Ocult Anterograde Flow Is an Under-Recognized but Crucial Predictor of Early Recanalization With Intravenous Tissue-Type Plasminogen Activator

Seong Hwan Ahn, MD; Christopher D. d’Esterre, PhD; Emmad M. Qazi, BSc; Mohammed Najm, BSc; Marta Rubiera, MD; Enrico Fainardi, MD; Michael D. Hill, MD; Mayank Goyal, MD; Andrew M. Demchuk, MD; Ting Y. Lee, PhD; Bijoy K. Menon, MD

Background and Purpose—Thrombolysis depends on the ability of blood and thrombolytic agents to permeate thrombus. We devised a novel technique to quantify blood permeating through thrombi and determine whether this parameter predicts early recanalization with intravenous tissue-type plasminogen activator.

Methods—Intravenous tissue-type plasminogen activator–treated patients with stroke and complete occlusion on computed tomographic angiography were analyzed using perfusion computed tomography and a delay insensitive algorithm. We generated maps that measure delay in arrival time of contrast within the intracranial arterial tree (T0 maps). A positive sloped regression line of T0 values measured along artery silhouette distal to thrombus was defined as marker of permeable thrombus (ocult anterograde flow). Median T0 values at proximal and distal thrombus interface were measured. Early recanalization was assessed on first angiography of subsequent intra-arterial procedure or on a 4-hour computed tomographic angiography.

Results—Of 66 patients, occult anterograde flow was detected in 17 (25.8%). Early recanalization was more in patients with occult anterograde flow versus not (66.7 versus 29.7%; P = 0.031). Median T0 value (in s) at distal thrombus interface (1.5 versus 3.8; P = 0.006) and difference in median T0 value between proximal and distal thrombus interface (1.3 versus 3.7; P = 0.014) were less in early recanalizers versus in nonrecanalizers. In multivariable analysis, patients with occult anterograde flow and T0 value difference between proximal and distal thrombus interface ≤ 2 s recanlalized most (71.4%; odds ratio, 12.15; 95% confidence interval, 2.05–71.91), whereas patients with retrograde flow and T0 value difference > 2 s recanalized least (25.9%; odds ratio, 1).

Conclusions—Ocult anterograde flow through thrombus can be assessed by perfusion computed tomography T0 maps and predicts early recanalization with intravenous tissue-type plasminogen activator robustly. (Stroke. 2015;46:968-975. DOI: 10.1161/STROKEAHA.114.008648.)

Key Words: perfusion imaging • recanalization • stroke • thrombolytic therapy

Early recanalization of an occluded cerebral artery is the most effective way to salvage ischemic penumbra in the acute stroke setting. Intravenous tissue-type plasminogen activator (tPA) is standard therapy for patients arriving within 4.5 hours of onset.1–4 Early recanalization rates with intravenous tPA are, however, low, especially in patients with proximal artery occlusions and large thrombus burden.1 In this context, if physicians are able to reliably estimate probability of early recanalization of intracranial arterial thrombi with intravenous tPA, they can make a more informed decision on whether resource intensive intra-arterial therapy should be administered additionally to these patients.

Thrombolysis in any vascular bed depends on the ability of blood and thrombolytic agents, such as tPA, to permeate thrombus.5–7 Permeable thrombi have previously been described on digital subtraction angiography (DSA), transcranial Doppler, conventional computed tomographic angiography (CTA), on dynamic CTA, and on CT perfusion (CTP) source images.8–11 DSA is no longer a diagnostic test in patients with acute stroke.12 Detecting permeable thrombi on transcranial Doppler, conventional CTA, dynamic CTA, and CTP source images is subjective and requires expertise.10,11 None of these techniques are quantitative; moreover, these techniques are difficult to apply to thrombi in M2 middle cerebral artery (MCA) and
beyond. However, CTP provides information on contrast arrival time within the whole arterial tree relative to that in the artery region chosen to generate the input curve, the T0 hemodynamic parameter.\textsuperscript{14} We sought to devise a novel quantitative technique using this parameter to detect permeable intracranial thrombus and then to assess whether this imaging construct predicted early recanalization with intravenous tPA.

### Methods

#### Patient Selection

Data are from a prospective imaging-based study (Precise and Rapid Assessment of Collaterals Using Multi-Phase CTA in the Triage of Patients With Acute Ischemic Stroke for IA Therapy [PRove-IT]). Patients with acute stroke are included in the study if they present within 12 hours from last seen normal. Inclusion criteria for the present study were as follows: (1) age >18 years, (2) received standard intravenous tPA treatment, (3) had multimodal CT imaging (noncontrast CT, multiphase CT angiography,\textsuperscript{15} and CTP images) at baseline with documented complete intracranial occlusion on CTA. Information on demographic and clinical characteristics, medical history, physical examination, relevant laboratory parameters, and interval times was collected prospectively. The local ethics board approved the study.

#### Imaging Protocol

CT images were obtained using a 64-slice high-definition CT scanner (Discovery CT750 HD; GE Healthcare). For CTP, 45-mL contrast was injected at 4.5 mL/s followed by a saline chase of 40 mL at 6 mL/s. Axial shuttle (step and shoot) mode was used to cover 8-cm section of the brain, including the intracranial internal carotid artery at 5-mm slice thickness. Scanning began after a delay of 5 s after contrast injection with 24 passes acquired >66 s. Early recanalization with intravenous tPA (the Thrombolysis in Cerebral Infarction scale 2b/3) was assessed either on first run DSA at beginning of intra-arterial procedure or on circle of Willis CTA within 4 hours of baseline imaging using a comparable CTA variant.\textsuperscript{16} An expert radiologist and a stroke neurologist analyzed images by consensus blinded to clinical data and follow-up imaging.

#### T0 Map Postprocessing and Measurement of Anterograde Flow Through Thrombus

CTP images were postprocessed using commercial CTP 4D software (GE Healthcare). The T0 map derived from a CTP study depicts the arrival time of contrast in vessels downstream from the arterial region used to generate the arterial input function for the CTP software. Although we used a shuttle mode for image acquisition so that both the arterial input and the tissue time–density curves were acquired at a time interval of 2.8 s, the arterial input function was interpolated to 0.5 s in the delay insensitive deconvolution algorithm of CTP. As such, the time delay between the contrast arrival time of the arterial input function and the tissue curves was determined at a precision of 0.5 s. We hypothesized that the presence of anterograde blood flow immediately distal to a complete occlusion on multiphase CT angiography (defined by consensus within expert readers) suggests the presence of a permeable thrombus. To determine direction of blood flow in the artery just downstream to intracranial thrombus, multiple regions of interest (ROI) were traced along that artery beginning immediately distal to the thrombus using CTP-average images (CTP images calculated as the average Hounsfield unit/voxel over first-pass acquisition) after confirming site of occlusion on CTA (Figures 1 and 2). After coregistering the CTP-average maps with the T0 maps, T0 values along the artery were plotted to determine the line of best-fit (artery profile) using linear regression; a statistically significant positive artery profile slope indicates blood flow away from the distal thrombus interface (occult anterograde flow [OAF]; Figure 1), whereas a negative slope indicates retrograde flow.
blood flow within the same artery toward the thrombus (Figure 2). We also measured median T0 values (using circular ROIs) at the proximal and distal thrombus interface on CTP-average images. The diameter of the circular ROIs was equal to the width of occluded vessel lumen (Figures 1 and 2). If a patient had tandem occlusions, such as internal carotid artery occlusion with distal MCA occlusion, the tandem middle cerebral arterial occlusion was selected for our analysis. We hypothesized that a low T0 value at the distal thrombus interface or a low difference in T0 value between distal and proximal thrombus interface in patients with a negative artery profile slope would suggest excellent retrograde flow because of good collaterals.

Statistics
Data were summarized using standard descriptive statistics. Clinical and imaging variables associated with anterograde versus retrograde flow (Table 1) and with early recanalization (Table 2) were assessed using univariate analysis. We looked at the relationships between the 3 imaging parameters: (1) slope of artery profile, (2) T0 value at distal thrombus interface, and (3) difference in T0 values between distal and proximal thrombus interface ROIs and the estimated probability of early recanalization using logistic regression one at a time. We used visual graphical analysis to show that the artery profile slope is best dichotomized as anterograde flow (positive slope) and retrograde flow (negative slope); we used receiver operating curve analysis and the Youden method to determine cutoff values with optimal sensitivity and specificity for the other 2 imaging parameters. Because significant correlation was noted between parameters (2) T0 value at distal thrombus interface and (3) difference in T0 values between distal and proximal thrombus interface ROIs, we omitted imaging parameter (2) for subsequent analysis. We then classified patients into 3 groups as per the remaining 2 imaging (ie, group 1 [retrograde flow by artery profile and T0 value difference between distal and proximal thrombus interface ROIs≥2 s]; group 2 [retrograde flow by artery profile and T0 value difference between distal and proximal thrombus interface ROIs≤2 s]; group 3 [anterograde flow by line profile and T0 value difference between distal and proximal thrombus interface ROIs≥2 s]) and report early recanalization rates within these 3 groups. There was only 1 patient with anterograde flow by artery profile and T0 value difference between distal and proximal thrombus interface ROI>2 s; this patient was included in group 2.

Finally, we used multivariable logistic regression to identify variables associated with early recanalization after intravenous tPA (Table 3). Only variables identified as statistically significant in univariate analyses (P<0.05) and hypothesized as biologically plausible were included in the multivariable model. The models were parsimonious; each model included the T0 groups, age and one another variable associated with early recanalization. All P values were 2 sided, with P<0.05 considered statistically significant. Difference in T0 values between parameters <0.5 s is not considered statistically significant given precision of measurement even if P<0.05. Analyses were performed using Stata SE 12.1 software (StataCorp LP, College Station, TX).

Results
Of 69 consecutively intravenous tPA-treated patients (with or without additional intra-arterial therapy), after excluding 3 patients with zero artery profile slope, 66 patients (intravenous tPA, n=42 and intravenous tPA+intra-arterial therapy, n=24) were included in the current study. Median age was 74 years (interquartile range [IQR], 21 years), 38 of 66 (57.6%) were women. Median baseline National Institute Health Stroke Scale was 15 (IQR, 8–18). Median stroke symptom onset to multimodal CT evaluation time was 100 (IQR, 72–143) minutes, whereas median time from stroke symptom onset to intravenous tPA injection was 118 (IQR, 85–180) minute. Sites of occlusion were as follows: internal carotid artery+tandem MCA (n=7), carotid T occlusion (n=2), M1 segment MCA (n=25), M2 MCA and beyond (n=26),
posterior circulation including posterior cerebral artery or basilar artery n=5, and proximal anterior cerebral artery (n=1).

**Evaluation of OAF**

Median length of the artery profile analyzed was 29.9 mm (range, 5.7–95.4 mm), whereas median number of pixels included in the artery profile was 68 (range, 14–206 pixels). OAF (defined as statistically significant positive slope for the distal artery profile) was detected in 17 patients (25.8%; mean slope for the artery profile, 0.056; SD=±0.063). Retrograde flow (defined as statistically significant negative slope for the distal artery profile) was detected in 49 patients (74.2%; mean slope for the artery profile, −0.068; SD=±0.072).

Median T0 values at distal thrombus interface were lower for thrombi with OAF (0.5 s; IQR, 0.2–1.5) when compared with those with retrograde flow (3.7 s; IQR, 2–5.7, P<0.001). Median T0 value difference between ROIs at distal and proximal thrombus interface was lower in patients with OAF versus those with retrograde flow (1.3 s; IQR, 0.1–3.7 versus 3.8 s; IQR, 1.5–6.5; P=0.011). Baseline demographics stratified by presence or absence of OAF are described in Table 1.

**Early Recanalization After Intravenous tPA**

Early recanalization assessment after intravenous tPA administration was available in 52 of 66 patients (on subsequent CTA in 29 patients and first run DSA in 23 patients). Median time from intravenous tPA injection to recanalization assessment was 175 (IQR, 61–290) minutes. Early recanalization was detected in 21 patients (40.4%). Early recanalization rates by site of arterial occlusion were as follows: internal carotid artery+tandem MCA 42.9% (3/7), carotid T occlusion 0% (0/1), M1 MCA 27.3% (6/22), M2 MCA and beyond 55.6% (10/18), and posterior circulation 50% (2/4). Early recanalization was significantly more common among patients with OAF than those with retrograde flow (66.7 versus 29.7%; P=0.031; odds ratio, 4.57; 95% confidence interval, 1.11–21.42; Table 3). Median T0 value at distal thrombus interface (1.5 s [IQR, 0.2–3.7 s] versus 3.8 s [IQR, 1.8–6.2 s]; P=0.006) was significantly lower in patients with OAF.
less in early recanalizers than in nonrecanalizers. Median T0 value difference between distal and proximal thrombus interface ROI was also significantly less in early recanalizers than in nonrecanalizers (1.3 s [IQR, 0.1–3.7 s] versus 3.7 s [IQR, 1.6–6.0 s]; P=0.014). A T0 value of ≤2.1 s at distal thrombus interface (sensitivity, 0.67; specificity, 0.70; c-statistic, 0.73) and a median T0 value difference between distal and proximal thrombus interface ROI of ≤2.0 s (sensitivity, 0.67; specificity, 0.68; c-statistic, 0.70) were the optimal thresholds for prediction of early recanalization with intravenous tPA.

Clinical predictors of early recanalization with intravenous tPA on univariate analysis are shown in Table 2. In multivariable logistic regression analysis, patients in group 3 (anterograde flow (OAF) by line profile and T0 value difference between distal and proximal thrombus interface ROI≤2 s) had age-adjusted odds of early recanalization 12× that of patients in group 1 (retrograde flow by line profile and T0 value difference between distal and proximal thrombus interface ROI>2 s; Table 3). Low WBC count was the only other variable associated with early recanalization.

**Discussion**

An ability to predict early recanalization with intravenous tPA could help physicians make appropriate clinical decisions on
which patients to take to the angiosuite for additional intraarterial therapy. In this study, we determine the arrival time of CT contrast relative to an arterial input, around the thrombus and along the artery just distal to the thrombus that can inform whether CT contrast is flowing through thrombus in an anterograde fashion (OAF; permeable thrombus). In a group of patients who have complete occlusion on multiphase CT angiography, our novel quantitative technique detects the presence and degree of permeable thrombus and predicts early recanalization with intravenous tPA.

Permeable thrombi in the intracranial arterial tree have been demonstrated previously using DSA, transcranial Doppler, conventional CTA, dynamic CTA, and CTP source images. A limitation of these imaging modalities is subjectivity in assessment. Studies using these techniques may also have included thrombi with evident flow through them on conventional CTA (intravascular nonocclusive thrombi). Moreover, some of these techniques cannot be applied to thrombi in the M2 MCA segment and beyond. Our goal was to use CTP T0 maps to develop a quantitative and objective measure of OAF (permeable anterograde filling thrombi) that appear as complete occlusions on multiphase CTA.

Although we chose to include patients with only complete occlusion on multiphase CTA, 1 of every 4 patients in our study had OAF (permeable thrombi). The prevalence of OAF with complete occlusion on routine CT angiography in our study is higher than in previous studies. Two of every 3 patients with OAF in our study achieve early recanalization/reperfusion with intravenous tPA, a rate that approaches recanalization rates achieved using mechanical endovascular devices. Our technique could, therefore, be more sensitive at detecting OAF and better at predicting early recanalization with intravenous tPA than other available imaging techniques. Nonetheless, as a word of caution, it is only by directly comparing these techniques with each other that we can determine which technique is better at predicting early recanalization with intravenous tPA.

Other predictors of early recanalization with intravenous tPA include thrombus location, thrombus length, and collateral status. Our results show that only 75% of patients had true retrograde filling distal to the thrombus; pial arterial filling in the remaining 25% would have been a combination of anterograde and retrograde blood flow and, therefore, not a true reflection of leptomeningeal collateral status. Studies reporting on an association between collateral status and recanalization with intravenous tPA may need to account for the presence of OAF confounding the association. Similarly, it is possible that OAF and resultant faster contrast filling of distal thrombus interface could result in shorter measured thrombus length on conventional nontime resolved CTA than when distal thrombus interface is filled in a retrograde manner through collaterals. Interestingly, on multiphase CTA, median thrombus length in our patients with antegrade flow was shorter than in those with retrograde flow (11.8 mm [IQR, 9.4–21.1 mm] versus 24.2 mm [IQR, 16.8–34.9 mm]).

In our study, 1 of every 3 patients with true retrograde filling because of collaterals achieved early recanalization with intravenous tPA. Within this group, patients with low difference in T0 value between distal and proximal thrombus interface (better retrograde filling because of good collaterals; group 2; Figure 3D) had a higher probability of early recanalization with intravenous tPA than patients with retrograde flow and higher difference in T0 value between distal and proximal thrombus interface (poorer collaterals). Therefore, our study suggests an independent effect of good collateral status on early recanalization; this effect of collaterals on recanalization could possibly because of larger surface of thrombus exposed to thrombolytics at the proximal and distal thrombus interface. Patients with slow retrograde flow (impermeable thrombi and poorer collaterals: group 1) had the least likelihood of early recanalization with intravenous tPA (Figure 3D).

Our study has limitations. CTP-based T0 maps and the artery profile method we developed may sometimes show a nonlinear oscillatory pattern because of noise amplification in the deconvolution algorithm used to extract T0 parameter from low signal-to-noise ischemic regions (even though the algorithm has already been optimized for noise stability). Therefore, it is crucial to sample several contiguous pixels within the artery profile to visualize a trend. A line oriented perpendicular to the CT slice distal to the thrombus results in overlapping pixels along the line profile, making an assessment of the regression slope difficult using our current technique. A 3-dimensional isotropic calculation of T0 could, in our opinion, overcome this limitation. Finally, we did not validate our measurements of anterograde or retrograde flow around and through thrombus using another imaging tool like DSA as has been done in previous studies; this is because thrombus outline sign or anterograde flow measured on DSA after intravenous tPA (Figure 3D).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
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<td>Group 1 (retrograde flow and T0 time difference over 2 s)*</td>
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<td>...</td>
</tr>
<tr>
<td>Group 2 (retrograde flow or T0 time difference over 2 s)</td>
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<td>0.35</td>
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<tr>
<td>Group 3 (anterograde flow and T0 time difference below 2 s)</td>
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<td>2.05–71.91</td>
<td>0.006</td>
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<tr>
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<td>0.59–0.98</td>
<td>0.037</td>
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<tr>
<td>Age, y</td>
<td>0.98</td>
<td>0.94–1.03</td>
<td>0.526</td>
</tr>
</tbody>
</table>

Group 1 (retrograde flow by artery profile, T0 value difference between distal and proximal thrombus interface ROI>2 s) is the reference group; group 2 (retrograde flow by artery profile or T0 value difference between distal and proximal thrombus interface ROI≤2 s); group 3 (anterograde flow by artery profile and T0 value difference between distal and proximal thrombus interface ROI≤2 s). CI indicates confidence interval; and ROI, regions of interest.
tPA administration will be confounded by the lytic effect of intravenous tPA. Measurement of flow on DSA after intravenous tPA administration will necessarily have to be an outcome measure and not a measure of criterion validity.

In conclusion, OAF through intracranial thrombi measured on standard CTP T0 maps using our novel technique is a robust predictor of early recanalization with intravenous tPA. We intend to develop a fully automated tool to measure and subsequently validate this construct in a future study.

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**Disclosures**

Dr Menon has received grant funding from the Canadian Institute of Health Research. Dr Hill has received grant funding from Covidien Inc and Hoffman-La Roche, owns stock in Calgary Scientific Inc, and has received compensation from Merck Canada for being on a trial Safety Committee. Dr Goyal has a licensing agreement with GE Healthcare for multiphase computed tomographic angiography. Dr Lee receives royalties from license of computed tomographic perfusion software to GE Healthcare. The other authors report no conflicts.

**References**


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潜在的な順行性血流は、まだ十分認識されていないが、経静脈組織型プラスミノーゲン活性化因子療法による早期再開通の重要な予測因子である

Occult Anterograde Flow Is an Under-Recognized but Crucial Predictor of Early Recanalization With Intraovensal Tissue-Type Plasminogen Activator

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結果：66例中17例（25.8%）に潜在的な順行性血流が検出された。潜在的な順行性血流が検出された患者は逆順行性血流が検出された患者に比べて早期再開通率が高かった（66.7% 対 29.7%, P = 0.031）。血栓遠位部境界のT0の中央値（1.5秒対3.8秒, P = 0.006）および血栓の近位部と遠位部境界のT0の中央値の差（1.3秒対3.7秒, P = 0.014）は、早期再開通した患者の方が再開通しなかった患者よりも小さかった。多変量解析では、潜在的な順行性血流が検出され血栓の近位部と遠位部境界のT0値の差が≦2秒の患者は最も再開通率が高かった（71.4%）、オッズ比 = 12.15, 95%信頼区間：2.05 ～ 71.91）。一方、逆順行性血流が検出されT0値の差が＞2秒の患者は最も再開通率が低かった（25.9%, オッズ比 = 1）。

結論：血栓を浸透して通過する潜在的な順行性血流はCT灌流画像T0マップによる評価が可能で、経静脈組織型プラスミノーゲン活性化因子療法による早期再開通を的確に予測する。

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表3 経静脈組織型プラスミノーゲン活性化因子療法後の早期再開通に関連する変数を決定する多変量ロジスティック回帰モデル

<table>
<thead>
<tr>
<th>変数</th>
<th>オッズ比</th>
<th>95% CI</th>
<th>P値</th>
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</thead>
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<tr>
<td>第1群（逆性血流およびT0値の差が＞2秒）*</td>
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<td>第2群（逆性血流またはT0値の差が＞2秒）</td>
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<td>0.35</td>
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<td>第3群（順行性血流およびT0値の差が≦2秒）</td>
<td>12.15</td>
<td>2.05-71.91</td>
<td>0.006</td>
</tr>
<tr>
<td>白血球数（1,000 cell/mL 毎）</td>
<td>0.76</td>
<td>0.59-0.98</td>
<td>0.037</td>
</tr>
<tr>
<td>年齢（歳）</td>
<td>0.98</td>
<td>0.94-1.03</td>
<td>0.526</td>
</tr>
</tbody>
</table>

第1群：基準群（運動の流れが逆性血流で、血栓の近位部および遠位部境界のROIのT0値の差が＞2秒）。第2群（運動の流れが逆性血流、または血栓の近位部および遠位部境界のROIのT0値の差が＞2秒）。第3群（運動の流れが順行性血流で、血栓の近位部および遠位部境界のROIのT0値の差が≦2秒）。CI：信頼区間、ROI：満血領域。

注：潜在的な順行性および逆性血流の測定法とT0マップの作成法については、英文原稿の Methods と Figure 1 および Figure 2 を参照されたい。