal of individually customizing the time window for tPA administration. If PS cannot assess the true potential risk of thrombolytic therapy, we suggest that this method of stroke evaluation is not yet optimal for the treating physician. PS may prevent treatment in patients who may experience some minor petechial hemorrhage but, ultimately, can benefit from restoration of blood flow and recover from potential neurological deficits. Further research with a larger number of patients is required to develop more refined criteria that can help the treating clinician identify patients with potential serious hemorrhagic complications.

There are a few limitations to this study. First, only 42 of the 84 acute ischemic stroke patients received follow-up CT exam after therapy, which reduced the sample size and the statistical power associated with determination of severity. Second, this study focused solely on the CTP-derived PS. MR imaging has also been used to study blood-brain barrier breakdown and is superior for hemorrhage detection. In cases of acute stroke, however, it is often not feasible to obtain an MR exam within the treatment time window. Thus, development of an extended CT stroke protocol may be more practical in the acute setting because it is the modality of choice for the initial investigation.

Pre-treatment PS can predict the occurrence of hemorrhagic transformation in AIS patients with relatively high sensitivity, specificity, positive and negative predictive value. However, PS may not predict hemorrhagic transformation severity, which is critical in the decision to treat.

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