

True first-pass effect in basilar artery occlusions: first-pass complete reperfusion improves clinical outcome in stroke thrombectomy patients

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Research article

Keywords: ischemic stroke, thrombectomy, true first pass, reperfusion, revascularization

Posted Date: March 4th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-15959/v1>

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Version of Record: A version of this preprint was published at Journal of Clinical Neuroscience on July 1st, 2021. See the published version at <https://doi.org/10.1016/j.jocn.2021.04.020>.

Abstract

Background Complete reperfusion (mTICI 3) in anterior circulation ischemic stroke patients after a single mechanical thrombectomy (MT) pass has been identified as a predictor of favorable outcome (modified Rankin Score 0-2) and defined as true first-pass effect recently. This effect has not yet been demonstrated in posterior circulation ischemic stroke. We hypothesized a true first-pass effect for the subgroup of acute basilar artery occlusions (BAO).

Methods Consecutive patients with acute thromboembolic occlusions in the posterior circulation, treated between 2010 and 2017, were screened and all BAO patients with complete angiographic reperfusion and known symptom onset included for unmatched and matched analysis after adjustment for multiple confounding factors (demographics, time intervals, stroke severity, posterior circulation Alberta Stroke Program early computed tomography Score and comorbidity). The primary objective was outcome at 90 days between matched cohorts of single pass vs. multi pass complete reperfusion patients.

Results 90 MTs in BAO were analyzed, yielding 56 patients with known symptom onset, in whom we achieved complete reperfusion (mTICI 3), depending on whether complete reperfusion was achieved after a single pass (n=28) or multiple passes (n=28). Multivariable analysis of 56 non-matched patients revealed a significant association between first-pass complete reperfusion and favorable outcome ($p < 0.01$). In matched cohorts (n=7 vs. n=7), favorable outcome was only seen if complete reperfusion was achieved after a single pass (86% vs. 0%).

Conclusion Single pass complete reperfusion in acute basilar artery occlusion is an independent predictor of favorable outcome. Achieving complete reperfusion after multiple passes might impair favorable patient recovery.

Background

Acute ischemic stroke (AIS) is a leading cause of acquired disability worldwide and the fourth most common cause of death in developed countries [1]. The state-of-the-art therapy of patients with AIS due to large vessel occlusions (LVO) of the anterior cerebral circulation is nowadays mechanical thrombectomy (MT) with or without concomitant intravenous thrombolysis (IVT) [2–6]. Refinements of current standard endovascular techniques and new technical developments have since been investigated in order to improve the rate of complete angiographic reperfusion and to identify factors which might positively influence the rate of favorable clinical outcome at 90 days [7–16]. The question whether stroke patients would benefit if thrombectomy resulted in complete reperfusion, defined as modified Thrombolysis in Cerebral Ischemia (mTICI) grade 3 [17] after one (single) instead of multiple passes remained open until recently, when Nikoubashman et al. reported on a so-called “true first-pass effect” [18]: Complete reperfusion with the first stent-retriever-based thrombectomy pass resulted significantly more often in favorable outcome at 90 days compared to complete reperfusion after multiple thrombectomy passes in otherwise matched cohorts. This implies that phenomena like

microembolizations into the distal vascular territories of the treated proximal vessel, which have been observed in-vitro [19] might be linked to the number of thrombus retrieval attempts in-vivo, impacting functional outcome independent of the elapsed time since symptom onset and the status of collateral flow.

Such a true first-pass effect has not been demonstrated yet in basilar artery occlusions (BAO). We addressed this issue by conducting a study in which we compared the clinical outcome of patients in whom we achieved complete reperfusion (mTICI 3) after a single pass with a matched cohort of patients, in whom we achieved complete reperfusion after ≥ 2 passes.

Methods

PATIENT SELECTION

All consecutive patients with AIS in the posterior circulation admitted to our hospital from October 2010 to December 2017 with imaging proven vertebrobasilar LVO were evaluated retrospectively on an intention-to-treat basis. We selected all consecutive patients with thromboembolic BAO, excluding patients where procedural or periprocedural imaging was highly suggestive of an underlying stenosis as etiology of the acute occlusion. Inconclusive cases were also excluded. We collected demographics, pre-existing cardiovascular risk factors and cerebrovascular events and comorbidities. The National Institutes of Health Stroke Scale (NIHSS) and modified Rankin scale (mRS) scores were assessed by a stroke neurologist.

Our standardized stroke imaging protocol comprises non-enhanced cranial computed tomography (NECT), CT angiography (CTA) and CT perfusion (CTP). All eligible patients receive IVT according to national guidelines. In case of posterior circulation LVO, e.g. BAO, patients are considered for MT regardless of the time window within 24 hours from symptom onset. In such patients with extended time-window and without contraindications for MR-imaging we aim at performing a concise MR stroke imaging protocol before deciding for MT. We also include patients with low posterior circulation Alberta Stroke Program early computed tomography Score (PC ASPECTS) if imaging implies that there is tissue at risk (so called “mismatch concept”) due to the fatal prognosis of untreated basilar artery thrombosis [20]. Patients are excluded when imaging reveals intracranial hemorrhage (ICH).

Postinterventional control imaging is routinely performed within 24 h after MT or immediately in case of a new neurological deficit in order to determine the extent of stroke and to exclude postinterventional ICH. Symptomatic ICH (sICH) is defined as any apparent extravascular blood in the brain or within the cranium that is associated with neurological deterioration defined by an increase of ≥ 4 points in the NIHSS score [21].

The study was approved by the local ethics committee (Registration ID: 16–347) and was conducted in accordance with the Declaration of Helsinki.

The primary study endpoint was favorable clinical outcome (mRS $0 \leq 2$) at 90 days. Secondary outcome measures were PC ASPECTS after 24 h and death at 90 days.

PRETREATMENT IMAGING ANALYSIS

The definition of BAO was adopted based on the anatomical and radiological criteria published by Archer and Horenstein [22]. Patients with CTA-proven occlusion in the proximal (involvement of the vertebrobasilar junction to the origins of the anterior inferior cerebellar arteries, (AICA)), or / and mid-basilar (segment between the AICA and the origin of the superior cerebellar arteries, (SUCA)), or / and distal (segment distal to the SUCA) portion of the basilar artery were included. The PC-ASPECTS was assessed on NECT source images or on diffusion-weighted imaging (DWI) sequences as described previously [23, 24].

ENDOVASCULAR PROCEDURE

All procedures were done in general anesthesia. Based on a triaxial approach with a guiding catheter in the vertebral artery (VA) or close to its orifice an intermediate (aspiration) catheter and microcatheter were subsequently introduced and navigated to the occlusion. Aspiration was used from the beginning as a basic technique with various catheters over time (Distal Access Catheter, Concentric, Mountain View, CA; Navien, Covidien, Dublin, Ireland; Sofia, Microvention, Tustin, CA), either in combination with a stent-retriever (Trepo variants, Stryker, Fremont, CA; Solitaire variants, Medtronic, Minneapolis, MN; EmboTrap variants, Cerenovus, Irvine, CA) in a so called “Solumbra” technique” [25] or as primary technique, termed “ADAPT” [13, 26, 27]. Starting in 2015, newly emerging combined techniques prevailed, namely SAVE [15, 16]. Thrombus retrieval attempts were repeated if necessary until the final reperfusion result was reached; the maximum number of attempts was up to the operator and did not exceed 10 in any case.

POSTTREATMENT ANALYSIS

To assess complete reperfusion rates, a reader (board-certified neuroradiologist), who was blinded to clinical and procedural data, re-evaluated all corresponding angiographic images of our prospectively captured database, in which reperfusion was reported as being mTICI 3 or mTICI 2b [24]. Patients with confirmed mTICI 2b or near complete reperfusion (e.g. reperfused BAO with a residual small occlusion of the distal posterior cerebral artery (PCA)) were excluded from analysis.

STATISTICS

We used IQR and Mann–Whitney U tests for data comparison, after testing data distribution for normality with a Shapiro Wilk test. Multivariable analysis was performed with a stepwise logistic regression test indicating odds ratios (OR) and confidence intervals (CI). All indicated CI are 95% confidence intervals. Statistical significance was defined as $p \leq 0.05$. All statistical analyses were performed with MedCalc V.19.04 (MedCalc Software, Ostende, Belgium).

Results

Between 2010 and 2017 a total number of 548 patients underwent MT for the treatment of AIS at our center. 122/548 patients (22%) suffered from an LVO of the posterior circulation, whereof 90 depicted a BAO (74% of posterior circulation LVOs and 16% of all LVOs). mTICI 3 reperfusion results were achieved in 56/90 patients (62%). Of those, 28 mTICI 3 reperfusions were achieved with one single thrombectomy pass (single pass cohort) and 28 mTICI 3 reperfusions were achieved with a median of 3 passes (multi pass cohort). These two groups were compared for demographical, clinical, imaging and procedural data (overview Table 1). Statistically significant differences were found for: pre-stroke mRS with 4 (IQR: 3–5) in the single pass cohort vs. 5 (IQR: 4–5) in the multi pass cohort, $p < 0.01$; posterior circulation (PC) ASPECTS with 10 (IQR: 10–10) vs. 9 (IQR: 9–10), $p < 0.01$; symptom onset to reperfusion with 251 (IQR: 220–284) min vs. 314 (IQR: 255–396), $p < 0.01$, 24 h PC ASPECTS with 9 (IQR: 9–10) vs. 8 (IQR: 5–9), $p < 0.01$; picture to puncture time with 31 (IQR: 20–45) vs. 66 (IQR: 35–134), $p < 0.01$ and for favorable outcome at 90 days with mRS 0–2 in 25/28 (89%) cases in the single pass cohort vs. 2/28 (7%) in the multi pass cohort, $p < 0.01$. Additionally, there was a significantly lower mortality rate at 90 days in the single pass cohort (7% vs. 36%, $p = 0.02$). All other data did not show statistically significant differences (Table 1). A stepwise logistic regression analysis resulted in NIHSS on admission and single pass mTICI 3 as significant contributors to the regression model for a favorable 90-day outcome (mRS 0–2) with $p < 0.05$ for NIHSS and $p < 0.01$ for single pass mTICI 3, whereas pre-stroke mRS, time from symptom onset to reperfusion, time from groin puncture to reperfusion and PC ASPECTS did not contribute significantly to the regression model. Odds ratios were calculated with 0.87 (95% CI: 0.78–0.97) for NIHSS on admission and with 256.14 (95% CI: 17.58–3731.15) for true first pass effect. The receiver operating characteristics (ROC) of the regression model had an area under curve (AUC) of 0.971 (95% CI: 0.886–0.997).

Table 1
Overview of demographic, clinical, imaging and procedural data

Patient characteristics and clinical data	Single pass	Multi pass	p-value
Age (years)	71 (IQR: 58–81)	77 (IQR: 68–83)	0.16
Male sex (n)	16 (57%)	16 (57%)	1.0
Arterial hypertension	18 (64%)	20 (71%)	0.78
Current smoker	6 (21%)	4 (14%)	0.73
Hyperlipoproteinemia	4 (14%)	4 (14%)	1.0
NIHSS on admission	8 (IQR: 5–16)	18 (IQR: 7–25)	0.08
Pre-stroke mRS	4 (IQR: 3–5)	5 (IQR: 4–5)	0.0005 ***
CT PC ASPECTS	10 (IQR: 10–10)	9 (IQR: 9–10)	0.0005 ***
IV thrombolysis	15 (54%)	14 (50%)	1.0
IA thrombolysis	1 (4%)	1 (4%)	1.0
Procedural data			
Symptom onset to reperfusion	251 (IQR: 220–284)	314 (IQR: 255–396)	0.0018 **
Door to image	24 (IQR: 12–30)	28 (IQR: 19–50)	0.09
Image to puncture	110 (IQR: 84–135)	116 (IQR: 98–136)	0.59
Puncture to reperfusion	31 (IQR: 20–45)	66 (IQR: 35–134)	0.0001***
sICH	2 (7%)	2 (7%)	1.0
SAH	0 (0%)	1 (4%)	1.0

Patient characteristics and clinical data	Single pass	Multi pass	p-value
Outcome data			
24 h PC ASPECTS	9 (IQR 9–10)	8 (IQR: 5–9)	0.0002 ***
mRS 0–2 at 90 days	25 (89%)	2 (7%)	< 0.0001 ****
mRS 0–3 at 90 days	25 (89%)	7 (25%)	< 0.0001 ****
Death at 90 days	2 (7%)	10 (36%)	0.02 *

The single pass versus the multi pass groups were further analyzed as matched cohorts by the following parameters: NIHSS on admission with a maximum difference of 5, pre-stroke mRS with a maximum difference of 1, pre-stroke PC ASPECTS with a maximum difference of 1 and time from symptom onset to reperfusion with a maximum difference of 30 min.

Matching yielded 7 patients in each subgroup. A stark difference was found in the rate of favorable outcome at 90 days for these perfectly reperfused BAO patients (86% in single pass vs. 0% in multi pass, $p < 0.01$, Table 2).

Table 2

Case control analysis; overview of demographic, clinical, imaging and procedural data

Patient characteristics and clinical data	Single pass, n = 7	Multi pass, n = 7	p-value
Age (years)	70 (IQR: 38–76)	77 (IQR: 69–85)	0.18
Male sex (n)	4 (57%)	2 (29%)	0.6
Arterial hypertension	5 (71%)	5 (71%)	1.0
Current smoker	3 (43%)	2 (29%)	1.0
Hyperlipoproteinemia	0 (0%)	0 (0%)	1.0
NIHSS on admission	9 (IQR: 7–13)	8 (IQR: 6–12)	0.74
Pre-stroke mRS	4 (IQR: 4–5)	4 (IQR: 4–5)	0.27
CT PC ASPECTS	10 (IQR: 10–10)	9 (IQR: 9–10)	0.27
IV thrombolysis	4 (57%)	4 (57%)	1.0
IA thrombolysis	1 (14%)	0 (0%)	1.0
Procedural data			
Symptom onset to reperfusion	242 (IQR: 231–289)	250 (IQR: 213–281)	0.78
Door to image	17 (IQR: 7–27)	22 (IQR: 11–30)	0.69
Image to puncture	96 (IQR: 91–186)	117 (IQR: 88–166)	0.87
Puncture to reperfusion	45 (IQR: 29–68)	41 (IQR: 26–57)	0.51
sICH	1 (14%)	2 (29%)	1.0
SAH	0 (0%)	0 (0%)	1.0
Outcome data			

Patient characteristics and clinical data	Single pass, n = 7	Multi pass, n = 7	p-value
24 h PC ASPECTS	9 (IQR: 8–9)	8 (IQR: 5–8)	0.19
mRS 0–2 at 90 days	6 (86%)	0 (0%)	0.005 **
mRS 0–3 at 90 days	6 (86%)	1 (14%)	0.029 *
Death at 90 days	1 (14%)	2 (29%)	1.0

Discussion

Several variables are known to influence the 90 days outcome in AIS. Part of them has been investigated in the pre-thrombectomy era, others after establishing endovascular treatment as the therapeutic mainstay in LVO of the cerebral vasculature. Nowadays “recanalization” (e.g. graded by the Arterial Occlusive Lesion (AOL) scale) is sometimes used interchangeably with the term “reperfusion” (most commonly graded by the TICl scale) in the literature, which involuntarily leads to a newer fundamental principle, which became more evident after the initial futile endovascular treatment approaches based on thrombus separation followed by aspiration without proximal flow control [28]: Creating a perfect local recanalization (AOL 3) does not necessarily lead to a perfect reperfusion of the corresponding downstream territory. In everyday endovascular stroke treating practice the average portion of patients with an mTICl 2b result ranges between 59% (self-reported) and 67.5% (core-lab controlled) in large registries [29, 30]. It remains largely unclear how many of these mTICl 2b results are due to thrombus fragmentation and therefore essentially iatrogenic, either for biochemical reasons after IVT and / or for mechanical reasons after thrombus manipulation with one of the various endovascular techniques. It would be important to know the exact location and extent of any embolus [31]; unfortunately, this important pre-interventional information is usually not known or not regularly reported in the literature. Having such information would be essential for being able to judge what really happened during an intervention with an imperfect final reperfusion result. Unfortunately, reliable data on the pre-interventional status of the whole extent of the cerebral vasculature is scarce. From the MRI study by Gratz et al. [32] we know that more than 90% of thrombi in LVO are unfragmented on admission MRI, leading to the question why we see such a high rate of imperfect reperfusion results (mTICl 2b & 2a). Furthermore, in-vitro bench testing data about what might happen during a thrombectomy maneuver indicate, that thousands of microemboli are sent downstream to cerebral microvasculature; the only questions are how many, and to what amount they impact the functional outcome of the patient [19].

Recently, based on the preliminary work of Zaidat et al., who proposed a “first-pass” effect as a new and more effective measure of MT-device performance, Nikoubashman et. al reported that in otherwise matched cohorts of anterior circulation AIS only first-pass complete reperfusion (mTICl 3) constitutes an independent predictor for favorable outcome at 90 days, with 2–3 times higher odds compared to complete reperfusion after multiple passes [18]. Consequently, they coined the term “true first pass

effect". Interestingly, with the time interval from symptom onset to final reperfusion being matched and thus taken out of the equation, the true first pass effect seems to have a prognostic value in itself, at least for the anterior cerebral circulation.

The posterior cerebral circulation might be a different story. So far, the evidence on how to optimally treat e.g. BAO is inferior in comparison to the evidence in anterior circulation LVO [33–36], most probably due to the fact that the recently published randomized studies excluded them. This is reflected in the cautious wording of the current guidelines [37]. In our study all outcome analyses showed that there was a significant association between first-pass complete reperfusion of BAO and favorable outcome. As anticipated, procedural time from puncture to reperfusion was always significantly shorter if only one pass was needed for complete reperfusion, as this time span is evidently linked to the number of passes. In accordance with the results of Zaidat et al. in regard to our unmatched analysis results and Nikoubashman et al. for the matched cohorts we found preliminary evidence that a true first-pass effect might also exist in BAO [17, 18]. Nonetheless, it cannot be completely ruled out that the results of our non-matched cohort as well as the results of Nikoubashman et al. are systematically biased and that the clinical impact of first-pass and multiple-pass reperfusion is an epiphenomenon that is in fact attributable to prolonged time spans between symptom onset and reperfusion; this limitation was also acknowledged in their work. For that reason, we also conducted a matched case-control analyses, adjusting our control cohorts among other patient variables most importantly for time as confounding factor. Unfortunately, the resulting matched subgroups suffer from small numbers (7 matched patients in each group), severely impacting the generalizability of our results: the significant association between first-pass complete reperfusion and favorable outcome was confirmed in our matched case-control cohorts with comparable periprocedural time-frames and baseline characteristics. To our surprise, not a single patient in the matched analysis multi pass cohort reached a favorable outcome at 90 days. The best explanation for this is the small sample size, yet the possibility of the in-vitro study by Chueh et al. observed effects impacting the outcome not only in the anterior circulation, but also comparably in BAO is intriguing and warrants further studies [38]. The delicate anatomy of the basilar artery with the angiographically barely visible yet clinically paramount pontine and mesencephalic perforators might be especially prone to mechanical thrombus manipulation by various techniques and repeated extraction maneuvers as we are currently able to reach comparable reperfusion rates but still not the same, relatively satisfactory rates of functional outcome we see in anterior circulation LVO [39]. The potential confounder of iatrogenic vessel perforation [40] was low and not significant between groups.

Finally, our study cannot address the question how to best achieve first-pass complete reperfusion. The evident advantage of flow arrest by a balloon guide catheter in the anterior circulation [41] is difficult if not practically impossible to achieve in all but the rare circumstance of pre-existing non-acute unilateral vertebral artery occlusion. Thus, those endovascular techniques which combine the effectiveness of aspiration with stent-retrievers and yield higher first-pass complete reperfusion results without a mandatory flow arrest might currently offer the best option in BAO [15, 16]. Further methodical studies, including possibilities to consistently achieve flow arrest in the posterior circulation are not only necessary but rather urgent, let alone a consistent proof of concept by proper randomization.

LIMITATIONS

This is a retrospective monocentric study design about consecutive BAO cases which were treated by MT based on an individual case by case clinical consensus process. The endovascular techniques were performed by the same team based on institutional principles, but varied nevertheless over time as the search for the best techniques is an ongoing process. We did not re-grade reperfusion results in a core lab, but relied instead on a blinded second reader to improve the validity of imaging interpretation.

Although our case-control design with matched patients has the highest degree of validity when randomization is lacking, the resulting sample size is very low, even though we started with 122 patients. Building on published preliminary results of anterior circulation LVO, we feel confident that our results could be interpreted as initial stimulus for more extensive research about the potentially decisive role of complete first-pass reperfusion in an otherwise devastating clinical condition of BAO.

Conclusion

We found preliminary evidence that first-pass complete reperfusion might constitute a decisive advantage in acute basilar artery occlusion. The choice of endovascular techniques should therefore focus on a successful first pass with a complete reperfusion of the dependent vascular territory without iatrogenic downstream embolization.

Declarations

Ethics approval and consent to participate - The study was approved by the local ethics committee (Ethics Commission of Cologne University's Faculty of Medicine) (Registration ID: 16-347) and was conducted in accordance with the Declaration of Helsinki.

Consent for publication - Not applicable

Availability of data and materials - The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests - The authors declare that they have no competing interests

Funding - No funding was obtained for this study

Authors' contributions - NA, CK, and AM made substantial contributions to the conception and design of the work. Data acquisition was performed by NA. VM, NA, EC, DB, LG, UB-B, JB and AM performed the data analysis. Interpretation of the data was done by NA, TL, MS, JB, SK, AS, UB-B, DB, VM and AM. NA, CK and AM drafted the manuscript and all of the other authors revised it critically for important intellectual content. All authors approved the final version to be published. They agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the manuscript are appropriately investigated and resolved.

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Abbreviations

MT - mechanical thrombectomy

BAO - basilar artery occlusion

AIS - acute ischemic stroke

LVO - large vessel occlusion

IVT - intravenous thrombolysis

mTICI - modified Thrombolysis in Cerebral Ischemia

CTA - CT angiography

CTP - CT perfusion

NECT - non-enhanced cranial computed tomography

DWI - diffusion-weighted imaging

PC ASPECTS - posterior circulation Alberta Stroke Program early computed tomography Score

ICH - intracranial hemorrhage

sICH – symptomatic intracranial hemorrhage

AICA - the anterior inferior cerebellar artery

SUCA - superior cerebellar artery

VA – vertebral artery