Neurology Asia 2021; 26(2) : 435 – 437

IMAGING HIGHLIGHT

"False ischaemic penumbra" complicates decision making in acute stroke thrombolysis

Aaron de Souza *MD FRACP*

Department of Medicine, Launceston General Hospital, Launceston, Tasmania, Australia

INTRODUCTION

Reperfusion forms the cornerstone of treatment for acute ischaemic stroke (AIS) aiming to salvage tissue in the ischaemic penumbra by exploiting a short therapeutic time window.[1,2] Intravenous thrombolysis with alteplase between 4.5 and 9 hours of stroke onset has recently been shown to be associated with better neurological recovery, provided that a favourable imaging profile can be demonstrated by perfusion imaging.[3] This tailored approach to treatment of AIS, where advanced imaging techniques distinguish irreversibly injured tissue (infarct core) from salvageable brain (critically hypoperfused, functionally ischaemic 'at-risk' tissue or penumbra) with a wider treatment window[4,5] is conceptually appealing. In this paradigm, discrimination of viable and ischaemic tissue using imaging techniques to measure quantitative cerebral perfusion parameters is fundamental in selecting patients for thrombolytic therapy.[1,6]

Computed tomography perfusion (CTP) is widely preferred in initial AIS assessment, usually in combination with non-contrast CT (NCCT) and "arch-to-vertex" CT angiography (CTA), being fast, increasingly available, safe when performed correctly, and affordable.[7,8] The "core" is typically operationally defined as the area with a matched decrease in both cerebral blood flow (CBF) and volume (CBV), and "penumbra," as the mean transit time (MTT) or CBF lesion volume, with CBV maintained or even elevated compared to contralateral values. However, not all anomalies in the CTP are specifically related to AIS, as CTP is susceptible to unrelated alterations in blood flow. We present two patients who presented with acute neurological symptoms and extensive perfusion abnormalities that were subsequently shown to be due to chronic oligaemia.

CASE REPORTS

Patient 1

A 93-year old man presented with 12 hours' history of difficulty getting a fork to his mouth with the right arm, and two hours before presentation was found unable to get up unaided or walk. National Institutes of Health Stroke Scale (NIHSS) score at initial evaluation was 7, improving in 6 hours to 4 with persistent aphasia, right hemianopia, arm weakness and hemianaesthesia. A tortuous left cervical internal carotid artery showed a high grade (>90%) stenosis on CTA. The basilar and bilateral posterior cerebral arteries (PCA, right > left) were narrowed, without prominent posterior communicating arteries. CTP revealed extensive hypoperfusion with a mismatch between CBF and CBV and elevated MTT in the left parietal, temporal and occipital lobes (Figure 1(A)), without definite core. DWI performed 24 hours later revealed left occipital infarction with additional foci of restricted diffusion more anteriorly, conforming to the left PCA territory (Figure 1(B)).

Patient 2

A 57-year old man with a previous right PCA stroke in 1993 presented with seven hours of numbness over the left side of the face and left upper limb with weakness of the left upper limb, which improved rapidly. At evaluation he had right hemianopia, pre-existing from his previous stroke, with no new deficits. NCCT/CTA showed a chronic right PCA infarct, with occlusion of the right PCA and stenosis in the proximal right middle cerebral artery (MCA). CTP revealed reduced CBF and delayed MTT with preserved CBV in the right temporo-parietal region (Figure 2(A)), stable since a prior imaging study in 2018. DWI 24 hours later showed no acute

Address correspondence to: Dr Aaron de Souza, Department of Medicine, Launceston General Hospital, 274-280 Charles Street, Launceston 7250 Tasmania Australia. Tel:+61-3-6777-6578, Email: aaron.de.souza@ths.tas.gov.au

Date of Submission: 11 December 2020; Date of Acceptance: 9 March 2021

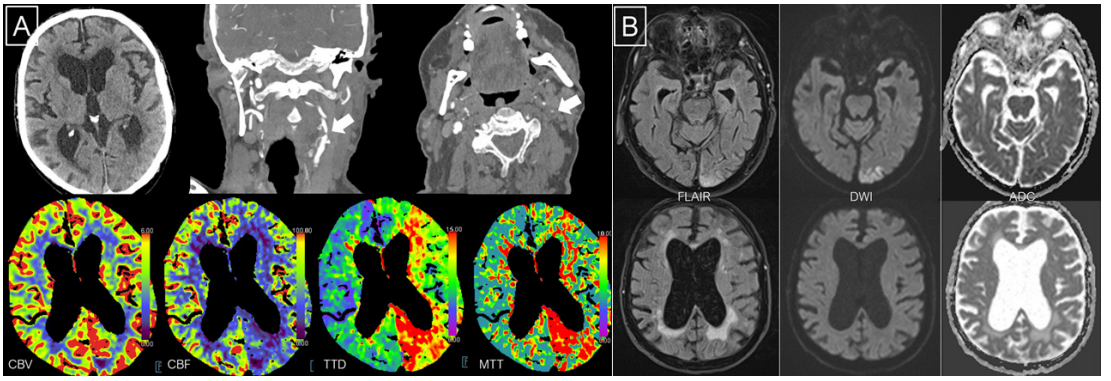

Figure 1 (A) Non contrast CT scan of Patient 1 shows no acute changes in cerebral parenchyma. CTA reveals high-grade stenosis in the left cervical internal carotid artery (arrows). CTP shows extensive hypoperfusion over the left hemisphere, with reduced CBF, elevated MTT and time to drain (TTD) and normal CBV. (B) MRI brain performed 24 hours later showed acute infarction in the left occipital lobe without infarction in the hypoperfused areas of the left parietal and temporal lobes. Age-appropriate cerebral atrophy and chronic subcortical microvascular ischaemic disease are evident.

infarction (Figure 2(B)). The patient subsequently had a left-sided focal-onset seizure with impaired awareness.

DISCUSSION

An apparent penumbra in an arterial territory that does not correspond to clinical symptoms, lack of completed infarction in the same area on follow-up imaging, vasculopathy on CTA without acute or subacute thrombosis, or a clinical history of seizures (as in our patients) as well as other conditions altering cerebral perfusion (migraine, hypertensive encephalopathy, or vasospasm), all indicate that a false ischaemic penumbra may be present, warranting caution while making the decision to initiate thrombolysis. Salvageable penumbra is overestimated by including brain tissue with "benign oligaemia," i.e. hypoperfused but functionally viable areas that demonstrate delay in contrast arrival time not severe enough to cause functional ischaemia.[9,10] Altered CTP findings may occur from cerebrovascular anatomical variations, chronic ischaemia and physiological conditions leading to cerebral blood flow limitation. Restriction of flow upstream is often responsible for benign oligaemia, leading to tissue hypoperfusion without actual ischaemia.[9] While MTT maps with appropriately selected

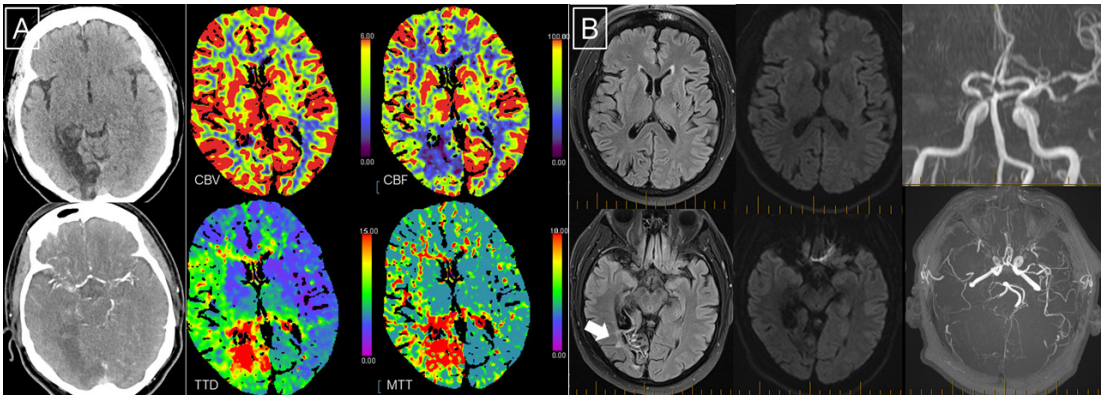

Figure 2 (A) Noncontrast CT scan of Patient 2 shows chronic right posterior cerebral territory infarct. CTA demonstrated chronic occlusion of the M1 segment of the right middle cerebral artery (not shown). CTP shows hypoperfusion over the right temporal and inferior frontal lobes corresponding to the right MCA territory with reduced CBF, elevated MTT and time to drain (TTD) and normal CBV. (B) MRI with time-of-flight angiography performed 24 hours later confirms chronic right PCA infarct (arrow) and distal M1 occlusion without acute infarction on DWI. A small right PCA may be related to the presence of a foetal posterior communicating artery.

thresholds can discriminate benign oligaemia and ischaemic tissue destined to infarct[11], MTT and time to peak (TTP) prolongation may be falsely positive in patients with oligemia and hypoperfusion, without true hypoxia, in the setting of a severe extracranial carotid stenosis.[8]

The penumbra as measured in clinical practice often includes regions of both benign oligaemia and true ischaemia[7,9,12], which may result in a bias towards treatment of patients who do not have true ischemic tissue at risk and are therefore not likely to benefit from recanalization therapy. This "false penumbra" can complicate the decision to initiate intravenous thrombolysis in AIS, and for this reason CTP parameters must be correlated with the clinical history and examination and results from NCCT, CTA and DWI.[9] Our patients had severe arterial stenosis, which has been associated with reduced CBF and increased MTT, and these findings may reverse upon successful carotid revascularisation.[9]

Seizure and migraine can lead to hyperaemia, and the apparent delays in perfusion may have resulted from comparison with perfusion on the symptomatic, hyperaemic side.[9] Around 100 seconds following seizure termination, the "post-ictal switch" occurs, leading to a rapid and transient reduction in cerebral perfusion with reduced CBV and CBF and prolonged MTT.[13-15] Postictal hypoperfusion may most commonly involve the whole hemisphere sparing the basal ganglia but can also present in multiple lobes not conforming to vascular territories, or restricted to the cerebral cortex, as an adaptive response to regional metabolic demands of the ictal and post-ictal brain.[13,14] CTP can distinguish ictal from ischaemic or postictal patterns but cannot reliably discriminate between AIS and the postictal state.[14,15] Though the CTP findings in Patient 2 could be considered consistent with post-ictal hypoperfusion, their stability from the previous study and association with an angiographic abnormality implied that chronic ischaemia was more relevant.

While the application of advanced imaging techniques such as CTP to identify tissue at risk of infarction represents a conceptual leap in the management of AIS, it is important to be aware of potential mimics that may confound interpretation. Correlation of CTP with clinical and angiographic findings, particularly in the time-pressured environment of AIS management, helps avoid subjecting the patient to the risks of unnecessary reperfusion therapies.

Keywords: Acute ischaemic stroke, CT perfusion, stroke thrombolysis, ischaemic penumbra

REFERENCES

1. Sims J, Schwamm LH. The evolving role of acute stroke imaging in intravenous thrombolytic therapy: patient selection and outcomes assessment. *Neuroimaging Clin N Am* 2005; 15:421-40.
2. Hacke W, Kaste M, Bluhmki E, *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; 359: 1317-29.
3. Campbell BCV, Parsons MW, Churilov L, *et al*. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. *N Engl J Med* 2019; 380:1795-803.
4. Bivard A, Spratt N, Levi C, Parsons M. Perfusion computer tomography: imaging and clinical validation in acute ischaemic stroke. *Brain* 2011; 134:3408-16.
5. Lansberg MG, Christensen S, Kemp S, *et al*. Computed tomographic perfusion to predict response to recanalization in ischemic stroke. *Ann Neurol* 2017; 81: 849-56.
6. Parsons MW, Christensen S, McElduff P, *et al*. Pretreatment diffusion- and perfusion-MR lesion volumes have a crucial influence on clinical response to stroke thrombolysis. *J Cereb Blood Flow Metab* 2010; 30:1214-25.
7. Konstas AA, Wintermark M, Lev MH. CT perfusion imaging in acute stroke. *Neuroimag Clin N Am* 2011; 21(2): 215-38.
8. Eastwood JD, Lev MH, Azhari T, *et al*. CT perfusion imaging with deconvolution analysis: A pilot study of patients with acute middle cerebral artery stroke. *Radiology* 2002; 222:227-37.
9. Best AC, Acosta NR, Fraser JE, *et al*. Recognizing false ischemic penumbras in CT brain perfusion studies. *RadioGraphics* 2012; 32:1179-96.
10. Donnan GA, Baron JC, Ma H, Davis SM. Penumbral selection of patients for trials of acute stroke therapy. *Lancet Neurol* 2009; 8:261-9.
11. Kamalian S, Kamalian S, Konstas AA, *et al*. CT perfusion mean transit time maps optimally distinguish benign oligemia from true "at-risk" ischemic penumbra, but thresholds vary by postprocessing technique. *AJNR Am J Neuroradiol* 33:545-9.
12. Geuskens RREG, Borst J, Lucas M, *et al*. Characteristics of misclassified CT perfusion ischemic core in patients with acute ischemic stroke. *PLoS ONE* 2015;10(11): e0141571.
13. Gelfand JM, Wintermark M, Josephson SA. Cerebral perfusion-CT patterns following seizure. *Eur J Neurol* 2010; 17: 594-601.
14. Van Cauwenberge MGA, Dekeyzer S, Nikoubashman O, Dafotakis M, Wiesmann M. Can perfusion CT unmask postictal stroke mimics? A case-control study of 133 patients. *Neurology* 2018; 91(20): e1918-e1927.
15. Masterson K, Vargas MI, Delavelle J. Postictal deficit mimicking stroke: role of perfusion CT. *J Neuroradiol* 2009; 36: 48-51.