Improving the Prediction of Spontaneous and Post-thrombolytic Recanalization in Ischemic Stroke Patients

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Background: Endovascular treatment for acute ischemic stroke patients was recently shown to improve recanalization rates and clinical outcome in a well-defined study population. Intravenous thrombolysis (IVT) alone is insufficiently effective to recanalize in certain patients or of little value in others. Accordingly, we aimed at identifying predictors of recanalization in patients treated with or without IVT. *Methods:* In the observational Acute Stroke Registry and Analysis of Lausanne (ASTRAL) registry, we selected those stroke patients (1) with an arterial occlusion on computed tomography angiography (CTA) imaging, (2) who had an arterial patency assessment at 24 hours (CTA/magnetic resonance angiography/transcranial Doppler), and (3) who were treated with IVT or had no revascularization treatment. Based on 2 separate logistic regression analyses, predictors of spontaneous and post-thrombolytic recanalization were generated. *Results:* Partial or complete recanalization was achieved in 121 of 210 (58%) thrombolyzed patients. Recanalization was associated with atrial fibrillation (odds ratio , 1.6; 95% confidence interval, 1.2-3.0) and absence of early ischemic changes on CT (1.1, 1.1-1.2) and inversely correlated with the presence of a significant extracranial (EC) stenosis or occlusion (.6, .3-.9). In nonthrombolyzed patients, partial or complete recanalization was significantly less frequent (37%, $P < .01$). The recanalization was independently associated with a history of hypercholesterolemia (2.6, 1.2-5.6) and the proximal site of the intracranial occlusion (2.5, 1.2-5.4), and inversely correlated with a decreased level of consciousness (.3, .1-.8), and EC (.3, .1-.6) and basilar artery pathology (.1, .0-.6). *Conclusions:* Various clinical findings, cardiovascular risk factors, and arterial pathology on acute CTA-based imaging are moderately associated with spontaneous and post-thrombolytic arterial recanalization at 24 hours. If confirmed in other studies, this information may influence patient selection toward the most appropriate revascularization strategy. **Key Words:** Ischemic stroke—acute stroke management—IV thrombolysis—recanalization—CT angiography.

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Introduction

Recanalization and reperfusion of threatened ischemic tissue are the most critical predictors for a favorable clinical outcome in acute ischemic stroke.[1] Chances of success also depend on the time to reperfusion,[1,2] the core size, and a favorable penumbra/core ratio.[3–5] The benefit of intravenous thrombolysis (IVT) is also highly time dependent as it is related to the speed and completeness of the clot breakup and the presence of collaterals.[1,6,7] Furthermore, patients with strokes caused by large-vessel occlusions have low recanalization rates with IVT alone and are associated with poor functional outcome despite treatment.[8,9] This may be explained by clot characteristics (composition, size, and location), collateral integrity, and metabolic and genetic factors. More aggressive endovascular treatment strategies are increasingly used to treat large-vessel occlusive strokes as they recanalize these occlusions more effectively and rapidly.[10] Identification of the predictors of recanalization in IVT-treated patients may influence the patient selection for endovascular recanalization therapies. So far, prior studies have detected milder baseline stroke deficits, elevated systolic blood pressures, normal glucose values, smoking history, absence of atrial fibrillation, distal vessel occlusion, and thrombus length to predict post-thrombolytic recanalization.[11–17] However, most of these studies were performed without a logistic regression analysis. The aim of the present study was to identify independent predictors of spontaneous and post-thrombolytic recanalization among multiple demographic, clinical, metabolic, and radiological variables and in a large consecutive cohort of large-vessel occlusive strokes.

Patients and Methods

Study Design and Patient Selection

From January 2003 to July 2012, all consecutive acute ischemic stroke patients admitted to the stroke unit and/or intensive care unit within 24 hours after last known well time were prospectively included in our acute stroke registry.[18] For the current analysis, only patients fulfilling the following inclusion criteria were selected: (1) acute computed tomography angiography (CTA) performed within 12 hours after last known well time, (2) arterial occlusion in cervical and/or cerebral arteries on CTA and in relation to the ischemic territory, (3) availability of a second noninvasive arterial imaging (CTA, magnetic resonance angiography [MRA], or duplex) after 24 hours of the initial treatment (maximal range, 12-48 hours), allowing assessment of recanalization, and (4) treated with IVT within proven time windows or untreated. CTA is performed in all patients without iodized contrast contraindications, such as known allergy or known renal failure. In the original ASTRAL study, 78% of all ischemic strokes had a CTA on arrival.[18] The up to 12 hours time window was selected because significant salvageable brain tissue may still be present, and the recanalization assessment at 24 hours as this time point is a stronger predictor for a favorable outcome at 3 months than earlier assessments (<2 hours).[19,20] IVT with recombinant tissue plasminogen activator was performed whenever indicated by the guidelines of the European Stroke Organization.

Demographics, previous cerebrovascular events, comorbidities, clinical symptoms and signs, and metabolic and physiological parameters were recorded at admission and 24 hours later. Cardiovascular risk factors (pre-existing or newly diagnosed) were systematically collected. National Institutes of Health Stroke Scale (NIHSS) assessment was performed at admission, 6 and 24 hours later, and at 7 days. Prestroke disability and 3-months outcome were assessed using the modified Rankin scale (mRs). Clinical outcome analysis was restricted to patients with prestroke mRs score of 2 or less and was defined as mRs greater than 2 at 3 months. Stroke etiology was categorized following the Trial of Org 10172 in Acute Stroke Treatment classification with dissection and multiple causes added as additional mechanisms.

The study (collection, analysis, and publication of data) was performed according to the ethical guidelines of the commission for research on humans of the Canton of Vaud, subcommission III.

Angiographic Analysis of Arterial Occlusion and Recanalization

On the acute and subacute CTA, extracranial (EC) and large intracranial (LIC) vessels were assessed using continuous axial and reformatted maximum intensity projection pictures of EC and IC arteries for thrombus presence, the most proximal location, and multiple sites of occlusion. The site of the artery occlusion in the ischemic territory (+/− in nonischemic territory) was categorized as follows: IC, EC, LIC, intermediate intracranial (IIC), anterior, and posterior circulation occlusion. LIC occlusion was defined as an occlusion in the trunk of the middle cerebral artery (M1), T-occlusion of the IC internal carotid artery, or basilar artery occlusion. The group of IIC occlusions contained occlusions in the anterior cerebral artery (A1 or A2 segments), distal middle cerebral artery (M2), posterior cerebral artery (P1 or P2 segments), IC part of the vertebral artery (V4), and the siphon of the internal carotid artery without distal T-occlusion; the latter 2 were considered "intermediate" because thrombus load and clinical symptoms are usually minor in the absence of extension into the basilar artery and the carotid T, respectively. Tandem arterial occlusions were defined as a combination of a LIC occlusion and an EC occlusion of the artery leading to the ischemic territory. Occlusion extension was categorized as occlusion in a single vessel segment or in multiple vessel segments. Recanalization of initially occluded IC/EC arteries was classified as absent, partial, or complete. More detailed information about the definitions for arterial pathology (occlusion and significant stenosis) and recanalization (none versus partial versus complete) has been published elsewhere.[21]

Statistical Analysis

Statistical analysis was performed with R STATA software (version 2-15-211, 2009; StataCorp, Texas, USA). Recanalization was dichotomized into favorable (complete or partial recanalization) and unfavorable (no recanalization). Five multiple computations were performed by Gibbs sampling to fill in incomplete data, before univariate logistic regression was implemented to identify potential predictors of arterial occlusion. Importance of interactions of the statistically significant main effects was also studied separately in each analysis, but none was found significant. Significance of predictors was assessed at 95% confidence level.

Results

Baseline Characteristics

From January 2003 to July 2012, 381 of 2765 stroke patients met the inclusion and exclusion criteria (Figure S1 in Appendix). Of the 381 patients, 210 (55%) were treated with IVT within the recommended time window, and 171 (45%) were not eligible for revascularization treatment. The following were the most frequent reasons for nontreatment with IVT: time between symptom onset and hospital arrival of more than 4.5 hours (32%), therapeutically anticoagulated (11%), minor stroke (NIHSS < 4 or no isolated aphasia or hemianopia; 15%), and a pre-existing neurologic deficit (mRs > 2; 10%). The examination on which the initial diagnosis of arterial occlusion was based was CTA in all our patients. The study on which 24-hour recanalization assessment was based was CTA in 60 patients (35%), MRA in 50 patients (29%), and transcranial Doppler (TCD) in 61 patients (36%). The occlusion site on initial imaging was LIC in 226 patients (59%), IIC in 151 patients (40%), and EC in 128 patients (34%). Tandem arterial occlusions were found in 65 patients (17%). Partial or complete recanalization of IC and EC vessels at 24 hours was seen in 226 (59%) of all patients. Baseline characteristics of both groups are given in Table S1 in Appendix. Comparison with data from patients excluded from the study shows similar patient profiles between the included and the radiological and/or treatment-related excluded strokes.

Recanalization after IVT

Complete or partial recanalization after IVT was observed in 58% of patients. Highest recanalization rates were seen in IIC occlusions (63%), followed by LIC occlusions (56%) and by EC occlusions or tandem occlusions (both 50%). An occlusion extension over more than one IC and/or EC vessel segment did not significantly decrease recanalization rates (54%; Table 1). In multiple regression analysis, presence of atrial fibrillation (odds ratio [OR], 1.6; 95% confidence interval [CI], 1.2-3.0) was found to be the only independent clinical sign of IVT-related recanalization. Both absence of early ischemic changes on the initial cerebral imaging (Alberta Stroke Program Early CT score [ASPECTS] = 10; OR, 1.1; 95% CI, 1.1-1.3) and absence of a symptomatic EC stenosis (50%-100% North American Symptomatic Carotid Endarterectomy Trial; OR, .6; 95% CI, .3-.9) were independent radiological predictors of the arterial recanalization rates (Table 2). The predictive model based on these 3 clinicoradiological items had a rather moderate receiver operating characteristic curve (area under the curve = .63). The median NIHSS decreased from 15 (interquartile range [IQR], 10) at admission to 7 (IQR, 10) after 24 hours in cases of complete or partial recanalization,

Table 1. *Recanalization rates dependent on baseline occlusion site and occlusion extension*

Occlusion location	Untreated patients (n = 171)	IV rt-PA-treated patients (n = 210)	*P* value
Proximal IC occlusion	44% (42)	56% (74)	<.05
Distal IC occlusion	34% (23)	63% (53)	<.05
EC occlusion	24% (17)	50% (29)	.10
Tandem occlusion	29% (12)	50% (27)	.06
Occlusion extension (≥2 segments)	29% (30)	54% (60)	<.05
All occlusions	37% (59)	58% (121)	<.01

Abbreviations: EC, extracranial; IC, intracranial; IV, intravenous; rt-PA, recombinant tissue plasminogen activator.

Table 2. *Results of the multivariable model for variables associated with IVT-induced complete or partial recanalization at 24 hours (12-48 hours) after documentation of initial large-vessel occlusion*

IV rt-PA-treated recanalization		
clinical-radiological variable	OR (95% CI)	*P* value
Symptomatic extracranial stenosis (50%-100%)	.6 (.3-.9)	.04
Atrial fibrillation	1.6 (1.2-3.0)	.02
ASPECTS adapted to the circulation	1.1 (1.1-1.2)	.05

Abbreviations: ASPECTS, Alberta Stroke Program Early CT score; CI, confidence interval; IVT, intravenous thrombolysis; OR, odds ratio; rt-PA, recombinant tissue plasminogen activator.

and from 16 (IQR, 11) to 13 (IQR, 12) in cases without recanalization. Among the 121 patients successfully recanalized within 24 hours (12-48 hours), 99 patients (82%) showed an early clinical improvement. This was defined by NIHSS improvement of at least 1 point in comparison with the baseline. However, in the long term, a quarter of the recanalized patients had an unfavorable outcome at 3 months (mRs > 2).

Spontaneous Recanalization

Spontaneous recanalization was observed in 59 untreated patients (37%). This is significantly lower than the detected recanalization rate after IVT (58%, $P < .01$). LIC clot locations had the highest recanalization rates (44%). EC occlusions, tandem occlusions, and prolonged occlusion extensions (>1 vessel segment) were recanalized in less than one third of the patients (Table 1). In logistic regression analysis, spontaneous recanalization was independently associated with a history of hypercholesterolemia (OR, 2.6; 95% CI, 1.2-5.6), decreased level of consciousness (OR, .3; 95% CI, .1-.8), and vessel characteristics on CTA. An LIC clot location was more likely to recanalize (OR, 2.5; 95% CI, 1.2-5.4). Lower recanalization rates were correlated with the presence of significant basilar (OR, .1; 95% CI, .0-.6) and EC arterial pathology (OR, .3; 95% CI, .1-.6; Table 3). The predictive model for spontaneous recanalization was found to have a moderate to good receiver operating characteristic curve (area under the curve = .77). Spontaneous recanalization rates are significantly influenced by the stroke etiology. In the recanalization group, cardioembolism was by far the most frequent etiology (44% versus 25%), in comparison with the higher numbers of large-artery atherosclerosis (38% versus 18%) in the nonrecanalization group.

Complete or partial recanalization lead to a median NIHSS decrease from 14 (at admission; IQR, 12) to 11 (after 24 hours; IQR, 11) in the recanalization group. Early clinical improvement was detected in 70% of the recanalized patients and in only 35% of nonrecanalized patients. The nonrecanalization group showed a net increase from 10 (IQR, 16) to 12 (IQR, 14) at 24 hours. Unfavorable outcome despite complete or partial recanalization was seen in 53%.

Table 3. *Results of the multivariable model for variables associated with spontaneous, complete, or partial recanalization of arterial occlusion at 24 hours (12-48 hours)*

Untreated recanalization		
clinical-radiological variable	OR (95% CI)	*P* value
Decreased level of consciousness	.3 (.1-.8)	.02
History of hypercholesterolemia	2.6 (1.2-5.6)	.01
Proximal intracranial occlusion (compared with any other site)	2.5 (1.2-5.4)	.02
Significant basilar artery pathology*	.1 (.0-.6)	.01
Significant extracranial pathology*	.3 (.1-.6)	<.01

Abbreviations: CI, confidence interval; OR, odds ratio.
*Stenosis ≥50% or occlusion in vessel leading to the ischemic territory.

Discussion

Our study of 381 patients presenting with large-vessel occlusion ischemic stroke found that the 24-hour spontaneous or post-thrombolytic recanalization rates were associated with clinical findings, cardiovascular risk factors, radiological features, and large-vessel characteristics.

In this study, the likelihood of IVT-related recanalization was positively influenced by not- or insufficiently-anticoagulated atrial fibrillation and normal pretreatment ASPECTS score on plain CT and negatively influenced by symptomatic EC vasculopathies. One might expect that most of the patients with pre-existing atrial fibrillation are therapeutically anticoagulated and are therefore excluded for IVT but some observational studies have reported conflicting results on the association between not- or insufficiently-anticoagulated atrial fibrillation and post-thrombolytic recanalization. Kimura et al detected that a history of atrial fibrillation was linked to absence of early recanalization. However, their study contained only 49 IVT-treated stroke patients, and recanalization assessment was performed within 30 minutes after IVT infusion by TCD.[12] Comparable with our results, Mendonca et al[17] and Molina et al[22] reported that early recanalization was more frequent in patients with cardioembolic strokes, especially in atrial fibrillation, compared to other stroke types. Cardioembolic, fibrin-rich clots may reopen by plasmin proteolysis more frequently than in situ thrombosis at an atherosclerotic plaque.[23] Furthermore, in cases of subtherapeutic oral anticoagulation, clot lysis during IVT will lead to more fragile emboli and the inhibition of the thrombotic system because anticoagulation will accelerate thrombolysis.[24]

Absence of early ischemic changes on CT was already demonstrated in a subgroup of IVT-treated acute middle cerebral artery occlusions[14] and may reflect the absence of a large core volume, or better collaterals. Moreover, our study confirmed that the concomitant presence of EC arterial stenosis or occlusion may lead to less recanalization because of a decreased inflow of blood into the blocked arteries, leading to lower arrival of IV recombinant tissue plasminogen activator and less clot washout. Mendonca et al[17] had described this in patients with a proximal middle cerebral artery occlusion. When looking at our IVT population, acute stroke severity (measured by baseline NIHSS) did not significantly differ between the patients with recanalization of the large-vessel occlusions versus no recanalization (median NIHSS 16 [IQR, 11] versus 15 [IQR, 10]). Other previously described predictors such as high serum glucose (*P* = .49) and elevated systolic blood pressure on admission (*P* = .75), history of diabetes (*P* = .26), smoking (*P* = .27), female gender (*P* = .79), and age (*P* = .69) were not identified in our logistic regression analysis.[11,14,16,17] This may be related to patient selection (only IVT or only endovascular treatment patients), the size of the study population, or the absence of multivariate analysis in the previous studies.

In our untreated study population, the recanalization rate of IC vessel occlusions was about two thirds that of IVT-treated patients (37% versus 58%). A known hypercholesterolemia and a proximal IC clot site (as opposed to EC and distal clot locations combined) independently influence these recanalization rates. This latter unexpected finding may be related to the comparison group where EC occlusions (with little likelihood of recanalization) were combined with distal IC occlusions; alternatively, it may relate to a false-positive finding from a limited number of observations. A decreased level of consciousness on clinical examination was inversely correlated with spontaneous recanalization. Older observations linking decreased level of consciousness with a poor clinical outcome may now be explained by lack of recanalization.

Despite evidence of the development of atherosclerosis and cardiovascular diseases in people with hypercholesterolemia, a beneficial effect of hypercholesterolemia on outcome after ischemic, noncardioembolic stroke and acute coronary artery disease has been previously described.[25–27] Possible explanations are the lipid's antioxidant effect and a lesser risk of infection.[25–28] Also, prestroke statin use in hyperlipidemic patients was associated with a better clinical outcome in a meta-analysis.[29] However, in our study, the association between hypercholesterolemia and spontaneous recanalization was independent of the proportion of patients with prestroke intake of lipid-lowering drugs (*P* = .70). Therefore, a direct relationship between lipid concentrations and improved outcome after stroke seems likely. Spontaneous recanalization was infrequent in patients with significant EC or basilar artery pathology (stenosis 50%-99% or occlusion). It has already been shown that EC carotid occlusion is a predictive factor in vessel recanalization after IVT.[8,17] This may be because of technical difficulties to recanalize EC arteries and to achieve complete recanalization of associated IC occlusions, as well as hemodynamic factors. Furthermore, PIC clots were more prone to resolve spontaneously than clots at other occlusion sites, especially EC vessel occlusions. Thrombus length extending over more than one vessel segment also decreased spontaneous recanalization by more than 50% (Table 1), but did not reach significance in multivariate analysis. Although statistical significance was not reached, these results are in line with prior studies linking recanalization after IVT to clot length.[30] This may be in line with the less precise estimation of the thrombus length.

Strengths of our study include the large number of patients, included variables, and the application of a robust statistical analysis. Identification of new and confirmation of known predictors of recanalization after IVT may guide future patient selection for endovascular recanalization therapies as they showed recently to improve clinical outcome in well-selected patients.

Several limitations apply to the generalizability of our results. First, we recorded arterial recanalization at 24 hours (range, 12-48 hours), although the optimal timing for reassessment of the vessel occlusion remains uncertain.[9,15] Yeo et al[6] demonstrated that persistent recanalization (at 24 hours on CTA) was a stronger predictor than early recanalization (first 2 hours on TCD) for a favorable outcome at 3 months. Second, in this retrospective analysis, a minority of patients with initial large-vessel occlusions had no follow-up vascular imaging and were excluded, which may introduce selection bias (320, 12%). Third, recanalization was measured with various methods (CTA, MRA, and TCD) to increase the number of patients; these methods are not exactly comparable with the initial CTA-based assessment but we used well-established methods for defining recanalization. Fourth, collateral adequacy, core/penumbra volume on CT perfusion, clot burden, and thrombus composition were not assessed as potential predictors because of lack of data. To compensate for clot burden, we used the variable "occlusion extension" as an indirect measure of thrombus extent. Nonetheless, as the field of acute stroke research is moving toward a more detailed assessment of the vessel characteristics, future research will need to focus on these radiological parameters. Finally, the imaging techniques were at their limits to detect distal emboli (beyond M2-A2 segments) and to determine distal branch revascularization.

Conclusion

In this study, acute ischemic stroke patients with a history of atrial fibrillation, absence of dysarthria, and absence of early ischemic changes on CT were more likely to achieve arterial recanalization (58%) after IVT. Spontaneous recanalization occurred in 37% and is best predicted by hypercholesterolemia and proximal intracranial clot location. A decreased vigilance, significant basilar artery, or EC artery pathology will independently have a negative impact on spontaneous recanalization. Moreover, large-vessel recanalization failed to improve clinical outcome in almost half of the patients, especially in untreated patients.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.04.002.

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