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Permeability surface area product analysis in malignant brain edema prediction – A pilot study

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ABSTRACT

Background and purpose: Using an extended CT perfusion acquisition (150s), we sought to determine the association between perfusion parameters and malignant edema after ischemic stroke.
Methods: Patients (from prospective study PROVE-IT, NCT02184936) with terminal internal carotid artery ± proximal middle cerebral occlusion were involved. CTA was assessed for clot location and status of leptomeningeal collaterals. The following CTP parameters were calculated within the ischemic territory and contralaterally: permeability surface area product (PS), cerebral blood flow (CBF) and cerebral blood volume (CBV). PS was calculated using the adiabatic approximation to the Johnson and Wilson model. Outcome was evaluated by midline shift and infarction volume on follow-up imaging.
Results: Of 200 patients enrolled, 7 patients (3.5%) had midline shift ≥ 5 mm (2 excluded for poor-quality scans). Five patients with midline shift and 5 matched controls were analysed. There was no significant difference in mean PS, CBF and CBV within the ischemic territory between the two groups. A CBV threshold of 1.7 ml/100 g had the highest AUC = 0.72, 95% CI = 0.54–0.90 for early midline shift prediction, sensitivity and specificity were 0.83 and 0.67 respectively.
Conclusion: Our preliminary results did not show significant differences in permeability surface area analysis if analysed for complete ischemic region. CBV parameter had the highest accuracy and there was a trend for the mean PS values for midline shift prediction.

1. Introduction

The incidence of malignant brain edema in anterior circulation ischemic stroke ranges between 3 and 10%. Even with adequate reperfusion, this severe complication has high rates of morbidity and mortality [1]. In clinical practice, an acute predictor/s to identify patients who would benefit from early decompressive hemicraniectomy before a midline shift develops remains elusive [2,3].

Increased tissue water during ischemia is caused by the combination of cytotoxic edema and vasogenic edema. The former, which results in swelling of cells of the neurovascular unit, occurs within minutes of ischemia and is often less severe than the latter, which results in an increase in extracellular free water due to BBB breakdown, occurring hour to days after stroke onset [4,5]. Pathophysiologically, an early impairment of cerebrovascular autoregulation in peri-infarct tissue, loss of integrity of the endothelial basal lamina and increased vascular permeability play key roles in the development of massive life-threatening brain edema in acute ischemic stroke patients [6,7]. Several radiological markers for the development of malignant edema in anterior circulation strokes have been studied, including admission non-contrast computed tomography (CT) hypodensity extending 50% of the MCA territory or diffusion weighted imaging (DWI) lesion extending 82 ml or 145 ml, and ^{11}C-flumazenil positron emission tomography (FMZ-PET) [8–11].

There have been also several CT perfusion (CTP) studies that have attempted to find acute biomarkers predictive of malignant MCA edema [12–16]. Acute differences in cerebral blood flow, blood brain barrier (BBB) permeability and cerebrovascular reserve did not correlate with malignant edema; however, these studies were hampered by limited CTP acquisition lengths, which are especially important for calculation of permeability surface area (PSA) as a marker of BBB disruption. Therefore, our study used multiple imaging modalities (multiphase CTA and an extended length CTP scanning protocol) along with several clinical variables from the prospective study PROVE-IT [Precise and Rapid assessment of collaterals using multi-phase CT angiography

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in the triage of patients with acute ischemic stroke for intravenous (IV) tPA or intra-arterial therapy (IAT)] to determine their relationship with the development malignant brain edema.

2. Methods

2.1. Patients

The preliminary analysis included first 200 patients from the PROVE-IT study (registered at ClinicalTrials.gov under the registration number NCT02184936) with proven terminal occlusion of the internal carotid artery (ICA) ± proximal occlusion of the middle cerebral artery (MCA). Patients with early midline shift ≥ 5 mm according to the control CT or MRI of the brain performed within 24–32 h were identified in the study group. They were subsequently matched with control patients (with no midline shift) who had a similar admission neurological deficit according to the National Institutes of Health Stroke Scale (NIHSS), comparable early ischemic changes assessed by Alberta Stroke Program Early CT Score (ASPECTS) and similar volume of infarction on the control imaging.

2.2. Imaging and image acquisition

Multiphase CT angiography (mCTA) and CTP (64-slice Lightspeed, GE Healthcare, Waukesha, WI, USA) were acquired within the scope of the study imaging protocol. Time-resolved cerebral angiograms of the brain vasculature were generated following the injection of 80 ml of contrast agent (Optiray® 320; Mallinckrodt Pharmaceuticals; Dublin, Ireland), injected at a rate of 5 ml/s followed by a saline flush of 50 ml at 6 ml/s. For the first phase, the aortic arch-to-vertex helical scan was timed to be in the peak arterial phase of normal brain by triggering the scan based on bolus tracking. This first phase acquisition was 7 s in length. The second phase was acquired after a delay of 4 s allowing for table repositioning to the skull base. Scan duration for each additional phase is 3.4 s. An advantage of mCTA is that it allows dynamic imaging of cerebral circulation and a detailed view of the leptomeningeal collaterals. For the CTP acquisition, 45 ml of CT contrast agent (Optiray® 320; Mallinckrodt Pharmaceuticals; Dublin, Ireland) was power injected at 4.5 ml/s followed by a saline flush of 40 ml at 6 ml/s. Sections of 8 cm thickness were acquired at 5 mm slice thickness. Scanning began after a delay of 5 s from contrast injection in up to two phases (scanning intervals): 1st phase every 2.8 s for 60 s (in 30 patients) and an additional 2nd phase every 15 s for 90 s (in 47 patients).

2.3. Image analysis

All imaging data were analysed at the imaging core lab of the Calgary Stroke Program (Canada). OsiriX version 3.5 (http://www.osirix-viewer.com). Leptomeningeal collaterals were assessed on baseline multiphase CTA by a consensus (O.V., P.C.) [17]. The CTP parameters permeability surface area product (PS), CBF, CBV and time to maximum (T_{max}) were calculated using commercially available software with a delay-insensitive deconvolution algorithm (CT Perfusion 4D, GE Electric Healthcare, Waukesha, WI, USA).

A physiologically appropriate deconvolution-based distributed parameter model was used for the CTP analysis [18]. This method corrects for the inability to administer a contrast bolus directly into an artery supplying a tissue of interest. Following the injection of contrast into a peripheral vein, the bolus undergoes delay and dispersion prior to arriving at region of interest within the brain [19]. To correct for this, an impulse residue function (IRF), which represents the tissue time-attenuation curve (TAC) obtained under the ideal hemodynamic injection conditions is calculated – essentially, this removes the effect of delay/dispersion (Fig. 1). The IRF can be interpreted as the volume of blood flow entering a capillary network that contains a fraction of contrast medium that is instantly deposited into the tissue of interest as

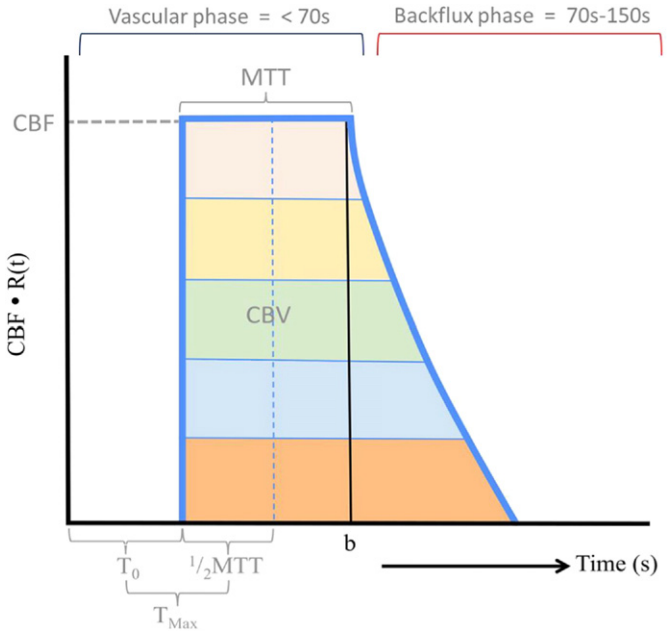

Fig. 1. Graphical representation of an ideal flow-scaled (CBF · $R(t)$) IRF. The IRF is obtained in the brain $R(t)$, using the deconvolution of the arterial enhancement curve $C_a(t)$ and tissue TAC $Q(t)$. The height of the IRF defines CBF, the area of the IRF represents the CBV, and "b" signifies the MTT, which is calculated as the area under the curve (CBV) divided by the height of the vertical line above "b" (CBV). T_0 is the time from the arrival of contrast at the AIF to the tissue of interest and adding $^1/_2$ MTT gives the time for the impulse residue $R(t)$ to reach its maximum (T_{max}). PS is calculated during the "backflux" phase.

time progresses and has been described previously for perfusion parameters, CBF, CBV, MTT and T_{max} [20,21].

PS of the BBB was calculated using the adiabatic approximation Johnson and Wilson model, which assumes that all contrast agent is distributed in either the capillaries or the extracellular space [18]. Contrast measured in the extracellular space is a surrogate of the degree of BBB compromise, which is correlated with quantitative measurements of PS [22]. This model can be illustrated as 1) a single cylinder of length (L) containing a specific blood volume (Vb) that represents the intravascular (capillary) space and 2) another cylinder that surrounds the capillary containing a volume (Ve) that represents the extravascular (interstitial) space (Fig. 2) [23]. A second assumption of this model comes from the fact that the capillary endothelium will have varying degrees of permeability and therefore a bidirectional movement of contrast between the two compartments [24]. To simplify things, it is also

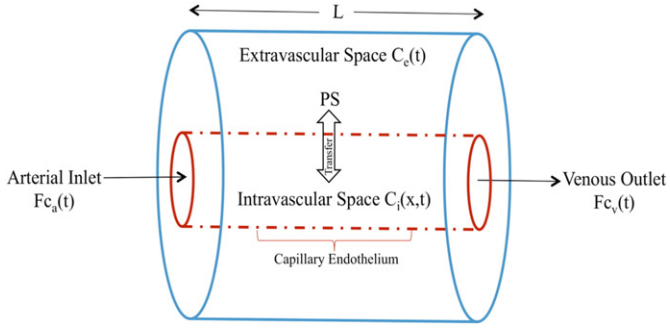

Fig. 2. A simplified diagram of the Johnson and Wilson model. The brain is divided into two principal compartments: the extravascular (interstitial) and intravascular space, separated by a permeable capillary endothelium. The concentration of contrast within the intravascular space is a function of time and length along the capillary, while the concentration of contrast in the extravascular space is assumed to be evenly distributed along the length of the capillary and is only a function of time. This model thereby describes the rate of change of contrast diffusion in the extravascular space, defined by the PS.