Flow augmentation STA-MCA bypass evaluation for patients with acute stroke and unilateral large vessel occlusion: a proposal for an urgent bypass flowchart

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Abstract: OBJECTIVE: Endovascular recanalization trials have shown a positive impact on the preservation of ischemic penumbra in patients with acute large vessel occlusion (LVO). The concept of penumbra salvation can be extended to surgical revascularization with bypass in highly selected patients. For selecting these patients, the authors propose a flowchart based on multimodal MRI. METHODS: All patients with acute stroke and persisting internal carotid artery (ICA) or M1 occlusion after intravenous lysis or mechanical thrombectomy undergo advanced neuroimaging in a time window of 72 hours after stroke onset including perfusion MRI, blood oxygenation level-dependent functional MRI to evaluate cerebrovascular reactivity (BOLD-CVR), and noninvasive optimal vessel analysis (NOVA) quantitative MRA to assess collateral circulation. RESULTS: Symptomatic patients exhibiting persistent hemodynamic impairment and insufficient collateral circulation could benefit from bypass surgery. According to the flowchart, a bypass is considered for patients 1) with low or moderate neurological impairment (National Institutes of Health Stroke Scale score 1-15, modified Rankin Scale score ≤ 3), 2) without large or malignant stroke, 3) without intracranial hemorrhage, 4) with MR perfusion/diffusion mismatch > 120%, 5) with paradoxical BOLD-CVR in the occluded vascular territory, and 6) with insufficient collateral circulation. CONCLUSIONS: The proposed flowchart is based on the patient's clinical condition and multimodal MR neuroimaging and aims to select patients with acute stroke due to LVO and persistent inadequate collateral flow, who could benefit from urgent bypass.

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Flow-augmentation STA-MCA bypass evaluation for patients with acute stroke and unilateral large vessel occlusion: a proposal for an urgent bypass flowchart.

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Abstract

Objective: Endovascular recanalization trials have shown positive impact on preservation of ischemic penumbra in patients with acute large vessel occlusion (LVO). The concept of penumbra salvation can be extended to surgical revascularization with bypass in highly selected patients. To select these patients, we propose a flowchart based on multimodal magnetic resonance imaging (MRI).

Methods: All patients with acute stroke and persisting ICA- or M1-occlusion after intravenous lysis or mechanical thrombectomy undergo advanced neuroimaging in a time window of 72 hours after stroke onset including perfusion-MRI, blood oxygenation level dependent functional-MRI to evaluate cerebrovascular reactivity (BOLD-CVR) and non-invasive optimal vessel analysis (NOVA) quantitative-MRA to assess collateral circulation.

Results: Symptomatic patients exhibiting persistent hemodynamic impairment and insufficient collateral circulation could benefit from bypass surgery. Using the flowchart, a bypass is considered for patients with: 1) low/moderate neurological impairment (NIHSS 1-15, mRS≤3), 2) without large/malignant stroke, 3) without intracranial hemorrhage, 4) MR perfusion/diffusion mismatch >120%, 5) paradoxical BOLD-CVR in the occluded vascular territory, 6) insufficient collateral circulation.

Conclusion: The proposed flowchart is based on the clinical condition and multimodal MR-neuroimaging and aims to select patients with acute stroke due to LVO and persistent inadequate collateral flow, who could benefit from an urgent bypass.

1 Introduction

The consequences of ischemic stroke on quality of life can be minimized by interventions in the acute phase with the aim to re-establish circulation and tissue perfusion.[1-5] The general concept of nonsurgical brain revascularization for penumbra preservation is proven in the clinical setting through endovascular recanalization trials.[3, 6, 7] Besides recanalization of large vessel occlusions (LVO), surgical treatments exist for augmenting flow to the ischemic tissue via collateral pathways. To augment the collateral flow to hypoperfused MCA territory, a superficial temporal artery to middle cerebral artery (STA-MCA) microsurgical bypass was first performed in Zurich by M.G. Yasargil in 1967 by application of microsurgical techniques and was subsequently applied worldwide.[8-11] We already reported on the use of STA-MCA bypass in an emergency setting to augment the flow in patients with stroke due to LVO presenting with penumbra after failure of maximal medical or endovascular treatment.[12] In a recent systematic review about flow-augmentation bypass in the management of acute ischemic stroke, we found only 16 level IV studies and 3 level III studies. This lack of evidence encouraged further research to explore the use of flow-augmentation bypass in the management of acute ischemic stroke. A major challenge is the adequate identification of patients with persistent hypoperfusion and insufficient collateral flow in the setting of acute stroke which will benefit from microsurgical revascularization.[13]

In this regard, blood oxygenation-level-dependent functional MRI cerebrovascular reactivity (BOLD-CVR) is known as an efficient tool for studying cerebral hemodynamics and assessing stroke risk in patients with symptomatic chronic cerebrovascular steno-occlusive atherosclerotic diseases. [14 15] NOVA (Non-invasive Optimal Vessel Analysis) quantitative magnetic resonance angiography (MRA) provides a precise quantitative (in ml/min) measure of blood flow in the cerebral vessels and allows a reliable quantification of cerebral collateral pathways in case of LVO.[16]

Currently, we conduct a prospective, observational “The Interplay of Microcirculation and Plasticity After Ischemic Stroke” (IMPreST) study to analyze brain hemodynamic compensation and collateral circulation in patients with acute stroke due to occlusion of the internal carotid artery (ICA) and/or of the M1-segment of the middle cerebral artery (MCA) using these aforementioned advanced multimodal magnetic resonance imaging (MRI) techniques.[17] The protocol being utilized is currently under investigation by trial (ClinicalTrials.gov Identifier: NCT04035746). Based on MR-neuroimaging

with assessment of hemodynamic impairment [12, 18] and collateral circulation status[16], we developed a flowchart to select patients with acute stroke due to LVO who could benefit of urgent flow-augmentation bypass surgery. The purpose of this report is to present the detailed flowchart (Figure 1).

2 Methods

2.1 Patients inclusion

Patients with acute stroke due to LVO consecutively admitted to the Stroke Unit (SU) of the Clinical Neuroscience Centre, University Hospital Zurich were screened for possible eligibility to participate in an interdisciplinary IMPreST study (ClinicalTrials.gov Identifier: NCT04035746), granted by University of Zurich as a Clinical Research Priority Program to promote strategically important areas of research.

Patients with first-ever clinical ischemic stroke ≤72h at hospital admission due to ICA- or M1-occlusion, ≥18 years and living independent before stroke (modified Rankin Scale[19] (mRS)≤3) are included in the study. Exclusion criteria consist of: major cardiac, psychiatric and/ or neurological diseases, early seizures, known or suspected non-compliance, drug and/or alcohol abuse and contra-indications for MRI.

The Cantonal Ethics Committee of the Canton Zurich, Switzerland (KEK-ZH-Nr. 2019-00750) approved the IMPreST study. Written informed consent of the patient or, when the patient was not able to participate in the consenting procedure, the written authorization of an independent doctor not involved in the research project followed by a consent of relative, was available for all study participants.

The decision for revascularization with STA-MCA bypass is made multidisciplinary and based on the clinical status and on results of the advanced multimodal MR-neuroimaging. The proposed urgent bypass flowchart is used exclusively for the patients included into the IMPreST study.

2.2 MRI protocol

Advanced MR imaging is performed within 72 hours after stroke with a 3 Tesla Siemens Skyra MRI scanner and lasts approximately 30 min. MR-protocol for selecting patients for flow-augmentation

bypass surgery consists of the following sequences: diffusion-weighted imaging (DWI), susceptibility weighted imaging (SWI), 3D time of flight angiography (TOF), and 2D phase contrast imaging using the 3D coordinates determined by NOVA, MR perfusion (MRP), BOLD functional-MRI with carbon dioxide (CO_2) stimulus to measure CVR.

2.3 Advanced MR modalities

Additional details of the specific MRI parameters are provided in the Supplementary material.

2.3.1 DWI and stroke volume calculation

The stroke volume is expressed in milliliter (ml) and is calculated with automated RAPID-software[20] using a cut-off of ADC<620.

2.3.2 Perfusion-weighted MRI

Estimation of the perfusion maps are performed off-line using OLEA Sphere (Version 3.0-SP6, Olea Medical SA, La Ciotat, France). These maps are derived using automatic vascular input determination and deconvolution.[21] Thereafter the perfusion maps are sent to the RAPID server, which automatically calculates the perfusion weighted imaging (PWI)/DWI mismatch.[20] PWI is defined as Tmax>6 s (from T2* images) and DWI as ADC<620. The mismatch volume (ml) and the mismatch ratio (%) are calculated.

2.3.3 BOLD-CVR

During the BOLD fMRI sequence, a standardized CO_2 stimulus is administered in order to calculate a highly detailed whole brain acquisition of CVR [22] and is safely implemented in routine clinical practice,[23] and can be used as a surrogate-imaging marker for hemodynamic failure in stroke patients.[14]

This stimulus is modulated by a computer-controlled gas blender with prospective gas targeting algorithms (RespirAct, Thornhill Research Institute, Toronto, Canada) for precise targeting of arterial partial pressure of oxygen and CO_2.[24] The controlled hypercapnic stimulus is derived to patients during the BOLD-CVR study according to previously published detailed protocol.[25, 26] The CVR calculations are performed according to a previously described analysis pipeline.[22]

2.3.4 NOVA qMRA

The technique of blood flow quantification by qMRA has been described previously and was implemented with commercially available software called Noninvasive Optimal Vessel Analysis (NOVA, VasSol, Inc, Chicago, Illinois).[27, 28] To optimize the length of MRI protocol, we obtain the volume flow rate (VFR) only of the following six vessels, to quantify the hemispheric perfusion and collateral pathways: first segment of MCA (M1), second segment of the anterior cerebral artery (A2) and second segment of the posterior cerebral artery (P2), bilaterally. This way, a measurement of the flow in MCA territory (M1-VFR) as well as of the hemispheric flow (hVFR) bilaterally are obtained.

2.4 STA-MCA bypass

The STA-MCA bypass is a direct revascularization procedure between the STA and a M4-branch classically used to augment flow to the MCA vascular territory.[10] Peri-operatively we aim at systolic blood pressure of at least 160 mmHg (or higher, depending on hemodynamic fluctuation of symptoms). We aim at normovolemia, normoventilation and normothermia. A detailed description of the emergency flow-augmentation bypass procedure is available in the supplementary material.

After the operation, patients are observed in an intensive care unit for the first night, before they move to the intermediate care unit and thereafter to the ward. The first post-operative MR-neuroimaging is performed within 48 hours after the bypass.

3 Results

Here, we present our flowchart that allows us, based on results of advanced multimodal MR-neuroimaging, to identify symptomatic patients with acute stroke due to ICA or M1-occlusion after failure of best medical or endovascular therapy with persisting salvageable brain tissue (penumbra), who may benefit from an urgent surgical revascularization with STA-MCA bypass.

The following parameters have to be fulfilled:

a) low or moderate neurological impairment (National Institutes of Health Stroke Scale[29] (NIHSS) 1-15)[12]
b) good clinical admission before hospital admission due to acute stroke (mRS≤3)

c) no large or malignant stroke (stroke volume on DWI: in patients <80 years of age <31 ml and in patients >80 years of age <21 ml) according to DAWN Trial criteria[30] and no significant (non-punctiform) intracranial hemorrhage on SWI sequence.

d) MR PWI/DWI mismatch >120%[31, 32] from the automated RAPID software.[20]

These patients undergo advanced MR-imaging and receive a bypass if the following criteria are fulfilled:

a) Paradoxical CVR in the affected ipsilateral vascular territory (by BOLD fMRI) [14, 33], indicating exhausted (=negative) cerebrovascular reserve, also known as steal phenomenon.[14, 34]
b) qMRA NOVA with insufficient collateralization expressed as: a pathological M1-VFR ratio <50% and a pathological hVFR ratio <70%.

The following formulae are currently used to define the pathological ratios:

M1-VFR ratio = $\frac{\text{diseased M1}}{\text{contralateral M1}} * 100\%$ and

hVFR-ratio = $\frac{\text{diseased hVFR}}{\text{contralateral hVFR}} * 100\%$, where hVFR is calculated as sum of VFR of A2+M1+P2.

The whole bypass decision flowchart can be found in Figure 1. In case of fulfilled criteria, the bypass surgery is performed within 48 hours from the decision for bypass.

3.1 Case presentations

Case 1: Bypass YES (Figure 2)

A 60-year-old man presented with acute ischemia in left centrum semiovale due to an internal carotid artery occlusion (white x). In neurological examination a discrete right facial palsy and a pronator drift of right arm (NIHSS 2/42) have been documented. Due to low NIHSS score, the patient underwent neither an intravenous thrombolysis nor a thrombectomy. Before this event, he had no disabilities or restrictions in everyday life (mRS 0). The stroke volume was 0.68 ml. On SWI sequence, no hemorrhage was seen. The mismatch volume was 289 ml. BOLD fMRI showed paradoxical CVR in whole left hemisphere (white arrows). NOVA showed clear asymmetry in M1-VFR with a pathological ratio of 44.9% (<50%) as well as asymmetrical hVFR with a pathological ratio of 42.9% (<70%). According to the proposed bypass flowchart, there is indication for revascularization with STA-MCA

flow-augmentation bypass. At 3-months follow-up the patient showed no neurological deficits (NIHSS was 0, mRS 0). BOLD fMRI showed significant CVR improvement in the left hemisphere and NOVA-MR documented that the hVFR ratio was not pathological anymore (post-operative left hVFR is calculated as sum of VFR of A2+M1+P2+bypass).

Case 2: Bypass NO (Figure 3)

A 79-year-old man presented with acute ischemia in left nucleus caudatus and putamen due to an internal carotid artery occlusion (white x). He suffered sudden onset of motoric dysphasia, and right facial palsy (NIHSS 4/42). Due to low NIHSS score, the patient underwent neither an intravenous thrombolysis nor a thrombectomy. Before this event, he had no disabilities or restrictions in everyday life (mRS 0). Stroke volume was 22 ml, and on SWI sequence, no hemorrhage was seen. The mismatch volume was 104 ml. BOLD fMRI showed bilateral symmetrically CVR reduction, but without paradoxical CVR in occluded vascular territory. NOVA showed a preserved M1-VFR ratio of 84.1% and a hVFR ratio of 85.3%, both considered non-pathological. According to the proposed bypass flowchart, there is no indication for revascularization with STA-MCA flow-augmentation bypass. At 3-months follow-up the patient presented no neurological deficits (NIHSS 0, mRS 0) and no clinical or radiological signs of recurrent ischemia. BOLD fMRI showed no paradoxical CVR in the occluded territory and the NOVA-derived VFR-ratios were non-pathological.

4 Discussion

Neuroimaging plays a pivotal role in the diagnosis and treatment of acute ischemic stroke patients due to LVO.[35] 'Standard' clinical MRI sequences (DWI and PW-MRI) help to identify the ischemic core and the salvageable brain tissue (=penumbra).[36] Advanced MR-neuroimaging allows to quantify hemodynamic impairment[14] as well as the status of collateral circulation.[16] The general concept of nonsurgical brain revascularization for penumbra preservation is proven through endovascular recanalization trials[3, 6, 7] with a level I evidence for endovascular interventions in the acute phase.[4,7,8]

Endovascular recanalization for symptomatic subacute/chronic LVO of anterior circulation has been described as feasible and relatively safe treatment in highly selected patients.[37, 38] Few case series

with limited number of patients reported on improvement of patients' symptoms and on reduction of the recurrence rate of TIA or stroke in the short-term. However, the procedure can be technically challenging and complications such as symptomatic distal embolism, symptomatic re-occlusions and intracerebral hemorrhage have been reported.[37, 38] Further studies are needed to determine the efficacy and long-term outcome associated with this treatment.

In this study, we hypothesize that after an unsuccessful maximal medical or endovascular treatment, the subgroup of patients exhibiting persistent hemodynamic impairment and insufficient collateral circulation could benefit from early cerebral revascularization surgery via flow-augmentation STA-MCA bypass. The use of advanced neuroimaging techniques plays a fundamental role to correctly identify these fragile patients in the acute phase of ischemic stroke.

4.1 PWI/DWI mismatch

Using DWI sequences, the ischemic lesions can be detected early and with high sensitivity.[35] Using gadolinium contrast, perfusion maps can be generated in a few minutes and used for defining the ischemic penumbra as well as to assess collateral flow status.[36] Critically hypoperfused tissue has a Tmax > 6 seconds, which has been validated in multiple studies[39, 40] and was, therefore, used as cut-off value in our definition of mismatch. Similarly, the PWI/DWI mismatch was set as > 1.2 (=120%) as previously published.[31, 32]

4.2 Hemodynamic of acute LVO and BOLD-CVR

Using BOLD fMRI, CVR is defined as the percentage BOLD fMRI signal change per change in mmHg CO_2 and is, therefore, a surrogate marker of the true CVR.[25, 41] In stroke patients, CVR imaging may reveal hemodynamic failure and dynamic information about the interplay between ischemia and perfusion since CVR reflects the brain's ability to increase cerebral blood flow in response to altered vascular or metabolic demands.[42] As an exhausted CVR is regarded as a major risk factor for subsequent cerebral infarction,[33 43] a proper identification of patients with impaired hemodynamic plays a crucial role, especially if there is a possibility to improve the collateral circulation. In fact, all studies have shown that bypass significantly improves hemodynamic parameters in patients with stroke in carefully selected patients.[43-45]

As no studies on impact of cerebral revascularization on CVR in acute stroke stage have been performed until now, we cannot use pre-tested CVR cut-off values to decide which patients will undergo a revascularization procedure with STA-MCA bypass. Based on our clinical experience and daily observation, we defined significant (at least half of the vascular territory) paradoxical (=negative) BOLD-CVR in the occluded vascular territory as indication for revascularization.

4.3 NOVA in evaluation of acute STA-MCA bypass

Beside the importance of studying the hemodynamic status, the investigation of the collateral blood supply plays a pivotal role to evaluate a bypass indication since collateral blood flow influences perfusion and hemodynamics.[16, 46] Status of the collateral circulation can be assessed with transcranial Doppler ultrasound (TCD), CTA/MRA, and digital subtraction angiography (DSA). However, none of these measurements provide quantitative flow (ml/min) values. Therefore, NOVA is thought to be a useful tool (also in the acute phase) in the management of stroke due to LVO of the anterior circulation to better understand collateral circulation.

In case of LVO, two collateral pathways may be activated. The first collateral pathway consists of primary collaterals via Willis circle (via anterior communicating artery (ACom) or via posterior communicating artery (PCom)). The second collateral pathway include: extra-to-intracranial collaterals via ophthalmic artery and intra -to-intracranial leptomeningeal collaterals (from ipsilateral ACA and PCA).[47] The six-vessel NOVA-qMRI may indicate if there is sufficient vs. insufficient compensation via collateral pathways.

The proposed cut-off values for pathological M1- and hVFR-ratio are based on current available literature.[16, 46] In one study evaluating symptomatic patients with subacute/acute stroke, the ratio ipsilateral over contralateral mean M1-VFR (m M1-VFR) was 46.2±26.8% and the ratio of total ipsilateral cerebral circulation flow to total contralateral cerebral circulation flow was 79.6±16.6%.[16] In another study, an increased flow in the posterior cerebral artery distal to the origin of the PCom was documented, indicating a compensatory flow ipsilateral to a hemodynamic relevant MCA or ICA stenosis.[46] Based on both published cohort studies, we proposed the cut-off value for pathological M1-VFR ratio by <50% and the pathological hVFR ratio by <70% as an index of insufficient activation of collateral flow.

5 Conclusions

We report an attempt to define an urgent bypass flowchart for selecting symptomatic patients with acute ischemic stroke who could benefit of flow-augmentation STA-MCA bypass after failure of emergent medical or endovascular therapy. Selection criteria are based on clinical condition and a combination of advanced multimodal MR-neuroimaging. Symptomatic patients with persistent penumbra, hemodynamic impairment (paradoxical CVR) and insufficient collateral circulation may represent a highly selected group of patients who could benefit from early cerebral revascularization surgery. In long run, these criteria should be tested in a randomized trial.

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Figure legend

Figure 1: The urgent bypass flowchart.

Caption: The decision for an urgent revascularization with STA-MCA bypass in patients with acute stroke due to large vessel occlusion is taken interdisciplinary and is based on the presented flowchart, which includes data about patients' clinical status and uses the results of multimodal MR-neuroimaging performed through the IMPreST study).

Figure 2: Illustrative case of a patient with indication for an urgent revascularization with STA-MCA bypass

Caption: A 60-year-old man presented with acute ischemia in left centrum semiovale due to an internal carotid artery occlusion (white x). In neurological examination a discrete right facial palsy and a pronator drift of right arm (NIHSS 2/42) have been documented. Due to low NIHSS score, the patient underwent neither an intravenous thrombolysis nor a thrombectomy. Before this event, he had no disabilities or restrictions in everyday life (mRS 0). The stroke volume was 0.68 ml. On SWI sequence, no hemorrhage was seen. The mismatch volume was 289 ml. BOLD fMRI showed paradoxical CVR in whole left hemisphere (white arrows). NOVA showed clear asymmetry in M1-VFR with a pathological ratio of 44.9% as well as asymmetrical hVFR with a pathological ratio of 42.9%. According to the proposed bypass flowchart, there is indication for revascularization with STA-MCA flow-augmentation bypass.

Figure 3: Illustrative case of a patient without an indication for an urgent revascularization with STA-MCA bypass

Caption: A 79-year-old man presented with acute ischemia in left nucleus caudatus and putamen due to an internal carotid artery occlusion (white x). He suffered sudden onset of motoric dysphasia, and right facial palsy (NIHSS 4/42). Due to low NIHSS score, the patient underwent neither an intravenous thrombolysis nor a thrombectomy. Before this event, he had no disabilities or restrictions in everyday life (mRS 0). Stroke volume was 22 ml, and on SWI sequence, no hemorrhage was seen. The mismatch volume was 104 ml. BOLD fMRI showed bilateral symmetrically CVR reduction, but without

paradoxical CVR in occluded vascular territory. NOVA showed a preserved M1-VFR ratio of 84.1% and a hVFR ratio of 85.3%, both considered non-pathological. According to the proposed bypass flowchart, there is no indication for revascularization with STA-MCA flow-augmentation bypass.