Blood-brain barrier permeability: quantification with computed tomography and application in acute ischemic stroke

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Stroke is the third leading cause of death and the first leading cause of long-term disability in the United States, where annual direct and indirect costs of stroke care totaled US$ 69 billion in 2006 [1]. Stroke may be ischemic or hemorrhagic in nature.

An ischemic stroke is defined as an infarction of central nervous system tissue [2] that may be either thrombotic or embolic in etiology, while a hemorrhagic stroke results from the rupture of a blood vessel in the brain. Ischemic stroke is the more common of the two subtypes, accounting for 87% of strokes in 2006 [1], and is most often caused by carotid atherosclerosis or cardioembolism.

Before the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator (NINDS rt-PA) stroke study, therapeutic options for stroke were nearly nonexistent; however, the NINDS study demonstrated the efficacy of treatment with intravenous rt-PA started within three hours of the onset of symptoms [3]. Meta-analysis of this and other major trials of IV rt-PA have confirmed the improved outcomes demonstrated by patients treated with rt-PA within the three-hour window. This also suggests that the treatment window may be widened to the potential benefit of patients [4].

The Safe Implementation of Treatments in Stroke (SITS) study, based on a prospective audit of the International Stroke Thrombolysis Registry (ISTR), concluded that rt-PA remains safe when given up to four and a half hours after the onset of acute ischemic stroke [5]. Research on later treatment with rt-PA continues, with indications that thrombolysis may still be safe and effective up to six hours or more after symptoms begin. This includes the context of "wake up" strokes where the initial onset of focal neurological deficit may be unknown [6].

However, despite the promise shown by these studies, the number of stroke patients receiving therapy to date has been limited to between 1% and 18% of those eligible [3, 7-9]. While there are many reasons for exclusion [9, 10], medical and legal concerns regarding symptomatic hemorrhagic transformation (HT) are primary causes of this underutilization [10].

While it is well accepted that “time is brain” during a stroke [11], it is also known that cerebral tissue viability depends not only on time, but also cerebral hemodynamics, tissue status, and the applied intervention [12]. Given this intricate balance, it has been suggested that advanced imaging techniques should play a role in moving from this “time is brain” paradigm to a “physiology is brain” paradigm [13].

In particular, practical imaging techniques sensitive and specific enough to identify patients who could simultaneously benefit most from thrombolytic therapy and be at the lowest risk for HT, could increase the administration of rt-PA within the currently approved time window. This could also facilitate an increase in the number of patients considered for thrombolysis through an extension of that time window.
This paper describes the risk of HT in acute ischemic stroke, the response of the blood-brain barrier to ischemic insult and its link to HT, and the role of computed tomography perfusion and permeability imaging in identifying patients who may benefit the most from thrombolytic therapy while being at the lowest risk for HT. A case study is also presented to demonstrate CT permeability imaging and its role in diagnosis and treatment planning for acute stroke.

**Hemorrhagic transformation in acute ischemic stroke**

The most feared complication in acute ischemic stroke is HT. The most severe form of HT has devastating clinical consequences and is associated with an over ten-fold increase in mortality [14]. While HT may occur spontaneously in patients with no recanalization therapy [15-17], and less severe forms are seen in many stroke patients, thrombolysis significantly increases the risk of symptomatic HT. Symptomatic HT within 36 hours from the onset of stroke symptoms is seen up to ten times more often in treated (6.4% HT) versus untreated (0.6% HT) patients, and 61% of the patients with symptomatic HT die within three months [3, 4, 18, 19].

Any extension of the thrombolytic treatment window also implies an increased risk of HT. Data shows that the occurrence of HT in patients treated within three hours of symptom onset was 4.8%, while for those treated between three and six hours after onset the occurrence rose to 6.4% [3, 4, 18, 19]. This has motivated the search for predictors of HT [20-22].

Blood-brain barrier (BBB) breakdown resulting from ischemia before reperfusion therapy is hypothesized to contribute to HT in acute ischemic stroke patients [23]. This breakdown shows a prognostic relevance and may indicate the possibility of detecting and weighing risks of thrombolytic therapy before treatment [15-17, 24, 25].

**The response of the blood-brain barrier to ischemic insult**

The blood-brain barrier (BBB) is a cellular structure in the central nervous system (CNS) that regulates the transfer of materials from the bloodstream to the neural tissue. In essence, the BBB restricts the passage of many chemicals and microscopic organisms that may be harmful to the CNS while maintaining passage of oxygen and other items necessary for metabolism.

Consequently, with an intact BBB, both the convection and diffusion of blood plasma and dissolved molecules are restricted [21], and permeability across the BBB for large hydrophilic molecules [23] is nearly nonexistent. Notably, permeability of contrast agents, such as the iodinated agents used in CT, is not commonly observed in the presence of an intact BBB. In most cases, contrast agent stays within the intravascular lumen during its passage through the CNS.

On the other hand, following an acute ischemic stroke the integrity of the BBB may be compromised by the ischemic insult to the vascular endothelium. While the exact mechanisms of this breakdown are not yet fully understood [21, 26, 27], multiple signaling molecules and mediators have been identified with respect to how rt-PA treatment may lead from BBB breakdown to HT [15].

Notably, the mechanisms of BBB breakdown lead to leakage of blood plasma across the now-open junctions between the endothelial cells of the BBB. Since cerebral endothelial cells are considered more resistant than neurons to ischemia, BBB breakdown is hypothesized to be an indicator for more significant ischemia and an increased likelihood of HT [17]. Of particular interest is that the resulting increase in BBB permeability may lead to observable contrast agent extravasation during CT imaging; hence, providing a quantitative imaging predictor of HT.

**CT brain perfusion and blood-brain barrier permeability imaging**

Computed tomography (CT) is the gold standard for the diagnosis of hemorrhagic stroke and is a mandated imaging test to rule out alternate etiologies for patients with stroke symptoms [28]. In addition, the rapid evolution of multidetector CT in the past decade has enabled perfusion CT imaging to quickly and quantitatively evaluate dynamic brain perfusion – including cerebral blood flow, cerebral blood volume, and mean transit time (Figure 1) [29, 30].
This functional information has the potential to identify infarcted tissue, while also identifying the ischemic penumbra that may be saved, and the technique has been shown to be accurate in comparison with acute and delayed diffusion-weighted and perfusion-weighted magnetic resonance imaging [31-33]. CT is particularly attractive since it is readily available in most emergency departments, thus enabling rapid diagnosis and treatment [11].

As noted earlier, BBB breakdown is not an “all or nothing” phenomenon [34, 35], but is a gradual process that needs quantification to assess its severity. The goal of such quantification is to predict HT that may cause clinical deterioration in patients with reperfusion injury and to use this quantitative information to weigh the risks and benefits of potential treatment options. Perfusion CT imaging allows quantification of the rate of BBB permeability.

The Patlak model can be used to quantify BBB permeability from perfusion CT data [36, 37]. As applied to perfusion CT, the Patlak model assumes unidirectional flow of contrast from the vascular lumen to the cerebral parenchyma during a steady-state phase, and allows the calculation of BBB permeability by graphical analysis of the Patlak plot.

This analysis follows image acquisition using a slightly modified perfusion CT protocol that includes a delayed phase of four minutes [38], since previous studies have shown that analysis of first-pass data leads to significant overestimations of BBB permeability [39]. In addition, it has been shown that a two-bolus technique can be used to extend the anatomical coverage of BBB permeability assessment without loss of accuracy [40].

Despite this acquisition extension, radiation exposure to the patient is minimized by using a lowered cycle time during the delayed phase, leading to an increase in effective dose of only ten percent beyond that of a standard perfusion CT acquisition.

**Clinical decision support in acute stroke**

Dynamic brain perfusion CT with maps of the infarct core and penumbra (Summary Maps, Brain Perfusion, Philips Healthcare, Cleveland, OH) provides a potential tool to move beyond the existing treatment time criteria to provide individualized imaging assessments of acute stroke patients [33]. As an automated procedure, this assessment will not only decrease the time...
to treatment, but also enables a reduction in the potential variability among measured parameters [41].

Building upon this paradigm, quantitative BBB permeability imaging may be used as a surrogate biomarker to identify patients that may benefit from therapy and those for whom therapy may only increase the risk of HT. The developed tools have already enabled a first study of age- and anatomy-related BBB permeability values that may permit detection of abnormal BBBP values when assessing acute ischemic stroke patients for the risk of HT [42].

**Case study**

An 85-year-old female presented with left hemiparesis. She underwent stroke CT imaging work-up (noncontrast CT, perfusion CT, CT angiography) within three hours after symptom onset. Noncontrast CT (Figure 2a, b) revealed...
no evidence of intracranial hemorrhage, and perfusion imaging indicated an acute M1 occlusion. The patient was treated with IV rt-PA at that time; however, 26 hours later she presented with symptoms suggesting HT. Follow-up noncontrast CT at that time demonstrated multiple new regions of intraparenchymal hemorrhage (Figure 3a, b).

Retrospective analysis with the prototype permeability analysis software indicates that the patient presented with elevated permeability (Figure 2c, d) on the baseline perfusion CT study in areas near the foci of significant hemorrhage in the patient’s eventual parenchymal hematoma. Of note, the areas of increased permeability occur in both the infarct and penumbra – not just in the infarct, where the vasculature has presumably undergone the most severe ischemia-induced damage. This highlights that permeability imaging provides information beyond what is provided by the standard perfusion CT parameters that can be used to define infarct and penumbra.

Discussion
Quantitative BBB permeability imaging in the acute stroke setting may provide individualized clinical decision support that can predict complications of thrombolytic therapy. This decision support may allow the extension of the rt-PA time window and may increase rt-PA administration rates by reducing the risk associated with treatment. Through these simultaneous actions, the population of stroke patients eligible for thrombolysis may increase substantially.

Informed consent
Imaging data referred to in this article were obtained as part of standard clinical stroke care at the University of California, San Francisco (UCSF), and were retrospectively reviewed with the approval of the UCSF institutional review board.

References