Smoking-Thrombolysis Paradox
Recanalization and Reperfusion Rates After Intravenous Tissue Plasminogen Activator in Smokers With Ischemic Stroke

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Background and Purpose—The so-called smoking-thrombolysis paradox of an improved outcome after thrombolysis was first described in smokers with myocardial infarction. We investigated whether reperfusion rates and clinical outcome differ between smokers and nonsmokers with ischemic stroke after intravenous tissue plasminogen activator.

Methods—Consecutive acute ischemic stroke patients, who had magnetic resonance imaging before and 1 day after thrombolysis, were included for analysis. All of the patients received intravenous tissue plasminogen activator within 4.5 hours. Reperfusion was defined as a 75% reduction in perfusion deficit (mean transit time >6 s) after thrombolysis compared with baseline. Magnetic resonance angiography was used to evaluate arterial stenosis and occlusion. Functional outcome was assessed 3 months after stroke using the modified Rankin Score.

Results—Of 148 patients, 21.6% were smokers (n=32). Smokers were younger (median, 61 years [SD, 11.6 years]; P<0.001), less often women (28% versus 51%; P=0.03), had lower baseline glucose levels (median, 6.2 mmol/L [interquartile range, 5.7–6.8 mmol/L] versus 6.7 mmol/L [interquartile range, 6.1–8.2 mmol/L]; P<0.01) and higher baseline perfusion deficits (median, 53 mL [interquartile range, 13–141 mL] versus 17 mL [interquartile range, 2–66 mL]; P=0.04). In a backward stepwise regression analysis including age, sex, hypertension, glucose, perfusion deficit, and smoking, smoking had an odds ratio of 4 (95% confidence interval, 1–16; P=0.03) for reperfusion and 6 (95% confidence interval, 1–30; P=0.05) for recanalization (regression analysis for recanalization also included localization of arterial occlusion). Smokers had a better outcome (modified Rankin Score=0–2) than nonsmokers (77% versus 55%; P=0.05).

Conclusions—Smoking is independently associated with recanalization and reperfusion, indicating that thrombolytic therapy acts more effectively in smokers; because of small numbers, these results should be considered preliminary.


Key Words: ischemic stroke • MRI • reperfusion • smoking • thrombolysis
To date, there has only been one study investigating how smoking affects response to thrombolysis in acute ischemic stroke patients. This study confirmed that smokers experience a better early outcome compared with nonsmokers posttreatment. However, the lack of imaging findings did not allow for conclusions to be drawn on the direct efficacy of tPA in smokers. Therefore, we investigated whether smoking is independently associated with recanalization and reperfusion and whether this may affect response to thrombolysis and functional recovery 3 months poststroke in patients with this risk factor.

Methods

Patients and Magnetic Resonance Imaging Protocol

This is a retrospective, single-center observational study conducted at the Center for Stroke Research Berlin at the Benjamin Franklin Campus of Charité University Hospital. Consecutive acute stroke patients recruited between March 2008 and August 2011 from the 1000+ study, who had magnetic resonance imaging (MRI) before and 1 day after thrombolysis, were included in this study after informed consent. Only patients who received intravenous tPA within 4.5 hours of symptom onset and had an MRI within 24 hours of treatment were included for analysis. Patients were excluded from final analysis if neither magnetic resonance angiography nor perfusion imaging was available or not rateable because of poor image quality.

All of the MRI examinations were conducted on a 3.0-Tesla MRI unit (Tim Trio; Siemens, Erlangen, Germany), which is available during working hours only. Standard MRI protocol included T2*, fluid attenuated inversion recovery, diffusion-weighted imaging (DWI), magnetic resonance angiography, and perfusion imaging.

Clinical Assessment

Each patient was evaluated for the following cerebrovascular risk factors on admission: smoking, arterial hypertension, diabetes mellitus, hypolipoproteinemia, and atrial fibrillation. Patients reporting active cigarette use were classified as smokers. Diagnosis of arterial hypertension was based on the use of medications against hypertension or consistent, repeated measurements of blood pressure >140/90 mm Hg. Hypolipoproteinemia was diagnosed based on the use of antidiabetic medication, history of diabetes mellitus, or an elevated glucose level of >7.6 mmol/L. Hypolipoproteinemia was diagnosed in patients with a fasting lipoprotein cholesterol level of ≥3.37 mmol/L, a fasting total cholesterol level of >5.18 mmol/L, or use of medications to lower cholesterol levels. Current medication use was recorded for each patient and categorized as statin or antiplatelet/anticoagulation agents. Stroke severity was assessed on admission, on the day after thrombolysis, and at discharge or on day 7 by an attending physician certified to use the National Institutes of Health Stroke Scale (NIHSS). Stroke etiology was determined and classified based on the Trial of Org 10172 in Acute Stroke Treatment classification criteria; however, severe atherosclerosis was considered satisfactory to claim macroangiopathic etiology. Functional outcome was assessed 3 months after stroke using the modified Rankin Score; scores were dichotomized into a favorable functional outcome (modified Rankin Score ≤2) and poor functional outcome (modified Rankin Score >2).

Procedures

Postprocessing of DWI images was performed using MRICroN (Advanced Brain Imaging) to assess DWI lesion volumes on acute and second scan images to determine relative infarct growth (DWI lesion volume after thrombolysis/baseline lesion volume). Perfusion deficit on mean transit time maps were defined as mean transit time >6 s using StrokeTool (Digital Image Solutions). Reperfusion was defined as a 75% reduction in perfusion deficit on the day after thrombolysis compared with baseline. Magnetic resonance angiography time-of-flight was used to evaluate arterial stenosis and occlusion. Arterial occlusions were categorized based on the size of the occluded vessel: large vessel occlusions (internal carotid artery and carotid T occlusions), medium vessel occlusions (ie, M1, M2, P1, P2, and vertebral occlusion), and small vessel occlusions (occlusion in distal arterial branches). Vessel patency was evaluated using the adapted thrombolysis in myocardial infarction criteria. Recanalization was defined as an increase in ≥2 thrombolyses in myocardial infarction score points the day after thrombolysis compared with baseline.

Statistics

We used a Fisher exact test and Mann-Whitney U test as appropriate in all 2-group analyses. We ran univariate analyses based on our 3 end points, recanalization, reperfusion, and 3-month clinical outcome.

We performed stepwise-backwards multivariable regression analyses including all parameters that turned out significant in univariate analysis based on smoking status and the dependent variable (recanalization and reperfusion). A logistic regression of recanalization (binary) on smoking (binary) with a sample size of 68 observations (of which 80% are nonsmokers and 20% are smokers) achieves 50% power at a 0.05 significance level to detect a change in recanalization from the baseline value of 47% to 78%. This change corresponds with an odds ratio of 4.0. An adjustment was made because a multiple regression of recanalization on the other independent variables in the logistic regression obtained an $r^2$ of 0.08. A logistic regression of reperfusion (binary) on smoking (binary) with a sample size of 93 observations (of which 80% are nonsmokers and 20% are smokers) achieves 61% power at a 0.05 significance level to detect a change in reperfusion from the baseline value of 37% to 67%. This change corresponds with an odds ratio of 3.46. An adjustment was made because a multiple regression of the independent variable of interest on the other independent variables in the logistic regression obtained an $r^2$ of 0.08.

We forced age into each regression analysis to appropriately adjust for this potentially confounding factor. Univariate $r^2$ values were calculated for each parameter included in the regression models using only one independent variable at a time to demonstrate strength of association of each variable with the dependent variable; multivariable $r^2$ values were calculated to reveal the overall strength of each model. All of the statistical analyses were performed using SPSS version 19 (Chicago, IL).

Results

Patient Characteristics

During the recruitment period, a total of 672 patients received intravenous tPA; 148 patients (22%) could be included for final analysis because these patients were able to undergo the 1000+ MRI protocol. Patients excluded from analysis were significantly older (median in years, 76 [interquartile range (IQR), 67–84 versus 73 [IQR, 63–81]; $P = 0.02$), had higher NIHSS on admission (11.0 [IQR, 6–17] versus 6.5 [IQR, 4–13]; $P < 0.001$), more often had atrial fibrillation (44% versus 30%; $P = 0.002$), and were admitted more often during nonworking hours (80% versus 18%; $P < 0.001$) where computed tomography was available only. Of those patients excluded from final analysis, 8% had a cardiac pacemaker. There was no significant difference in distribution of sex, medication use, or other cardiovascular risk factors. All of the baseline characteristics of the primary analysis group of this study (N=148) are summarized in Table 1.

Univariate Analysis of Recanalization, Reperfusion, and Functional Outcome

In the general cohort (N=148), the overall rate of recanalization was 47% (N=67); 36.8% of patients reperfused (N=35) and 59% (N=79) had a favorable outcome (Table 2). Recanalization
For favorable outcome (modified Rankin Score, 0–2) 3 months after stroke, age, sex, atrial fibrillation, smoking, NIHSS on admission, and baseline lesion volume were entered into the regression analysis. Age, NIHSS on admission, and baseline DWI lesion volume were the only variables that remained in the model, revealing NIHSS on admission and age as significant independent predictors of a favorable outcome 3 months poststroke (Table 3).

### Smoking Status and Response to Thrombolysis

In the general cohort (N=148), smokers were significantly younger (mean age, 61 years [SD, 9.4] versus 74.6 years [SD, 11.6]; P<0.001), less often female (28% versus 51%; P=0.03), had lower rates of arterial hypertension (66% versus 84%; P=0.04), and had lower serum glucose levels on admission compared with nonsmokers (6.2 mmol/L [IQR, 5.7–6.8 mmol/L] versus 6.7 mmol/L [IQR, 6.1–8.2 mmol/L]; P<0.01). Smokers and nonsmokers did not differ significantly in terms of rates of arterial occlusion (66% versus 50%; P=0.2), perfusion-diffusion mismatch (78% versus 62%; P=0.17), NIHSS on admission (4 [IQR, 3–9] versus 7 [IQR 4–12]; P=0.053), or mean baseline DWI lesion volumes (2.2 mL [IQR, 0.3–12.0 mL] versus 1.2 mL [IQR, 0.2–5.0 mL]; P=0.2). Smokers had significantly larger mean baseline perfusion deficits (53 mL [IQR, 13.0–140.0 mL] versus 17 mL [IQR, 1.7–66.0 mL]; P=0.04).

In a subgroup analysis including only those patients with proven vessel occlusion (N=79), smokers did not differ significantly in terms of localization of arterial occlusion, baseline infarct volume, or baseline perfusion deficit compared with nonsmokers. Smokers had significantly reduced relative infarct growth and higher rates of recanalization and reperfusion (Table 4). In a subgroup analysis including only those patients that recanlized (N=47), smokers had higher rates of reperfusion than nonsmokers, albeit this result did not reach the level of significance (75% versus 37%; P=0.06).

### Discussion

This is the first study to show that smoking is associated with recanalization and reperfusion in acute ischemic stroke patients treated with intravenous tPA. Despite similar arterial status, smokers showed reduced relative infarct growth compared with nonsmokers, indicating a possible causal treatment effect in patients with this risk factor. Smokers had a better functional outcome 3 months poststroke, most likely because of their low clinical risk profiles and low NIHSS scores on admission. Nonetheless, a favorable functional outcome after stroke was positively associated with reperfusion, suggesting that increased tPA efficacy in smokers may partially contribute to the observed smoking-thrombolysis paradox phenomenon. After all, several trials have shown that reperfusion leads to an improved outcome after ischemic stroke.20–22

The overall rate of smoking (21%) reported in this study is similar to previously published studies when adjusted for age.23,24 As expected, smoking was associated with younger age, lower serum glucose levels,9 and lower rates of atrial fibrillation.25 These baseline differences may explain the slightly lower NIHSS scores observed in patients with this risk factor, which may have contributed to the improved 3-month outcome.26
This study confirms that the infarct-related arterial occlusion recanalizes more often in smokers compared with non-smokers with ischemic stroke, a phenomenon that has been described in several angiographic trials in myocardial infarction patients.2,27,28 Despite adjustment for age and other confounding factors, smoking seems to play a crucial role in clot dissolution, revealing an odds ratio of 7 and 4 for recanalization and reperfusion, respectively. As expected, localization of the occlusion was also highly associated with recanalization (Table 3).29,30 Univariate $r^2$ values demonstrate that smoking accounts for 17% of variance in recanalization and 12% of variance in reperfusion. In line with these paradoxical findings, the Safe Implementation of Thrombolysis in Stroke-Monitoring Study showed in an analysis of 6483 patients that current smokers had significantly lower rates of symptomatic intracerebral hemorrhage.31

These findings further support the hypothesis that thrombolytic therapy acts more aggressively in smokers.11 Restoration of blood flow, however, which more accurately predicts response to thrombolysis, does not necessarily follow vascular recanalization.32 Even so, we observed that smokers were more likely to reperfuse after vessel recanalization.

Cho et al13 found an association between pretreatment T2*-weighted gradient echo imaging-susceptibility vessel sign and subsequent recanalization in patients with large vessel occlusion; the assumption is that gradient echo imaging-susceptibility vessel sign predicts cardioembolic stroke and indicates fibrin-rich thrombi. In a post hoc analysis of this cohort, we rated the presence of gradient echo imaging-susceptibility vessel sign in patients with large vessel occlusion (N=66); 28% had gradient echo imaging-susceptibility vessel sign but we found no association with smoking status, stroke etiology, or subsequent recanalization.

Smoking was not an independent predictor of functional outcome 3 months poststroke. As expected, NIHSS on admission was a significant independent predictor of functional recovery.26 Although in a general cohort analysis smokers had an increased chance of a favorable outcome (Table 2),

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### Table 2. Univariate Analyses of the Primary End Points: Recanalization, Reperfusion, and Favorable Outcome (Modified Rankin Score, 0–2; 90 d Poststroke)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recanalization</th>
<th>Reperfusion</th>
<th>Favorable Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>P Value</td>
</tr>
<tr>
<td>n</td>
<td>47</td>
<td>53</td>
<td>0.063</td>
</tr>
<tr>
<td>Age (≥70 y), % (n)</td>
<td>55.3 (26)</td>
<td>73.6 (39)</td>
<td>0.26</td>
</tr>
<tr>
<td>Sex, % female (n)</td>
<td>42.6 (20)</td>
<td>47.2 (25)</td>
<td>0.69</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension, % (n)</td>
<td>76.6 (36)</td>
<td>86.8 (46)</td>
<td>0.20</td>
</tr>
<tr>
<td>Diabetes mellitus, % (n)</td>
<td>21.3 (10)</td>
<td>32.1 (17)</td>
<td>0.26</td>
</tr>
<tr>
<td>Hypolipoproteinemia, % (n)</td>
<td>48.9 (23)</td>
<td>43.4 (23)</td>
<td>0.87</td>
</tr>
<tr>
<td>Atrial fibrillation, % (n)</td>
<td>36.2 (17)</td>
<td>35.8 (19)</td>
<td>1.0</td>
</tr>
<tr>
<td>Smoking, % (n)</td>
<td>38.3 (18)</td>
<td>9.4 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum glucose levels &gt;120 mmol/L, % (n)</td>
<td>51.1 (23)</td>
<td>52.1 (25)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; and NIHSS, National Institutes of Health Stroke Scale.
this effect disappeared after adjustment for arterial occlusion (Table 4). On the other hand, smokers presented with larger baseline perfusion deficits and slightly higher rates of arterial occlusion and therefore may be more likely to benefit from reperfusion therapy in the first place.34 As one might anticipate, favorable outcome was positively associated with recanalization and reperfusion; the combination of these effects may jointly contribute to this paradoxical phenomenon.

This study has limitations. Foremost, this is a retrospective, exploratory analysis. With relatively low patient numbers, our study runs the risk of type I errors. Therefore, these results should be interpreted with caution. In addition, reperfusion status was unavailable in 24 patients because of a disturbance in either the pretreatment or posttreatment perfusion imaging. The inclusion of only those patients with pretreatment and posttreatment MRI introduces a bias, excluding older and more severely affected patients. Finally, records of pack-years and previous smoking behavior of patients were not available. Studies have demonstrated a dose-dependent increase in plasma-fibrinogen levels in smokers35 and a rapid change in fibrin levels after cessation.36 The crude definition of smoking used in this study remains a substantial limitation of this analysis. A prospective study with more detailed information of smoking behavior is warranted to validate these results.
Table 4. Response to Thrombolysis Based on Smoking Status in Patients With Proven Vessel Occlusion: Imaging Findings and Clinical Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonsmokers</th>
<th>Smokers</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>58</td>
<td>21</td>
<td>0.90</td>
</tr>
<tr>
<td>Localization of arterial occlusion, % (n)</td>
<td>1.4 (4)</td>
<td>9.5 (2)</td>
<td></td>
</tr>
<tr>
<td>Large vessel occlusion</td>
<td>7.1 (4)</td>
<td>9.5 (2)</td>
<td></td>
</tr>
<tr>
<td>Mainstem occlusion</td>
<td>78.6 (44)</td>
<td>47.6 (19)</td>
<td></td>
</tr>
<tr>
<td>Small vessel occlusion</td>
<td>8 (14.3)</td>
<td>42.9 (9)</td>
<td></td>
</tr>
<tr>
<td>Perfusion-diffusion mismatch, % (n)</td>
<td>82.4 (42)</td>
<td>88.2 (15)</td>
<td>0.72</td>
</tr>
<tr>
<td>Baseline lesion volume, median (IQR)</td>
<td>2.8 (0.3 to 10.6)</td>
<td>2.7 (1.2 to 15.4)</td>
<td>0.33</td>
</tr>
<tr>
<td>Baseline perfusion deficit, median (IQR)</td>
<td>63.7 (18.2 to 112.6)</td>
<td>84.9 (32.3 to 194.9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Recanalization, % (n)</td>
<td>50 (28)</td>
<td>81.1 (17)</td>
<td>0.02</td>
</tr>
<tr>
<td>Reperfusion, % (n)</td>
<td>30.6 (11)</td>
<td>75 (9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Relative infarct growth, median (IQR)</td>
<td>3.0 (1.7 to 9.0)</td>
<td>1.5 (1.2 to 3.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>Change in NIHSS day 7, median (IQR)</td>
<td>–3.5 (–7.5 to –0.25)</td>
<td>–3 (–7.5 to –1.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Mortality at 3 mo, % (n)</td>
<td>19.2 (10)</td>
<td>0 (0)</td>
<td>0.054</td>
</tr>
<tr>
<td>Good outcome at 3 mo % (n)</td>
<td>48.1 (59)</td>
<td>66.7 (12)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; and NIHSS, National Institutes of Health Stroke Scale.

Additional analyses of trials that include recanalization and reperfusion data of intravenous tPA-treated patients, such as the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) and Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE), would be excellent databases to explore this topic further.

Summary and Conclusions

The principle mechanism underlying the smoking-thrombolysis paradox remains a matter of debate. Most likely there is a cumulative effect of younger age, low clinical risk profiles, and more aggressive treatment effect that explains the better prognosis in patients with this risk factor. Naturally, we by no means encourage smoking; smoking is a proven risk factor for stroke and has detrimental effects on the cardiovascular system. Needless to say, no stroke is always better than a recanalized stroke. Here, we merely show increased tPA efficacy in smokers after acute ischemic stroke, which may partially explain the frequently observed smoking-thrombolysis paradox phenomenon.

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Disclosures

A. Kufner has no disclosures; she occasionally smokes. Dr Nolte reports payments for lectures and travel grants from Boehringer-Ingehringheim and Takeda-Pharma; he is a nonsmoker. Drs Galinovic, Brunecker, G. Kufner, and Ebinger have no disclosures; they are nonsmokers. Dr Endres reports the following consultancies, grants, and/or payments for lectures including service on speakers bureaus: Astra Zeneca, Bayer, Berlin Chemie, BMS, Boehringer-Ingehringheim, Glaxo Smith Kline, Novartis, Pfizer, Sanofi-Aventis, and Trommsdorff; he holds a patent for the upregulation of type III endothelial cell nitric oxide synthase by HMG-CoA reductase inhibitors (US patent No. 6,147,109); he smoked during college but never inhaled. Dr Fiebach reports the following board memberships, consultancies, and/or payments for lectures including service on speakers bureaus: Boehringer-Ingelheim, Lundbeck, Siemens, Sygnis, and Synarc; he is a nonsmoker.

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