Feasibility and safety of intraoperative BOLD functional MRI cerebrovascular reactivity to evaluate extracranial-to-intracranial bypass efficacy

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Blood oxygenation level–dependent functional MRI cerebrovascular reactivity (BOLD-CVR) is a contemporary technique to assess brain tissue hemodynamic changes after extracranial-intracranial (EC-IC) bypass flow augmentation surgery. The authors conducted a preliminary study to investigate the feasibility and safety of intraoperative 3-T MRI BOLD-CVR after EC-IC bypass flow augmentation surgery. Five consecutive patients selected for EC-IC bypass revascularization underwent an intraoperative BOLD-CVR examination to assess early hemodynamic changes after revascularization and to confirm the safety of this technique. All patients had a normal postoperative course, and none of the patients exhibited complications or radiological alterations related to prolonged anesthesia time. In addition to intraoperative flow measurements of the bypass graft, BOLD-CVR maps added information on the hemodynamic status and changes at the brain tissue level. Intraoperative BOLD-CVR is feasible and safe in patients undergoing EC-IC bypass revascularization. This technique can offer immediate hemodynamic feedback on brain tissue revascularization after bypass flow augmentation surgery.

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KEYWORDS EC-IC bypass; BOLD; functional MRI; steno-occlusive disease; cerebrovascular

Intraoperative hemodynamic assessment tools greatly assist in evaluating function and patency of extracranial-intracranial (EC-IC) bypass revascularization for flow augmentation.1,12 In particular, the use of intraoperative volumetric flow measurements and video-assisted indocyanine green (ICG), including the recent development of infrared local flow analysis,16,17 have unequivocally shown their benefit.2,5,13 This hemodynamic information, however, is only provided on a vascular level and gives no insight into the hemodynamic state at the brain tissue level, and it does not reveal changes in brain tissue perfusion immediately after bypass revascularization, especially in areas distant from the anastomosis. Therefore, it can only be assumed that the flow measured through the bypass graft is sufficient for the vascular territory downstream to maintain brain tissue function and integrity. Obtaining early information on brain tissue reperfusion could further expand our knowledge on bypass performance and, therefore, allow for better evaluation of its efficacy.

Such early hemodynamic feedback may be of interest when the measured flow through the bypass anastomosis is lower than expected. Furthermore, the recipient artery may only perfuse an isolated vascular territory, i.e., brain tissue volume can remain that has, in effect, not been revascularized. On the other hand, hyperperfusion syndrome may be detected, prompting an adapted perioperative management in order to prevent hemorrhage during the postoperative course.

Information about brain tissue integrity and perfusion is usually assessed during the postoperative course using ABBREVIATIONS ACA = anterior cerebral artery; BOLD = blood oxygen level–dependent; CVR = cerebrovascular reactivity; EC = extracranial; IC = intracranial; ICA = internal carotid artery; ICG = indocyanine green; MCA = middle cerebral artery; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; STA = superficial temporal artery.

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PET,\textsuperscript{19} perfusion MRI,\textsuperscript{4,14} perfusion CT,\textsuperscript{23} or cerebrovascular reactivity (CVR).\textsuperscript{11,15} The application of intraoperative high-field MRI may deliver such information directly after the bypass anastomosis. By obtaining functional MRI blood oxygenation level–dependent (BOLD) volumes during repeated cycles of apnea, CVR can be measured at the brain tissue level. We previously reported the feasibility of intraoperative 3-T MRI BOLD-CVR and its preliminary application for neurovascular surgery.\textsuperscript{6}

The purpose of this study was to assess whether intraoperative BOLD-CVR can offer hemodynamic information at the brain tissue level directly after revascularization and whether this imaging technique is feasible and safe in patients undergoing an EC-IC bypass revascularization for flow augmentation.

### Methods

The study was approved by the ethics board of our institution. All patients electively selected for a superficial temporal artery–middle cerebral artery (STA-MCA) bypass flow augmentation surgery from January 2015 until July 2016 were invited to participate in this study and gave informed consent. Exclusion criteria were the general MRI contraindications and/or refusal to participate in the study. No patient had to be excluded. Table 1 summarizes the patients’ characteristics. All patients had also undergone preoperative $^{15}\text{O}$-PET scanning to assess hemodynamic failure, according to standard clinical protocol.

#### Intraoperative CVR Data Acquisition and Analysis

After successful STA-MCA microanastomosis, each patient underwent intraoperative scanning on a 3-T MRI scanner according to an established protocol and BOLD-CVR analysis as previously published by our group.\textsuperscript{6} Before the MRI transfer, a checklist was used to minimize any risk to the patient.\textsuperscript{22} A sedated and intubated patient was transferred to the intraoperative MR suite (3T Skyra VDI3 MRI, Siemens).\textsuperscript{22} Whole-brain BOLD volumes were collected with an axial 7.20 min 2D EPI (echo planar imaging) BOLD sequence with voxel size $3 \times 3 \times 3$ mm\textsuperscript{3}, acquisition of matrix $64 \times 64$, 35 slices with ascending interleaved acquisition, slice gap 0.3 mm, GRAPPA (generalized autocalibrating partially parallel acquisitions) factor 2 with 32 reference lines, adaptive coil combination, auto coil selection, TR 2000 msec, TE 30 msec, flip

### Table 1. Characteristics of the patients included in the study

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs), sex</td>
<td>68, F</td>
<td>66, F</td>
<td>49, F</td>
<td>62, F</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Rt hemisindrome</td>
<td>Rt arm &amp; leg paresis</td>
<td>Motoric apraxia, rt hemisindrome</td>
<td>Rt hand apraxia, aphasia</td>
</tr>
<tr>
<td>Acute/chronic symptoms</td>
<td>Chronic</td>
<td>Chronic</td>
<td>Chronic</td>
<td>Chronic</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Lt ICA occlusion</td>
<td>Lt ICA compression w/ pseudoclosure (cavernous sinus tumor)</td>
<td>Moyamoya syndrome w/ atypical Lt hemispheric bleeding</td>
<td>Rt intracranial ICA, MCA, &amp; ACA occlusion</td>
</tr>
<tr>
<td>Hemodynamic failure stage</td>
<td>II</td>
<td>I</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Smoking</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Obesity</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Previous bleedings</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Family history</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>NIHSS score at presentation</td>
<td>2</td>
<td>1</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>mRS score at presentation</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Involved territory</td>
<td>Lt MCA+ACA</td>
<td>Lt MCA</td>
<td>Lt MCA</td>
<td>Rt MCA</td>
</tr>
<tr>
<td>Preamastomatic flow (recipient vessel)</td>
<td>1 ml/min</td>
<td>1 ml/min</td>
<td>3 ml/min</td>
<td>NA</td>
</tr>
<tr>
<td>Postanastomatic flow (recipient vessel)</td>
<td>14 ml/min</td>
<td>10 ml/min</td>
<td>15 ml/min (Double barrel)</td>
<td>40+48 ml/min</td>
</tr>
<tr>
<td>Recipient vessel</td>
<td>M\textsubscript{4}</td>
<td>M\textsubscript{4}</td>
<td>M\textsubscript{4}</td>
<td>M\textsubscript{4}+M\textsubscript{4}</td>
</tr>
<tr>
<td>Bypass patency (ICG)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bypass patency (intraop MRA)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Postop complications</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Hyperperfusion syndrome</td>
</tr>
<tr>
<td>Bypass patency (postop CTA)</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NA = not available.
angle 85°, bandwidth 2368 Hz/Px, 220 volumes, and field of view 192 × 192 mm. For coregistration of the functional sequence, skull stripping, and overlay purposes, an anatomical T1-weighted MPRAGE (magnetization prepared rapid acquisition) sequence (voxel size 0.5 × 0.5 × 0.9 mm; field of view read 240 mm; slice thickness 0.90 mm; TR 1900.0 msec; TE 2.60 msec; filter: prescan normalize, flip angle 9°; base resolution 256; phase resolution 100%; interpolation to 512 × 512; and PAT [parallel acquisition techniques] mode GRAPPA) from the clinical protocol was used. The field of view from the BOLD image acquisition was copied to the T1-weighted image for better early realignment of both images. After obtaining the BOLD and non–contrast-enhanced T1-weighted sequences, additional diffusion-weighted imaging, T2-weighted sequences, and time-of-flight MRA were obtained. Carbon dioxide changes (hypercapnia) were induced by three 44-second separated blocks of apnea with an interval period of 88 seconds of ventilated breathing.6 CVR calculations were done based on the frequency-adjusted sine model as described previously.24

CVR values, calculated as the average BOLD signal change between apnea and baseline (%ΔBOLD signal), were color-coded (from blue: −3% to red: +3%) and overlaid on T1 anatomical scans (Figs. 1–3).

Results
Patient Characteristics

Five patients (4 women) were included, with a mean age of 58.6 ± 9.1 years (Table 1). The mean anesthesia time was 487 ± 75.7 minutes including surgery and intraoperative MRI. The mean duration of the surgical procedures was 237 ± 92.8 minutes, with the mean dedicated MRI duration (scanning plus transfer time) being 63 ± 23.9 minutes.

Intraoperatively, no new diffusion restrictions were seen on MRI, and postoperatively none of the patients exhibited new neurological symptoms. On day 3, 1 patient (case 4) presented with a 2-fold episode of generalized seizures without evidence of new ischemia or hemorrhages. None of the patients exhibited novel persistent neurological symptoms during the immediate postoperative course.

Table 2 shows intraoperative CVR values for all patients. On average, patients presented with marked lower CVR on the affected hemisphere (affected hemisphere vs unaffected hemisphere: 0.67 ± 0.68 vs 1.1 ± 0.69, p = 0.04 t-test). During the qualitative assessment, a strong cortical CVR response was seen for each patient at the anatomical location of the bypass (Figs. 1–3).
Illustrative Cases

Case 5

A 50-year-old man presented to our institution after 2 episodes of dysarthria, left-hand dysesthesia, and mild paresis of the left leg (National Institutes of Health Stroke Scale [NIHSS] score 4; modified Rankin Scale [mRS] score: 2). Vascular risk factors were hypercholesterolemia and hypertension. The patient underwent MRI/MRA assessment and was diagnosed with an occlusion of the right internal carotid artery (ICA; Fig. 1A). Consecutive evaluation of the cerebral hemodynamic status with $^{15}$O-PET scanning, in combination with an acetazolamide challenge, showed stage II hemodynamic failure in the right anterior cerebral artery (ACA) and MCA territories (Fig. 1B). Despite optimal medical treatment, the patient exhibited a worsening of symptoms and was selected for a right-sided STA-MCA bypass procedure. A temporal M$_3$ branch was chosen as a recipient vessel.

The preanastomosis flow in the recipient vessel, measured with a microflow probe, was less than 1 ml/min (HT 313 Transonic flow-QC meter, Transonic System Inc.). The flow in the recipient vessel increased to 16 ml/min after the bypass anastomosis, which, in concordance with the video-assisted ICG findings, was interpreted as a patent bypass. Intraoperative MRA confirmed a patent bypass, and concomitant BOLD-CVR clearly showed a CVR change in the cortical areas surrounding the STA-MCA bypass anastomosis, which was only a local improvement in comparison with the preoperative PET study (Fig. 1C and D). In the following months, the patient experienced recurrent symptoms. At 3 months, the $^{15}$O-PET scan showed persistence of stage II hemodynamic failure (Fig. 1F). The microanastomosis, as well as the distal M$_4$ segment vessels of the MCA, remained visible on MRA, consistent with a patent bypass (Fig. 1E). The patient’s symptoms slowly improved after 8 months postsurgery.

Case 2

This 66-year-old woman presented to our clinic with a recurrent transient right brachiocephalic paresis (NIHSS score 1; mRS score 0 on admission). Neuroimaging revealed a high-grade stenosis of the left intracavernous segment of the ICA secondary to compression of a progressive invasive left cavernous sinus meningioma (Fig. 2A). $^{15}$O-PET imaging demonstrated stage I hemodynamic failure in the left MCA territory as shown in Fig. 2B. Since the patient presented with progressive neurological symptoms despite optimal medical treatment, she was se-
lected to undergo a left STA-MCA bypass flow augmentation procedure. Intraoperative preanastomosis flow on the recipient vessel showed a flow of 1 ml/min, whereas the postanastomosis values reached 10 ml/min. Video-assisted ICG confirmed the bypass patency, although with weak flow, which was also confirmed on intraoperative MRA (Fig. 2C). Intraoperative CVR improved in the entire revascularized hemisphere (Fig. 2D). The follow-up \( H_2(15\text{O})\)-PET image (Fig. 2F) showed a clear improvement in the range of normal perfusion reserve values, but with an occluded bypass on MRA (Fig. 2E). In the postoperative course, the patient did not develop any new transient neurological symptoms.

**Discussion**

In this study, we show the feasibility and safety of intraoperative BOLD-CVR measurements in patients undergoing bypass flow augmentation surgery. The prolonged anesthesia time due to the addition of intraoperative MRI did not result in increased morbidity peri- or postoperatively. However, a longer anesthesia time could represent a matter of concern, due to the possible higher complication rate in such fragile patients.

The potential additional benefit of BOLD-CVR is the possibility of obtaining early hemodynamic information at the brain tissue level, rather than simply registering the flow inside the vessels of interest. Such early hemodynamic feedback may be of interest when the measured flow through the bypass anastomosis is lower than expected. Furthermore, the recipient artery may only perfuse an isolated vascular territory, i.e., brain tissue volume can remain that has, in effect, not been revascularized. On the other hand, hyperperfusion syndrome may be detected, prompting an adapted perioperative management in order to prevent hemorrhage during the postoperative course. As our illustrative cases show, the data obtained with intraoperative BOLD-CVR can add information to those obtained with conventional methods, such as ICG or MRA.

As previously demonstrated, low CVR is associated with a higher stroke risk. Patients with persistent symptoms and low BOLD-CVR values postoperatively (as in case 1) are still at risk of major stroke events until their BOLD-CVR and symptoms improve. Therefore, even if intraoperative BOLD-CVR assessment could prove to be nonsuperior to other techniques for predicting the ultimate bypass efficacy in the long term, it nevertheless offers

**TABLE 2. Mean intraoperative CVR values for each patient**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Whole Brain</th>
<th>Gray Matter</th>
<th>White Matter</th>
<th>Preop Intraop</th>
<th>Preop Intraop</th>
<th>Preop Intraop</th>
<th>Preop Intraop</th>
<th>Unaffected vs Affected Hemisphere*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Affected Hemisphere</td>
<td>Unaffected Hemisphere</td>
<td>Affected Hemisphere</td>
<td>Unaffected Hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.4 1.72 1.01</td>
<td>0.07 0.13</td>
<td>1.00 1.95</td>
<td>84.8% 95.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.08 2.35 1.62</td>
<td>0.02 0.11</td>
<td>1.54 2.61</td>
<td>367.1% 69.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.44 1.67 1.04</td>
<td>0.17 0.21</td>
<td>1.64 1.22</td>
<td>24.9% −25.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.16 0.18 0.16</td>
<td>0.13 0.26</td>
<td>0.03 0.28</td>
<td>102.2% 817.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.76 0.84 0.58</td>
<td>0.27 0.32</td>
<td>0.71 0.81</td>
<td>19% 15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CVR is calculated as percentage change of BOLD signal during the breath-hold challenge.

* The ratios between CVR values in the unaffected and affected hemispheres were calculated as percentages using the following formula: \( \frac{\text{CVR}_\text{unaffected hemisphere} - \text{CVR}_\text{affected hemisphere}}{\text{CVR}_\text{affected hemisphere}} \times 100\)
unique insight into the hemodynamics associated with revascularization and allows for prediction of postoperative clinical evolution and stroke risk. However, these assumptions need to be confirmed by future studies with larger cohorts and longer follow-up.

**BOLD-CVR in Chronic Steno-Occlusive Diseases**

Cerebrovascular reactivity is a functional imaging marker describing the degree of vasodilation of a vessel in response to a vasoactive stimulus and is often measured using BOLD MRI in combination with CO₂ as a vasoactive agent. CO₂-induced BOLD-CVR imaging is known to be useful in predicting stroke risk, especially in the presence of areas with negative CVR (i.e., steal phenomena or stage II hemodynamic failure), where postoperative CVR imaging is predictive of clinical outcome, as well as brain tissue changes following revascularization surgery.

Still, little is known about the potential of intraoperative CVR imaging and we only recently reported the feasibility of obtaining valuable BOLD MRI sequences to study CVR. A relevant change in intraoperative CVR after revascularization surgery might be a first sign of a proper blood supply to previous ischemic territories and, on the contrary, a low CVR in territories expected to show a rise in CVR values, could suggest the inefficacy of the bypass.

**Alternative Novel Intraoperative Blood Flow Imaging Techniques**

A previous intraoperative study using MRI in patients undergoing EC-IC bypass was conducted by Wang et al. They concluded that this knowledge can help anticipate a hyperperfusion syndrome. Intraoperative data of cerebral blood flow changes after revascularization surgery were obtained with perfusion CT by Xue et al. in patients undergoing carotid endarterectomy. In comparison with perfusion CT scanning, MRI has the advantage of no ionizing radiation and less contrast-induced adverse reactions, as well as a higher spatial resolution, allowing for better detection of early and more-subtle hemodynamic changes.

In addition to all of these advantages, contrast agents are not needed for BOLD-CVR.

**Limitations**

We have to stress that these BOLD-CVR images were not used for clinical decision-making. Such hemodynamic maps need to be carefully interpreted, and their potential prognostic value in actually predicting the success of EC-IC revascularization surgery obviously needs to be confirmed. The ultimate goal would be to have intraoperative quantitative CVR values as a predictor of bypass efficacy and functional outcome. We aim to answer this in the future with a larger patient cohort and longer follow-up. Even though we found no complications related to the intraoperative BOLD-CVR assessment, we are limited by the small number of our cohort.

Furthermore, the breath-holding technique is a practical method of delivering CO₂ to a patient, but its quantification and therefore the reproducibility of the vasoactive stimulus remain challenging. CVR values were not live, but were obtained in postprocessing after the scan. In order to obtain information, MR data must be processed separately, as previously described. This could take up to 30 minutes. Nevertheless, as described by our illustrative cases, this information could be relevant for further surgical decisions on whether to perform bypass revision or not.

Further development of this technique and automation of data analysis can help in providing important information for surgical decision-making.

The information obtained at the brain tissue level could suggest the need to revise the anastomosis, but this may not be feasible in some circumstances due to difficulty in finding other recipient vessels or technical nuisances in performing a new anastomosis. However, other techniques like ICG, flow measurements, and eventually angiography or MRA are used frequently to assess the bypass. Even though revising an anastomosis might be hard or unfeasible in some cases, we think intraoperative assessment is and will be a valuable tool in revascularization surgery. This technique is not appropriate for indirect revascularization techniques like encephalomyosynangiosis, encephaloduroarteriosynangiosis, or encephaloduromyoarteriosynangiosis, because they are based on neangiogenesis occurring weeks to months after the procedure. Measuring intraoperative BOLD-CVR in patients undergoing these types of revascularization would not show any immediate change to the hemodynamic status in comparison to the preoperative situation.

**Conclusions**

Intraoperative BOLD-CVR assessment in patients undergoing EC-IC bypass revascularization is feasible and safe. Its efficacy in providing immediate hemodynamic information following bypass flow augmentation surgery will need to be studied in further detail.

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Disclosures
Siemens provides reference site visits for the Department of Neurosurgery, University Hospital Zurich.

Author Contributions
Conception and design: Muscas, van Niftrik, Fierstra, Sebök, Burkhardt, Valavanis, Regli, Bozinov. Acquisition of data: all authors. Analysis and interpretation of data: Muscas, van Niftrik, Piccirelli, Pangalu. Drafting the article: Muscas, van Niftrik, Bozinov. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Muscas. Statistical analysis: Muscas, van Niftrik, Administrative/technical/material support: Valavanis, Regli, Bozinov. Study supervision: Valavanis, Regli, Bozinov.

Supplemental Information
Previous Presentations
Portions of this work were presented in abstract form at the 69th Congress of the German Neurosurgical Society in Münster, Germany, June 7, 2018; at the 7th Meeting of the Vascular Section of the European Association of Neurosurgical Societies in Nice, France, September 8, 2018; and in poster form at the Joint Annual Meeting of the Swiss Societies of Neurosurgery and Neuroradiology, Lugano, Switzerland, May 24–26, 2018.

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