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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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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KEYWORDS acute stroke; mismatch; cerebrovascular reactivity; revascularization; STA-MCA bypass; vascular disorders

THE consequences of ischemic stroke on quality of life can be minimized by interventions in the acute phase with the aim of reestablishing circulation and tissue perfusion.1–5 The general concept of nonsurgical brain revascularization for penumbra preservation has been proven in the clinical setting through endovascular recanalization trials.1,6,7 Besides recanalization of large vessel occlusions (LVOs), surgical treatments exist for augmenting flow to the ischemic tissue via collateral pathways. To augment collateral flow to the hypoperfused middle cerebral artery (MCA) territory, a superficial temporal artery (STA)-MCA microsurgical bypass was first performed in Zurich by M. G. Yaşargil in 1967 using microsurgical techniques and was subsequently ap-
plied worldwide. However, we have already reported on the use of STA-MCA bypass in an emergency setting to augment the flow in patients with stroke due to LVO and presenting with penumbra after the failure of maximal medical or endovascular treatment. In a recent systematic review about the flow in patients with stroke due to LVO and presenting with penumbra after the failure of maximal medical or endovascular treatment, 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 accurate identification of patients with persistent hypoperfusion and insufficient collateral flow in the setting of acute stroke who will benefit from microsurgical revascularization.

In this regard, blood oxygenation level–dependent functional MRI (BOLD fMRI) of cerebrovascular reactivity (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. Noninvasive optimal vessel analysis (NOVA; VasSol Inc.) quantitative MRA (qMRA) provides a precise quantitative (in ml/min) measure of blood flow in the cerebral vessels and allows reliable quantification of cerebral collateral pathways in cases of LVO.

Currently, we are conducting a prospective observational study, The Interplay of Microcirculation and Plasticity After Ischemic Stroke (IMPReST), to analyze brain hemodynamic compensation and collateral circulation in patients with acute stroke due to occlusion of the internal carotid artery (ICA) or the M1 segment of the MCA by using these aforementioned advanced multimodal MRI techniques. The protocol being utilized is currently under investigation by trial and is registered with the ClinicalTrials.gov database (http://clinicaltrials.gov), and its registration no. is NCT04035746. On the basis of MR neuroimaging with assessment of hemodynamic impairment and collateral circulation status, we developed a flowchart to select patients with acute stroke due to LVO who could benefit from urgent flow augmentation bypass surgery. The purpose of this report is to present the detailed flowchart (Fig. 1).

**Methods**

**Patient Inclusion**

Patients with acute stroke due to LVO who had been consecutively admitted to the Stroke Unit of the Clinical Neuroscience Center of the University Hospital Zurich were screened for possible eligibility to participate in the interdisciplinary IMPReST study, which was granted by the University of Zurich as a Clinical Research Priority interdisciplinary IMPreST study, which was granted by the University of Zurich as a Clinical Research Priority Program to promote strategically important areas of research. Patients with first-ever clinical ischemic stroke occurring ≤ 72 hours from hospital admission as a result of ICA or M1 occlusion, with an age ≥ 18 years, and living independent before the stroke (modified Rankin Scale [mRS] score ≤ 3) were included in the study. Exclusion criteria consisted of major cardiac, psychiatric, and/or neurological diseases; early seizures; known or suspected noncompliance; drug and/or alcohol abuse; and contraindications for MRI.

The Cantonal Ethics Committee of the Canton Zurich, Switzerland, approved the IMPReST study. Written informed consent by the patient or, when the patient was unable to participate in the consenting procedure, the written authorization of an independent doctor not involved in the research project followed by consent of a relative was available for all study participants.

The decision for revascularization with an STA-MCA bypass is a multidisciplinary one and is based on the patient’s clinical status and the results of advanced multimodal MR neuroimaging. The proposed urgent bypass flowchart was used exclusively for patients included in the IMPReST study.

**MRI Protocol**

Advanced MRI is performed within 72 hours after stroke with a 3-T Siemens Skyra MRI scanner and lasts approximately 30 minutes. The MRI 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, and 2D phase-contrast imaging using the 3D coordinates determined by NOVA, MR perfusion, and BOLD fMRI with CO2 stimulus to measure CVR (BOLD-CVR).

**Advanced MRI Modalities**

Additional details on the specific MRI parameters are provided in the Supplementary Methods.

**DWI and Stroke Volume Calculation**

The stroke volume is expressed in milliliters and is calculated with automated RAPID (rapid processing of perfusion and diffusion) software using a cutoff for apparent diffusion coefficient (ADC) < 620.

**Perfusion-Weighted MRI**

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

**BOLD-CVR**

During the BOLD fMRI sequence, a standardized CO2 stimulus is administered in order to calculate a highly detailed whole-brain acquisition of CVR, is safely implemented in routine clinical practice, and can be used as a surrogate imaging marker for hemodynamic failure in stroke patients. This stimulus is modulated by a computer-controlled gas blender with prospective gas targeting algorithms (RespirAct, Thornhill Research Inc.) for precise targeting of arterial partial pressure of O2 and CO2. The controlled hypercapnic stimulus is derived for each patient during the BOLD-CVR study according to a pre-
Previously published detailed protocol. The CVR calculations are performed according to a previously described analysis pipeline.

**NOVA qMRA**

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

**STA-MCA Bypass**

The STA-MCA bypass is a direct revascularization procedure between the STA and an M4 branch classically used to augment flow to the MCA vascular territory. Perioperatively, we aim for systolic blood pressure of at least 160 mm Hg (or higher, depending on hemodynamic fluctuation of symptoms). We aim for normovolemia, normoventilation, and normothermia. A detailed description of the emergency flow augmentation bypass procedure is available in Supplementary Methods.

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 postoperative MR neuroimaging is performed within 48 hours after the bypass.

**Results**

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

The following parameters must be fulfilled: 1) low or moderate neurological impairment (National Institutes of Health Stroke Scale [NIHSS] score 1–15); 2) good clinical condition before hospital admission due to acute stroke (mRS score ≤ 3); 3) no large or malignant stroke (stroke volume on DWI: < 31 ml in patients aged < 80 years and < 21 ml in patients aged > 80 years), according to DAWN trial (Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) criteria, and no significant (nonpunctiform) intracranial hemorrhage on the SWI sequence; and 4) PWI/DWI mismatch > 120%.

The proposed bypass flowchart, there is no indication for revascularization with an STA-MCA flow augmentation bypass. At the 3-month follow-up, the patient showed no neurological deficits (NIHSS score 0, mRS score 0). BOLD fMRI showed significant CVR improvement in the left hemisphere, and NOVA qMRA documented that the hVFR ratio was not pathological anymore (postoperative left hVFR is calculated as the sum of VFR of A2 + M1 + P2 + bypass).

**Case 2: No Bypass**

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

**Discussion**

Neuroimaging plays a pivotal role in the diagnosis and treatment of acute ischemic stroke due to LVO. Standard clinical MRI sequences (DWI and PWI) help to identify the ischemic core and salvageable brain tissue (penumbra). Advanced MR neuroimaging allows one to quantify hemodynamic impairment as well as the status of collateral circulation. The general concept of nonsurgical brain revascularization for penumbra preservation has been proven through endovascular recanalization trials with level I evidence for endovascular interventions in the acute phase.
Case 1. A 60-year-old man presented with acute ischemia in the left centrum semiovale due to an ICA occlusion (white ×). On neurological examination, a discrete right facial palsy and pronator drift of the right arm (NIHSS score 2/42) were documented. Because of a low NIHSS score, the patient underwent neither intravenous thrombolysis nor thrombectomy. **FIG. 2.** (continued)
chronic LVO of the anterior circulation has been described as a feasible and relatively safe treatment in highly selected patients.37,38 Few case series with a limited number of patients have reported on the improvement of patient symptoms and a reduction in the recurrence rate of transient ischemic attack or stroke in the short term. However, the procedure can be technically challenging, and complications such as symptomatic distal embolism, symptomatic reocclusions, and intracerebral hemorrhage have been reported.37,38 Further studies are needed to determine the efficacy and long-term outcomes associated with this treatment.

In this study, we hypothesized 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 in correctly identifying these vulnerable patients in the acute phase of ischemic stroke.

**PWI/DWI Mismatch**

With DWI sequences, ischemic lesions can be detected early and with high sensitivity.35 With gadolinium contrast, perfusion maps can be generated in a few minutes and used for defining the ischemic penumbra as well as assessing collateral flow status.36 Critically hypoperfused tissue has a Tmax > 6 seconds, which has been validated in multiple studies36,40 and was, therefore, used as cutoff value in our definition of mismatch. Similarly, the PWI/DWI mismatch was set as > 1.2 (120%), as previously published.31,32

**Hemodynamics of Acute LVO and BOLD-CVR**

Using BOLD fMRI, one defines CVR as the percentage BOLD fMRI signal change per change in mm Hg of CO₂ and is, therefore, a surrogate marker of 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.32 As an exhausted CVR is regarded as a major risk factor for subsequent cerebral infarction,32 proper identification of patients with impaired hemodynamics plays a crucial role, especially if there is a possibility of improving collateral circulation. In fact, all studies have shown that bypass significantly improves hemodynamic parameters in stroke in carefully selected patients.43-45

As no studies on the impact of cerebral revascularization on CVR in the acute stroke stage have been performed until now, we cannot use pretested CVR cutoff values to decide which patients will undergo a revascularization procedure with STA-MCA bypass. On the basis of 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 an indication for revascularization.

**NOVA in the Evaluation of Acute STA-MCA Bypass**

Besides the importance of studying hemodynamic status, investigation of the collateral blood supply plays a pivotal role in evaluating a bypass indication since collateral blood flow influences perfusion and hemodynamics.16,46 The status of collateral circulation can be assessed with transcranial Doppler ultrasonography, CTA/MRA, and digital subtraction angiography. However, none of these modalities 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 the case of LVO, two collateral pathways may be activated. The first collateral pathway consists of primary collaterals via the circle of Willis (via the anterior communicating artery or posterior communicating artery [PCoA]). The second collateral pathway includes extra- to intracranial collaterals via the ophthalmic artery and intracranial to intracranial leptomeningeal collaterals (from the ipsilateral anterior cerebral artery and posterior cerebral artery).47 The six-vessel NOVA qMRA may indicate if there is sufficient versus insufficient compensation via collateral pathways.

The proposed cutoff values for the pathological M1-VFR and hVFR ratios are based on the available literature.16,46 In one study evaluating symptomatic patients with subacute/acute stroke, the ratio of ipsilateral to contralateral mean 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%.46 In another study, an increased flow in the posterior cerebral artery distal to the origin of the PCoA was documented, indicating a compensatory flow ipsilateral to a hemodynamically relevant MCA or ICA stenosis.46 On the basis of both published cohort studies, we proposed the cutoff values for the pathological M1-VFR ratio as < 50% and the pathological hVFR ratio as < 70% as indices of insufficient activation of collateral flow.

**Conclusions**

We report an attempt to define an urgent bypass flowchart for selecting symptomatic patients with acute ischemic stroke who could benefit from flow augmentation STA-MCA bypass after the failure of emergent medical or endovascular therapy. Selection criteria are based on the patient’s clinical condition and a combination of advanced multimodal MR neuroimaging. Symptomatic patients with persistent penumbra, hemodynamic impairment (paradoxical CVR), and insufficient collateral circulation may...
FIG. 3. Case 2. A 79-year-old man presented with acute ischemia in the left caudate nucleus and putamen due to an ICA occlusion (.white ×). He experienced the sudden onset of motoric dysphasia, as well as a right facial palsy (NIHSS score 4/42).
represent a highly selected group of patients who could benefit from early cerebral revascularization surgery. In the long run, these criteria should be tested in a randomized trial.

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References


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Supplemental Information
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