ORIGINAL ARTICLES

TOF-MRA is reliable to evaluate the degree of MCA obstruction in acute stroke: an inter- and intra-observer study

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Abstract

Introduction: Artery recanalization is one of the best predictors of good clinical outcome after acute ischemic stroke thrombolysis and it could be used as a surrogate marker for outcome if it can be graded reliably. The purpose of this study was to analyze the inter- and intra-observer reliability of the degree of MCA obstruction on TOF-MRA.

Methods: 91 patients with a MCA stroke were prospectively included in a multicenter study. They underwent MRI including a TOF-MRA within the first 12 hours after symptoms onset. Two blinded observers quantified the degree of MCA obstruction on TOF-MRA according to a modified TIMI grading system. To assess intra-observer reliability, evaluations by the same investigators were repeated 15 days apart. Dichotomized (TIMI 0-1 versus 2-3) and ordinal TIMI score analyses were performed. Inter- and intra-observer reliability was categorized from poor to excellent based on kappa values.

Results: The mean delay between symptom onset and MRI was 6.3 ± 3.3 hours. Analysis of TOF-MRA was impossible in 2.6 % for M1 segment and 6.9% for M2 segment due to technical limitations. The inter- and intra-observer reliability was good to excellent for the dichotomized TIMI score (kappa ranging from 0.77 to 0.91) as well as for the ordinal TIMI score (kappa ranging from 0.82 to 0.96).

Conclusion: The substantial reproducibility of the dichotomized and the ordinal TIMI grading system makes the TOF-MRA sequence a reliable tool to evaluate the degree of MCA obstruction and thus recanalization in clinical practice as well as in clinical research.

Keywords

Magnetic resonance angiography, Inter-observer reliability, Intra-observer reliability, Recanalization, Acute stroke

1 Introduction

Early artery recanalization is strongly associated with improved functional outcome and reduced mortality after ischemic stroke [1-4]. Therefore, artery recanalization has already been used as a surrogate marker in therapeutic trials with thrombolytic agents [5] or thrombectomy devices [6-8]. However, for a definitive validation, a biomarker must not only correlate to functional clinical outcome but also be assessed and graded reliably.

Revascularization grading systems in acute ischemic stroke therapies are a controversial topic of current interest [9, 10]. Many different grading systems are used in clinical studies, case series and reviews including the TIMI, TICI (Thrombolysis In Cerebral Ischemia), TIBI (Thrombolysis In Brain Ischemia), AOL (Arterial Occlusion Lesion) and Mori reperfusion scales. This lack of consensus makes comparisons of the results of endovascular and intravenous treatments challenging. A better standardization of revascularization grading systems and evaluation of their inter- and intra-revascularization agreement are urgently required [11].

While for endovascular treatment, recanalization is assessed on conventional angiography at a single time-point immediately after the procedure, for intravenous thrombolysis, recanalization is assessed on non-invasive imaging such as CT- or MR-angiography by comparing pre- and post-treatment vessel status. The TOF-MRA sequence is particularly useful to evaluate initial degree of arterial obstruction and post-thrombolysis recanalization since it is non-invasive, requires minimal post-processing and is combined with other stroke MRI sequences which allow a comprehensive assessment of tissue status at the same time. These advantages have made of TOF-MRA a widely used imaging modality to assess the degree of arterial obstruction and recanalization in large thrombolytic studies [5, 12, 13].

The TIMI scale [14] used to be the most common grading system to determine recanalization on conventional angiography in stroke studies, but it is currently being replaced by the TICI scale which might be more specific for cerebral vasculature [11]. However, since it requires dynamic evaluations, the TICI scale can’t be adapted to TOF-MRA. Conversely, the TIMI scale has been previously adapted and used in a relevant way with TOF-MRA [15]. Two major thrombolytic trials have defined recanalization on TOF-MRA as an improvement of TIMI grading $\geqslant 2$ from baseline to post-treatment MRA [5, 16]. On-going trials testing new thrombolytic agents [17] or aiming at extending the thrombolysis time-window [18] are also using the TIMI scale with TOF-MRA to assess recanalization as an endpoint. Despite this widespread utilization, the reproducibility of the degree of MCA obstruction on TOF-MRA using the TIMI scale has never been evaluated.

In the present paper, we aim to determine the inter- and intra-observer reliability of the degree of MCA obstruction using a modified TIMI scale by reviewing a dataset of TOF-MRAs prospectively collected at the acute phase of stroke.

2 Methods

2.1 Patients

A total of 91 patients with a first MCA acute ischemic stroke evolving for less than 12 hours were prospectively included in the “VIRAGE” study. Details of the VIRAGE study methodology have been previously described [19]. In summary, VIRAGE is a national multicenter observational cohort including 4 university hospitals in France. The study was approved by the institutional review board, and written informed consent was obtained from all participants. Primary inclusion criteria were as follows: men and women, older than 18 years, with a clinical diagnosis of minor-to-severe cerebral infarct (NIHSS scores between 4 and 20) in the left or right MCA territory evolving for < 12 hours. Exclusion criteria were the following: coma, transient ischemic attacks or lacunar syndrome, pregnant or breast-feeding women or women without a negative pregnancy test, and contraindications to MR imaging.

2.2 MR imaging protocol

MRIs with TOF-MRA were performed on 1.5 T magnets within 12 hours after the symptoms onset. TOF-MRA protocol was standardized across centers and typically consisted on 200 slices, TR/TE 35ms/7ms, 20cm FOV and 5122 matrix. MR imaging studies were centralized by using an independent core laboratory (Bio-Imaging, Lyon, France), which developed dedicated software tools for randomized image-review sessions. Results were automatically extracted by Bio-Imaging and then sent directly to the core statistical unit.

2.3 MRA analysis

The two readers, a neuroradiologist (TT) and a stroke neurologist (PR), reviewed all TOF-MRAs in a randomized order, including the native images, the reconstructions in 3 orthogonal planes, and 3D maximum intensity projections. The readers were blinded to the clinical data, to the localization of the infarcts and to each other. The status of M1 and M2 segments of the MCAs were categorized according to a modified TIMI scale including a more precise definition of TIMI 1 and 2: 0= no recanalization, 1= minimal recanalization corresponding to flow signal detectable beyond the area of obstruction but not in most of the distal vascular bed, 2= partial recanalization defined by an incomplete recanalization but filling most of the vascular bed, 3= complete recanalization (see Figure 1) [15]. Images could be judged technically inadequate. Both readers had a prior training session using the modified TIMI scale on a sample of 10 MRAs. To assess the intra-observer reliability of the classification, the 2 readers performed a second analysis with an interval of 15 days to avoid memory bias.

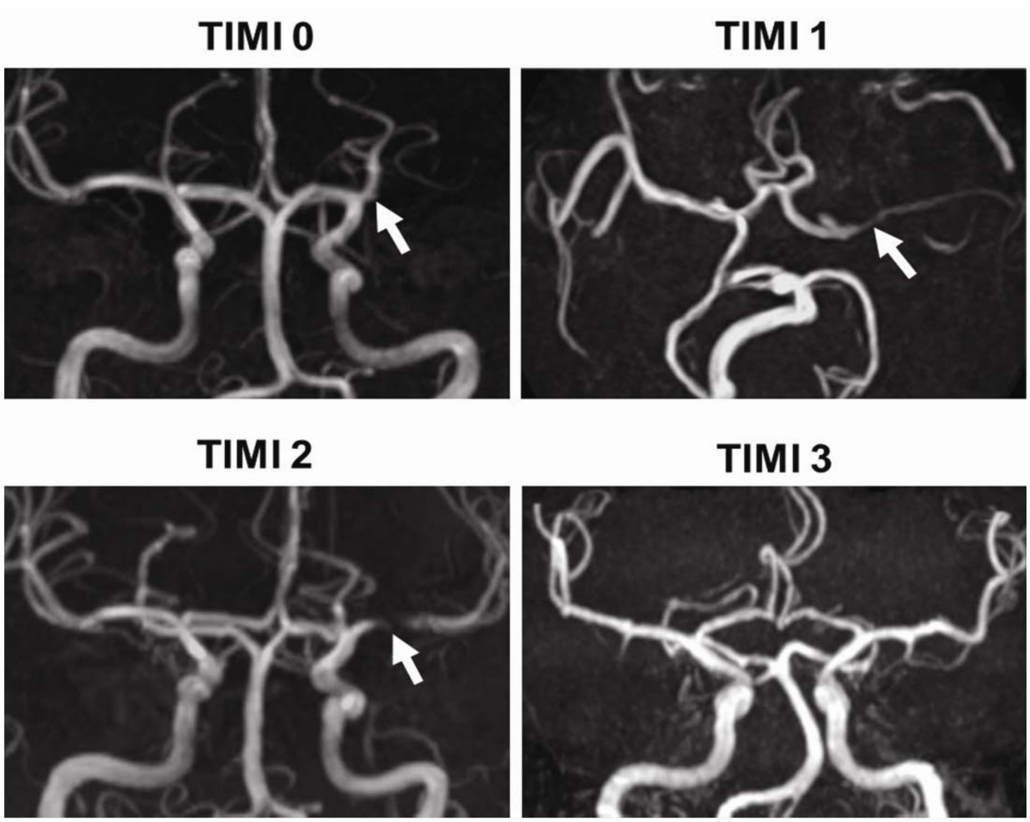

Figure 1. Evaluation of the degree of MCA obstruction on TOF-MRA using the modified TIMI grading system

TIMI 0: no recanalization. TIMI 1: minimal recanalization corresponding to flow signal detectable beyond the area of obstruction but not in most of the distal vascular bed. TIMI 2: partial recanalization defined by an incomplete recanalization but filling most of the vascular bed. TIMI 3: complete recanalization

We decided to evaluate the degree of MCA obstruction only on TOF-MRAs performed at a single time-point since recanalization evaluation consists of a comparison of the degree of MCA obstruction between pre- and post-treatment TOF-MRAs.

2.4 Statistical analysis

The descriptive statistics used were mean and standard deviation. Inter- and intra-observer agreement was assessed by calculating the Cohen's Kappa for dichotomized classification and the weighted Cohen's Kappa for ordinal classification (using the quadratic weighting). Kappa values < 0.20, 0.21-0.40, 0.41-0.60, 0.61-0.80 and 0.81-1.00 were considered to indicate poor, fair, moderate, good and excellent agreement, respectively. Only interpretable images were analysed. Inter-observer agreement was assessed for the 2 readings and intra-observer agreement for the 2 readers. We analysed the reliability of: (i) a dichotomized classification between an occluded status (TIMI 0-1) and a permeable status (TIMI 2-3), (ii) an ordinal classification using the 4 points of the TIMI scale. 95% confidence intervals were calculated using the asymptotic variance formula.

3 Results

Baselines characteristics of the 91 patients are presented in Table 1. MRIs were performed at a mean time of 6.3 hours (+/- 3.3 hours) after the symptom onset. Analyses of TOF-MRA were impossible for 2.6% of the M1 segments and 6.9% of the M2 segments, according to the reader. The prevalence of segments graded TIMI 0-1 accounted for 12.6% of M1 segments and for 16.2% of M2 segments.

Table 1. Baseline characteristics of the 91 patients

Characteristics	Values
Age, year, mean ± SD	63 ± 13.1
Sex, male (No.) (%)	54 (59.3)
NIHSS score at presentation, mean ± SD	11,9 ± 6
Rankin score at 1 month, mean ± SD	2,1 ± 1.7
Intravenous thrombolysis (No.) (%)	42 (46.2)
Mean time from symptom onset to MRI (hours)	6.3 ± 3.3
Distribution of TIMI grade flow on 728 readings, No (%)	
MCA M1 portion:	
TIMI 0	59 (8.1)
TIMI 1	33 (4.5)
TIMI 2	20 (2.7)
TIMI 3	597 (82)
Technically inadequate	19 (2.6)
MCA M2 portion	
TIMI 0	86 (11.8)
TIMI 1	32 (4.4)
TIMI 2	25 (3.4)
TIMI 3	535 (73.5)
Technically inadequate	50 (6.9)

SD, Standard Deviation; NIHSS, National Institute of Health Stroke Scale; MCA, middle cerebral artery

Results of the inter- and intra-observer reliability are reported in the Table 2. For the dichotomized TIMI grades (0-1 versus 2-3), the inter-observer reliability was good to excellent for both M1 and M2 segments with kappa values from 0.77 to 0.78 for M1 segment and 0.78 to 0.82 for M2 segment. For the intra-observer reliability, kappa also reached high values from 0.77 to 0.83 for M1 segment and from 0.88 to 0.91 for M2 segment. For the ordinal TIMI grades, the inter-observer reliability was excellent for M1 segments with kappa values from 0.84 to 0.85 and for M2 segments with kappa values from 0.88 to 0.96. For the intra-observer reliability, kappa values were excellent both for M1 segment (0.82 to 0.90) and for M2 segment (0.88 to 0.96)

Table 2. Inter and intra-observer reliability of the dichotomized and ordinal TIMI scales

Localisation	Dichotomized classification (0-1 vs 2-3)		Ordinal classification	
	Inter-observer*	Intra-observer†	Inter-observer*	Intra-observer†
M1 segment	0.78 [0.64-0.92]	0.83 [0.70-0.96]	0.84 [0.73-0.94]	0.90 [0.82-0.98]
	0.77 [0.63-0.91]	0.77 [0.64-0.91]	0.85 [0.76-0.95]	0.82 [0.71-0.93]
M2 segment	0.82 [0.70-0.93]	0.91 [0.83-1.00)	0.87 [0.79-0.95]	0.96 [0.93-0.99]
	0.78 [0.66-0.91]	0.88 [0.79-0.97]	0.84 [0.74-0.94]	0.88 [0.79-0.97]

* The two values correspond to the Kappa values for the inter-observer reliabilities during the first and second readings

† The two values correspond to the Kappa values for the intra-observer reliabilities for the first and second readers.

4 Discussion

Our study reports the first data of reproducibility to assess recanalization on TOF-MRA and shows that inter and intra-observer agreements for the evaluation of the degree of MCA obstruction using a modified TIMI scale on TOF-MRA at the acute phase of stroke were good to excellent.

Criteria for an optimal revascularization scale were published previously [11] and should typically include a good inter and intra-rater reliability as well as an easy application in daily practice. In our study, we decided to evaluate the modified TIMI scale because: 1) it has been previously adapted to TOF-MRA [5, 13, 15], 2) it has been correlated with clinical outcome [15], 3) it is a simple scale and 4) it is well-known from neuroradiologists and stroke neurologists. We demonstrated that both dichotomized and ordinal TIMI scales were highly reproducible. The dichotomized analyse, which doesn’t require an expert evaluation, is relevant for clinical practice such as thrombolysis decision or evaluation of thrombolysis efficiency. The ordinal TIMI scale, which relies on a more expert evaluation, is particularly interesting for clinical research such as phase 2 trials of thrombolytic agents.

Different imaging modalities are available to assess the degree of obstruction of intracranial arteries. TOF-MRA was chosen because it is a widely available non-invasive technique that provides a direct 3 dimensional projection of the circle of Willis. Moreover, it can be combined with other MRI sequences allowing an exhaustive assessment of acute ischemic stroke. For these reasons, TOF-MRA has been previously used to evaluate recanalization in some of the largest clinical trials on intravenous thrombolysis [5, 12, 13]. Compared to conventional angiography and CT angiography, limitations of TOF-MRA include lower spatial resolution and signal intensity dependence on vascular flow which in turn may lead to an overestimation of the degree of stenosis. Therefore, despite high Negative Predictive Values (NPV= 91%-98%), TOF-MRA has modest Positive Predictive Values (PPV= 63%-66%) compared to angiography [20, 21]. Because of this modest PPV and the presumed difficulty to differentiate TIMI grade 1 from 2, some studies preferred to use simplified 3 points scales rating: “occlusion, decreased flow and normal flow”, instead of the four points modified TIMI scale [1, 22]. Nevertheless, thanks to technical development of higher field-strength MR imaging, the accuracy of TOF-MRA for the assessment of intracranial stenosis has improved [23]. Furthermore, Neumann-Haefelin et al confirmed the relevance of the 4 points modified TIMI scale on TOF-MRA, including a more precise definition of TIMI 1 and 2. The authors demonstrated that the functional outcome and the ischemic lesion growth were different not only between TIMI 0 and TIMI 1 but also between TIMI 1 and TIMI 2 [15]. In our study, we demonstrated that TOF-MRA modality can be proposed at the acute phase of stroke with few technical limitations: only 2.5% of M1 segment and 7% of M2 segments were non-interpretable. Moreover, the excellent inter and intra-observer reliability of the ordinal TIMI grade strengthens the feasibility of a TIMI1-TIMI2 distinction.

The reliability of recanalization grading systems has been poorly investigated previously. To our knowledge, there is no study about the reliability of MRI-based grading scale and there are only two recent contradictory studies about conventional angiographic recanalization using TICI scale: one of these studies showed good inter-rater agreement [24] whereas the other showed poor inter-rater agreement [25]. This latter result is surprising because conventional angiography is supposed to be the gold standard. Different points could account for the discrepancy between this poor reliability on conventional angiography and the good reliability reported in our study with TOF-MRA: first, the TICI scale is more complex than the TIMI scale because of a sub-categorization of the second perfusion score into 2a and 2b; second, the images were graded by other neuroradiologists than the ones who performed the procedures and a lack a training with the TICI grading is suspected.

Our study has some limitations. First, we did not evaluate the reproducibility of recanalization itself but rather the reproducibility of the degree of obstruction, as the observers graded the MCAs with TIMI scale only at a single time-point. However, we assume that our results can also be interpreted as recanalization reproducibility since recanalization evaluation consists of a comparison between pre- and post-treatment TIMI grades. Moreover, the reproducibility of the assessment of the degree of MCA obstruction is also relevant in itself regarding the association between the initial artery obstruction and a greater effect of intravenous thrombolysis [22]. Another limitation is that the 2 observers have expertise in stroke imaging and had a previous training session using the TIMI scale on TOF-MRA. This could partly explain our high inter-rater agreement. However, training and certification is a practical and effective method to standardize the use of examination scales. A parallel could be drawn with the NIHSS certification that is often required for participation in modern stroke clinical trials and is part of good clinical practice in stroke centers. Our study supports the idea that TIMI training and certification should also be required for clinical trials including recanalization evaluation on angiography as well as on TOF-MRA.

5 Conclusion

The evaluation of MCA recanalization using the modified TIMI scale on TOF-MRA showed good inter- and intra-observer agreement providing the opportunity to use this tool as a relevant surrogate marker of stroke outcome in clinical studies as well as for the daily practice.

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Disclosure of potential conflicts and interest

The authors declare that they have no conflict of interest

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