Early treatment of ischemic stroke with recombinant tissue-type plasminogen activator (rtPA) has been shown to improve functional outcome and to reduce disability. However, this benefit is coupled with the potential risk of intracerebral hemorrhage, a potentially life-threatening complication. In prospective trials and meta-analyses, the rate of significant intracerebral hemorrhage has been reported to be between 2.4% and 11% with rtPA and between 0% and 3.4% with placebo. Large stroke thrombolysis registries have reported symptomatic intracerebral hemorrhage rates of between 1.6% and 4.8% with rtPA. Moreover, mortality rates of up to 45% have been attributed directly to rtPA-related intracerebral hemorrhage, and it remains the most feared potential complication of an otherwise highly effective therapy.

Several clinical risk factors for thrombolysis-related cerebral hemorrhage have been identified, including advancing age, stroke severity, pretreatment hypertension, and concurrent use of antithrombotic agents, in addition to imaging and laboratory factors, such as hyperglycemia, thrombocytopenia, and extensive early ischemic changes on computed tomography (CT), or the hyperdense middle cerebral artery sign.

The use of MRI, including perfusion imaging, provides more detailed assessment of acute stroke pathophysiology...
than noncontrast CT and has led to advanced imaging predictive parameters for hemorrhagic transformation after thrombolysis. However, multimodal CT, including CT perfusion (CTP), remains more rapidly accessible and more widely available than MRI and is part of routine acute stroke care in many stroke centers. It has also recently been studied in prediction of hemorrhage after thrombolysis. In series ranging from 68 to 96 patients, various perfusion parameters, including relative cerebral blood flow (rCBF), relative mean transit time, relative cerebral blood volume (rCBV), and time to peak, have been found to be associated with hemorrhagic transformation. Given that minor hemorrhagic transformation is common and generally not clinically relevant, we sought to identify the optimal whole-brain CTP parameter for prediction of cerebral parenchymal hematoma (PH) after stroke.

**Methods**

Whole-brain CTP was performed in consecutive patients with suspected acute stroke at a single center (John Hunter Hospital) between December 2009 and July 2012. Most of the patients were scanned using a Toshiba Aquilion One 320-slice CT scanner (Toshiba Medical Systems; Tokyo, Japan). Noncontrast CT was performed, followed by whole-brain CTP (16 cm z–coverage). A total of 19 acquisitions occurred in 60 s. Twelve cases were scanned using a 64-slice Philips Brilliance CT Scanner (Philips; Cleveland, OH). Noncontrast CT was followed by CTP (gj mode; 8 cm z–coverage), with 45 time points acquired each 1.33 s (total acquisition, 60 s). Images were formatted as 5- or 10-mm slices. Forty mL of contrast agent (Ultravist 370; Bayer HealthCare; Berlin, Germany) was injected at 6 mL/s, followed by 30 mL of saline. Perfusion maps were created using in-house software running in MatLab (v.2012a, Mathworks; Natick, MA). Perfusion data were motion corrected and then downsampled to a 128 × 128 matrix with 1-cm slice thickness. Gj mode maps were resampled to 1.5-s resolution in the temporal dimension to allow comparison across acquisition modes. An arterial input function was selected from the anterior cerebral artery and venous outflow function from the superior sagittal sinus by a user-supervised (N.Y.) arterial input function detection algorithm. Singular value decomposition deconvolution was performed with a standard (delay-sensitive) algorithm to create maps of CBF and time to maximum (T\textsubscript{max}). CBF and time to peak were calculated from the concentration–time curve. The hemispheres were manually bisected, and CBF and CBV maps were normalized to the mean of the normal hemisphere to give relative CBF (rCBF) and rCBV. An a priori region of interest representing the perfusion abnormality was created by segmenting regions with relative time to peak >4 s. Receiver operating characteristic (ROC) analysis was performed using the a priori time-to-peak region of interest as the reference region. Preliminary ROC analysis was performed using PH as the outcome variable, and the lesion volume was defined using a particular T\textsubscript{max}<, rCBV, or rCBF threshold in each individual patient on a voxel-by-voxel basis. These thresholds were iterated across the range of values present in the data to determine the threshold for each parameter that generated the highest area under the curve. This optimal threshold was taken forward in the analysis to compare the sensitivity and specificity of each perfusion parameter. Youden Index (sensitivity+specificity–1) was then calculated for this optimized threshold to determine the optimal volume of rCBF, rCBV, and T\textsubscript{max} to predict the development of PH. Follow-up imaging (MRI or CT) within 10 days) was independently assessed for hemorrhagic transformation by 2 stroke neurologists (N.Y. and B.C.V.C.), who then reached consensus using the European Cooperative Acute Stroke Study (ECASS) scoring system. This classifies hemorrhagic infarction 1 (HI1) as small petechiae along the pereiphery of the infarct region; hemorrhagic infarction 2 (HI2) as confluent petechiae within the infarct, without space-occupying effect; parenchymal hematoma 1 (PH1) as bleeding ≤30% of the infarcted area, with mild space-occupying effect; and parenchymal hematoma 2 (PH2) as bleeding >30% of the infarcted area, with space-occupying effect.

Statistical analysis was performed using IBM SPSS Statistics (version 21.0.0.1; IBM Corp, Armonk, NY) and Stata (v.12.1, Statacorp; College Station, TX). Mann–Whitney U and Fisher exact tests were used to determine the association between baseline clinical characteristics, treatment allocation, and outcome. ROC analysis was performed to determine the optimal CTP parameter for prediction of PH. Sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios were determined for each parameter at different volumetric thresholds. The best performing CTP parameters in ROC analysis were subsequently transformed to the fifth root to approximate normality and tested in a multivariate logistic regression model including age, baseline National Institutes of Health Stroke Scale score, and treatment with thrombolyis. The goodness of fit of these models was compared using the Bayesian information criterion. Differences in Bayesian information criterion ranging from 2 to 6 are regarded as positive, 6 to 10 as strong, and >10 as very strong.

**Results**

Of 136 consecutive ischemic stroke patients imaged with multimodal CT, 132 were included in the analysis. The reasons for exclusion were severely motion-degraded perfusion data (n=2) and inadequate contrast bolus quality (n=11). Another patient who developed hemorrhage at a location remote from the initial perfusion lesion was not analyzed because this uncommon form of hemorrhage cannot be predicted using CTP. Follow-up MRI and CT were performed in 118 and 14 patients, respectively. PH occurred in 14 patients overall (10.6%), of whom 6 were symptomatic. Table 1 shows baseline clinical characteristics, stroke risk factors, time to imaging, and treatment decision classified by outcome. Overall, 54.3% of patients received intravenous thrombolysis. Three patients (2.3%) were enrolled in double-blinded randomized-controlled trials of thrombolyis versus placebo, and treatment allocation data were not available for these patients at the time of analysis. Two patients had received warfarin therapy before presentation, with an international normalized ratio of 1.8 in both cases. Neither of these patients received rtPA. One of these patients developed PH on follow-up. One patient was auto-anticoagulated because of hepatic dysfunction (international normalized ratio, 1.5), was on dual antplatelet therapy, and also developed PH.

Thrombolysis was significantly associated with both PH (P=0.003) and any hemorrhagic transformation (P=0.024). Baseline National Institutes of Health Stroke Scale score was significantly associated with PH (P=0.033) but not with any hemorrhagic transformation.

The preliminary ROC analysis for association of PH across the range of values in each CTP parameter identified T\textsubscript{max}>14 s as the optimal threshold for further analysis (area under the curve=0.748; P=0.002), followed by rCBF <30% (area under the curve=0.689; P=0.021), and rCBV <35% (area under the curve=0.646; P=0.074). Mean T\textsubscript{max}>14 s volume was 7.0 mL (interquartile range [IQR], 0–8.1) in the no-PH group and 49.9 mL (IQR, 21.8–55.7) in the PH group (P=0.002; Mann–Whitney U test). Mean rCBF <30% volume was 31.2 mL (IQR, 2.9–45.4) in the no-PH group and 49.9 mL (IQR, 21.8–55.7) in the PH group (P=0.021; Mann–Whitney U test). Mean rCBV <35% volume was 13.2 mL (IQR, 0.3–18.0) in the no-PH group and 22.7 mL (IQR, 6.9–17.5) in the PH group (P=0.05; Figure 1).

The pattern of results was similar using PH2 as the outcome but did not reach statistical significance because of a reduced number of events.
Table 1. Baseline Stroke Risk Factors, Time to Imaging, and Treatment Decisions by Outcome

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>PH</th>
<th>PValue</th>
<th>Any HT</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (IQR)</td>
<td>74 (65–83)</td>
<td>81 (67–86)</td>
<td>0.213</td>
<td>74 (63–82)</td>
<td>0.771</td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
<td>13 (9–18)</td>
<td>18 (10–20)</td>
<td>0.033*</td>
<td>14 (9–18)</td>
<td>0.473</td>
</tr>
<tr>
<td>Median to acute CT, min</td>
<td>158 (108–240)</td>
<td>120 (106–162)</td>
<td>0.071</td>
<td>135 (105–210)</td>
<td>0.240</td>
</tr>
<tr>
<td>Median time to follow-up imaging, h (IQR)</td>
<td>27 (23–48)</td>
<td>25 (22–37)</td>
<td>0.291</td>
<td>28 (24–54)</td>
<td>0.207</td>
</tr>
<tr>
<td>Thrombolysis, N (%)</td>
<td>70 (53.0)</td>
<td>13 (92.9)</td>
<td>0.003*</td>
<td>29 (67.4)</td>
<td>0.024*</td>
</tr>
<tr>
<td>Diabetes mellitus, N (%)</td>
<td>22 (21.0)</td>
<td>1 (10)</td>
<td>0.684</td>
<td>7 (19.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension, N (%)</td>
<td>66 (61.7)</td>
<td>7 (63.6)</td>
<td>1.00</td>
<td>27 (73.0)</td>
<td>0.097</td>
</tr>
<tr>
<td>Dyslipidemia, N (%)</td>
<td>35 (33.0)</td>
<td>1 (10)</td>
<td>0.160</td>
<td>9 (25.0)</td>
<td>0.276</td>
</tr>
<tr>
<td>Smoker, N (%)</td>
<td>33 (31.4)</td>
<td>4 (40.0)</td>
<td>0.380</td>
<td>15 (41.7)</td>
<td>0.124</td>
</tr>
<tr>
<td>Previous smoking, N (%)</td>
<td>31 (34.3)</td>
<td>4 (40.0)</td>
<td>0.721</td>
<td>15 (41.7)</td>
<td>0.124</td>
</tr>
<tr>
<td>Median age, y (IQR)</td>
<td>42 (38.9)</td>
<td>6 (54.5)</td>
<td>0.332</td>
<td>15 (39.5)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; HT, hemorrhagic transformation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; and PH, parenchymal hematoma. Statistical comparison was performed using Fisher exact test for categorical variables and Mann–Whitney U test for continuous variables.

*P<0.05 (Fisher exact test for thrombolysis excludes 3 patients randomized into thrombolysis trials beyond 4.5 h).

Based on the ROC analysis and Youden index, the optimal volume of $T_{\text{max}} > 14$ s for the association with PH was $>5$ mL. There were 83 of 132 (63%) patients with $T_{\text{max}} > 14$ s volumes of $<5$ mL, of whom 3 (3.6%) patients developed PH compared with the overall rate of 10.6%. This indicated a low risk of PH in this group, with a negative predictive value of 0.96 (95% confidence interval, 0.90–0.99) and a negative likelihood ratio of 3.16 (1.15–8.69). For volumes $>5$ mL of $T_{\text{max}} > 14$ s, the sensitivity for PH was 0.79 (0.49–0.95), the specificity: 0.68 (0.59–0.76), the positive predictive value: 0.22 (0.12–0.37), and the positive likelihood ratio: 2.44 (1.67–3.56).

It has previously been demonstrated that rCBF $<31\%$ on CTP corresponds closely to contemporaneous diffusion-weighted imaging lesion volume using similar processing techniques.32 This equates closely to the parameter rCBF $<30\%$, which was found to be associated with PH in the current data set. Youden index for this parameter suggested an optimal threshold of 12 mL of rCBF $<30\%$. At this threshold, this test was found to be 100% sensitive (none of the 46 patients with rCBF $<30\%$ volumes $<12$ mL developed PH). However, specificity was limited at 0.39 (0.30–0.48), with a positive predictive value of 0.16 (0.09–0.26).

A goodness-of-fit comparison was performed between $T_{\text{max}} > 14$ s and rCBF $<30\%$ for prediction of PH in a univariate logistic regression model (after transformation to the fifth root to approximate normality). The difference in Bayesian information criterion was $+2.6$ in support of $T_{\text{max}} > 14$ s. In backward stepwise elimination logistic regression, including age, baseline National Institutes of Health Stroke Scale score, thrombolysis, and $T_{\text{max}} > 14$ s, both rtPA administration and volume of $T_{\text{max}} > 14$ s were independently associated with PH (Table 2).

An illustrative case with an area of severely delayed $T_{\text{max}}$ and reduced CBF, with subsequent PH after thrombolysis corresponding to the site of abnormal $T_{\text{max}}$ is shown in Figure 2.

**Discussion**

We have shown that the optimal CTP parameter for prediction of parenchymal hemorrhage was $T_{\text{max}} > 14$ s in a cohort of 132 patients, of whom approximately half received thrombolysis. This concept of severe perfusion delay, as determined by $T_{\text{max}}$ being predictive of hemorrhagic transformation, is in line with similar work using MRI.21,22,33 Interestingly, rCBF $<30\%$ of contralateral mean was also found to be of some utility for predicting PH. This is closely related to CTP estimates of ischemic core volume32 and is consistent with MRI data indicating that ischemic core volume also predicts the risk of hemorrhagic transformation.19,20,22 We found thresholds at more extreme reductions in rCBF and rCBV, which have been previously shown to be useful in MRI, to be of limited utility using CTP, mainly because of a lack of sensitivity to very low levels of contrast within the severely hypoperfused region, which produces a relatively large region of undetectable CBF and CBV. On the contrary, $T_{\text{max}}$ seems to be more robust in identifying regions of severe ischemia on CTP.

Although purely clinical factors are useful in the decision-making process before rtPA administration, in practice, most of these are insufficiently powerful in isolation to alter decision making regarding treatment with thrombolysis, apart from absolute contraindications such as anticoagulant use or severe refractory hypertension. This has led to the recent development of various hemorrhage prediction scoring systems based on results of large stroke treatment databases and using a variety of clinical and imaging-based predictors to estimate the pretreatment risk of cerebral hemorrhage.9–11,34
In contrast with established noncontrast CT hypodensity, the assessment of subtle loss of grey–white differentiation has not been associated with hemorrhage and is subject to substantial interobserver variability. Moreover, the hyperdense middle cerebral artery sign, which has been proposed to be a marker of increased risk of hemorrhage, identifies a target population with vessel occlusion who may derive the most benefit from thrombolysis, making its utility in predicting the risk of hemorrhagic transformation somewhat questionable. Thus, the use of noncontrast CT in the pretreatment identification of patients at risk of hemorrhage is of limited value.

MRI-based parameters for prediction of post-thrombolysis hemorrhage include diffusion-weighted imaging–based lesion volume, particularly the malignant middle cerebral artery stroke profile,19,20 severe hypoperfusion measured by high \( T_{\text{max}} \), regional very low CBV,21,22 and increased permeability (as defined by late-phase \( T_2^* \) signal loss in perfusion sequences or postcontrast fluid-attenuated inversion recovery enhancement). However, MRI is not routinely available in the acute setting, whereas CTP is widely and rapidly accessible in most stroke centers.

This study has some limitations. Although a moderate number of patients were included in the analysis, there is, fortunately, a relatively low frequency of outcome events. A backward elimination logistic regression model was used to account for this and minimize the number of variables in the final model. Nonetheless, the results require validation in a larger data set. This would also permit analysis of the more clinically relevant end point of symptomatic intracerebral hemorrhage. The inclusion of 12 cases in which CTP was acquired using jog mode may also be viewed as a potential limitation. Interpolation of the data in the temporal dimension aims to correct for this and allow more robust comparison between acquisition modes. In addition, we believe that the applicability of an imaging-based prediction model to multiple scanner acquisition techniques adds to its strength. A single case of PH remote to the initial perfusion lesion was excluded as perfusion-based models cannot predict remote PH. Fortunately, this is an infrequent complication after rtPA. Reperfusion of the ischemic core is an important cofactor in the pathogenesis of hemorrhage, and PH is very unlikely to occur in the absence of reperfusion. Unfortunately, because of the clinical practice setting of this study, data on reperfusion were not routinely available. However, the relatively low reperfusion rates achieved by rtPA are likely to have led to underestimation of the specificity of the \( T_{\text{max}}>14 \) s threshold derived in this study. Finally, although there may be differences in the sensitivity of CT and MRI to detect hemorrhagic transformation, we do not think this is likely to have significantly affected our result because the majority of patients (89%) had MRI for follow-up assessment.

This study reinforces the importance of severely ischemic tissue in the pathogenesis of hemorrhagic transformation and demonstrates the feasibility of assessing this phenomenon using CTP. The incorporation of readily available CTP parameters into the clinical decision-making algorithm may allow for a greater appreciation of the risk–benefit profile before

<table>
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<th>Table 2. Logistic Regression Analysis</th>
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<td><strong>Variable</strong></td>
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<tr>
<td>Step 1</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>NIHSS score</td>
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<td>Thrombolysis</td>
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<td>( T_{\text{max}}&gt;14 ) s</td>
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<tr>
<td>Step 2</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Thrombolysis</td>
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<td>( T_{\text{max}}&gt;14 ) s</td>
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<tr>
<td>Step 3</td>
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<tr>
<td>Thrombolysis</td>
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<tr>
<td>( T_{\text{max}}&gt;14 ) s</td>
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</tbody>
</table>

CI indicates 95% confidence interval; and NIHSS, National Institutes of Health Stroke Scale.

*P<0.05 (logistic regression analysis excludes 3 patients randomized into thrombolysis trials beyond 4.5 h).

Figure 2. Example of initial perfusion imaging demonstrating cerebral blood flow (A) in a 67-year-old man 90 min after onset of right hemiparesis and dysphasia. Relative cerebral blood flow is reduced throughout a significant proportion of the left cerebral hemisphere. The patient subsequently developed a parenchymal hematoma after thrombolysis. B. Post-treatment parenchymal hematoma, with initial region of severely increased \( T_{\text{max}} \) overlay, demonstrating better anatomic localization using \( T_{\text{max}} \).
decisions with a larger number of patients and clinical end points in an independent data set is required to optimize and validate the methodology and potentially make this technique more applicable in the clinical setting.

Disclosures
Dr Yassi is supported by the University of Melbourne, Neurosciences Victoria, and the Royal Melbourne Hospital Neurosciences Foundation. The other authors have no conflicts to report.

References
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Nawaf Yassi, Mark W. Parsons, Søren Christensen, Gagan Sharma, Andrew Bivard, Geoffrey A. Donnan, Christopher R. Levi, Patricia M. Desmond, Stephen M. Davis and Bruce C.V. Campbell

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