Model-based permeability estimates are preferable to model-free initial area under the curve (IAUC) measures in the identification of hemorrhagic transformation in acute ischemic stroke

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INTRODUCTION:

Therapeutic use of recombinant tissue plasminogen activator (rtPA) in acute ischemic stroke (AIS) is currently limited to patients who present within 4.5 hours of symptom onset [1]. Beyond this time-window, rtPA is known to increase the risk of blood-brain-barrier (BBB) disruption and bleeding into the surrounding tissue or 'hemorrhagic transformation' (HT). What is needed for successful treatment guidance is a method for identifying patients at increased risk of HT. Advances in permeability estimation with dynamic contrast-enhanced (DCE) MRI can delineate areas of BBB disruption and thereby identify patients at increased risk of HT with high diagnostic accuracy [2]. However, successful estimation of permeability coefficients requires the measurement of an arterial input function (AIF) and pharmacokinetic modeling. Recent work has suggested that model-free or semi-quantitative methods such as the initial area under the contrast-concentration curve (IAUC) may provide robust and computationally parsimonious alternatives [3,4]. The IAUC metric has been predominantly reported in tumor studies, with the ultimate objective of evaluating novel drug therapies [4]. However, the physiological salience of IAUC is unclear [5] and, to the best of our knowledge, this model-free alternative has not been investigated in the setting of AIS for identifying BBB disruption prior to HT. Thus, the purpose of this study was to determine whether IAUC can identify HT and to assess its relationship to model-based permeability estimates.

MATERIALS AND METHODS:

Twenty-nine patients aged 40-89 years (average age ± SD 70 ± 12.5 years; 17 men and 12 women) with a working diagnosis of AIS were examined within 6 hours of symptom onset. MRI was performed on a 1.5T clinical MR system (GE Healthcare, Milwaukee, USA) equipped with Echo-Speed gradients and an 8-channel head coil. DCE-MRI with a 3D-GRE sequence was performed as part of the AIS protocol: TR 5.9 ms, TE 1.5 ms, FOV 240 mm, matrix 128 × 128, flip angle 20º, slice thickness 7 mm, temporal resolution 5 s × 31 volumes. Gadodiamide was injected as a bolus (0.1 mmol/kg) following initiation of the 3D-GRE sequence. HT was determined by follow-up CT and/or MRI 24-72 h after initial imaging. Data were analyzed on an independent workstation, using in-house software (MR Analyst v. 4.0) developed in MATLAB (The MathWorks, Natick, MA). Two tissue regions of interest (ROIs) were defined on diffusion-weighted images (DWI), one placed within the core region of the DWI abnormality (infarct) and the second within the homologous location in the contralateral hemisphere. Both tissue ROIs were then copied to the equivalent 3D-GRE slices. We then calculated the IAUC corresponding to each ROI using trapezoidal integration of the signal-intensity time-series corresponding to infarct and contralateral ROIs ($IAUC_{inf}$ and $IAUC_{contra}$, FIG. 1) from t=0 to 90 seconds following the arrival of the contrast-agent in the tissue (t=0, which was identified as the first point of inflection in the SI vs. time curve). Voxel-by-voxel maps of permeability coefficients (KPS) were derived from the same 3D-GRE DCE image data-sets. An ROI was positioned within the sagittal sinus for the estimation of the blood plasma contrast concentration (AIF). As previously described, we implemented a graphical Patlak model [6] using linear regression to determine KPS coefficients [2]. Mean KPS values were calculated for the same two tissue ROIs utilized to calculate IAUC. The mean KPS and mean ratios of $IAUC_{inf}/IAUC_{contra}$ for patients who proceeded to HT were compared to those of patients who did not using Student's t-tests. Similar comparisons were performed between patients treated with and without rtPA. Finally, the relationship between KPS and $IAUC_{inf}/IAUC_{contra}$ was investigated using linear regression.

RESULTS:

Thirteen out of 29 patients proceeded to HT, including 6 who received an IV infusion of rtPA. The mean ± SD for both KPS and $IAUC_{inf}/IAUC_{contra}$ ratios are provided in FIG. 2. The mean KPS obtained from HT patients was significantly increased (1.24 ± 0.54 v. 0.63 ± 0.29 ml/min/100g, P =0.005). Conversely, there was a trend toward decreased $IAUC_{inf}/IAUC_{contra}$ ratio detected in patients who proceeded to HT, compared to those who did not (0.88 ± 0.18 v. 0.99 ± 0.13, P =0.06). Meanwhile, the mean KPS and $IAUC_{inf}/IAUC_{contra}$ were both elevated in patients treated with rtPA (KPS: 1.08 ± 0.44 v. 0.71 ± 0.54 ml/min/100g, P =0.05; $IAUC_{inf}/IAUC_{contra}$: 1.00 ± 0.09 v. 0.88 ± 0.19, P =0.03). Linear regression did not reveal a significant correlation between KPS and $IAUC_{inf}/IAUC_{contra}$ (r=0.17, P=0.39).

DISCUSSION:

While this study suggests that both model-based (KPS) and model-free (IAUC) parameters appear capable of detecting an rtPA treatment effect in AIS patients, only KPS successfully delineated HT from non-HT infarcts. When considered together with the lack of a significant correlation between KPS and $IAUC_{inf}/IAUC_{contra}$, it is unlikely that IAUC reflects BBB permeability in this group of AIS patients. One possible explanation is that the time-interval over which we are integrating the tissue signal-intensity curves is too brief (90 s) to adequately capture the contrast-leakage rate associated with HT [7]. Simulations performed by others [5,8] have indicated that the IAUC more accurately reflects a superposition of multiple hemodynamic and tissue parameters and that its physiological interpretation may depend on having *a priori* knowledge regarding the expected range of these same parameters. Furthermore, since the IAUC is necessarily weighted toward the data corresponding to the first-pass of the tissue curve, the temporal resolution will have an impact on IAUC and should be investigated. Thus, despite the additional demands imposed by model-based permeability estimation, we conclude that KPS is preferable to the IAUC metric for guiding AIS treatment decision-making.

FIGURE 1: KPS and IAUC measurements obtained from an AIS patient who was treated with rtPA and later experienced HT.

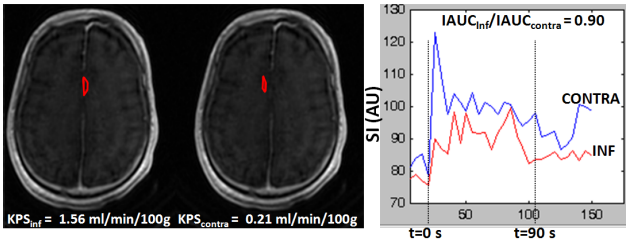
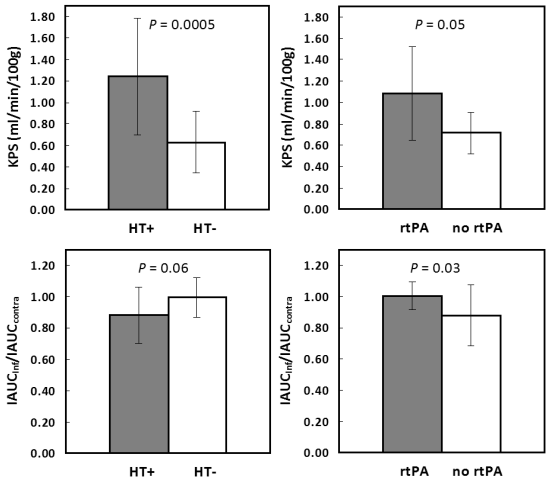


FIGURE 2:



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