Longitudinal Reproducibility of CO₂-Triggered BOLD MRI for the Hemodynamic Evaluation of Adult Patients with Moyamoya Angiopathy

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Keywords

Moyamoya · PET/CT · Cerebrovascular reserve · BOLD MRI · Revascularization

Abstract

Background and Purpose: Hemodynamic evaluation of moyamoya patients is crucial to decide the treatment strategy. Recently, CO₂-triggered BOLD MRI has been shown to be a promising tool for the hemodynamic evaluation of moyamoya patients. However, the longitudinal reliability of this technique in follow-up examinations is unknown. This study aims to analyze longitudinal follow-up data of CO₂-triggered BOLD MRI to prove the reliability of this technique for long-term control examinations in moyamoya patients. **Methods:** Longitudinal CO₂ BOLD MRI follow-up examinations of moyamoya patients with and without surgical revascularization have been analyzed for all 6 vascular territories retrospectively. If revascularization was performed, any directly (by the disease or the bypass) or indirectly (due to change of collateral flow after revascularization) affected territory was excluded based on angiography findings (group 1). In patients without surgical revascularization between the MRI examinations, all territories were analyzed (group 2). **Results:** Eight-

teen moyamoya patients with 39 CO₂ BOLD MRI examinations fulfilled the inclusion criteria. The median follow-up between the 2 examinations was 12 months (range 4–29 months). For 106 vascular territories analyzed in group 1, the intraclass correlation coefficient was 0.784, $p < 0.001$, and for group 2 (84 territories), it was 0.899, $p < 0.001$. Within the total follow-up duration of 140 patient months, none of the patients experienced a new stroke. **Conclusions:** CO₂ BOLD MRI is a promising tool for mid- and long-term follow-up examinations of cerebral hemodynamics in moyamoya patients. Systematic prospective evaluation is required prior to making it a routine examination.

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Introduction

Precise evaluation of cerebral perfusion is crucial for adequate treatment and follow-up of patients with moyamoya angiopathy. Based on this information, surgical revascularization is indicated and performed in hemodynamically affected patients [1, 2]. For patients with disease-affected territories and as yet normal perfusion and

Fig. 1. Depiction of absolute CO₂ BOLD MRI signal change of 2 follow-up examinations of 1 patient 12 months apart without any surgical intervention in between. Differences of the absolute maximum values (signal change in percent) can be seen for all territories, and therefore normalization to the cerebellum is calculated for each case (ratio). ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.

reserves (not hemodynamically affected patients), strict and regular follow-ups are recommended [1, 3, 4]. Such hemodynamic evaluation can be performed by H₂¹⁵O PET with acetazolamide (ACZ) challenge, among others [5–8]. This however has disadvantages such as limited availability, need of ACZ injection, high costs, and radiation exposure [9]. Recently, CO₂-triggered blood-oxygen-level-dependent (BOLD) MRI has been used increasingly to evaluate cerebral hemodynamics [10, 11]. This technique depicts the change of the BOLD signal after a vasodilatory stimulus due to changes of the CO₂ concentration in the blood. The so-called cerebrovascular reactivity (CVR) can be triggered by exogenous changes of the CO₂ concentration with a breathing mask, or endogenously by breathing pauses, commonly called breath-hold [9, 12]. CO₂ BOLD MRI has been validated for different stimuli, in comparison with PET and SPECT, before and after cerebral revascularization and for different MR field strengths [9, 12–16]. To our knowledge, longitudinal early and long-term follow-up examinations have not been evaluated in terms of their reliability in monitoring untreated, hemodynamically affected, and not-affected vascular territories in moyamoya patients.

This however is of importance as moyamoya disease can progress over time resulting in worsening of CVR, supporting the need for surgical revascularization [17]. The aim of this study is to analyze longitudinal CO₂ BOLD MRI follow-up data of moyamoya patients to prove reproducibility of this technique in hemodynamically not-affected and untreated vascular territories.

Materials and Methods

A retrospective analysis of existing CO₂ BOLD MRI examinations of adult moyamoya patients at our center was performed for all vascular territories (anterior cerebral artery [ACA], middle cerebral artery [MCA], and posterior cerebral artery [PCA]). All patients were treated according to a routine protocol consisting of an initial CO₂ BOLD MRI and conventional angiography, as well as PET-CT with ACZ challenge. Depending on the results of these examinations, surgical revascularization was scheduled if indicated, or follow-up examinations were planned. To indicate revascularization, always all imaging modalities and clinical symptoms have been evaluated. There was no isolated cutoff value for any of the modalities. Generally spoken, results of PET-CT with ACZ challenge were of highest importance for the decision-making [2]. If the cerebrovascular reserve measured in PET-CT was reduced >50% compared to the cerebellum (e.g., if the increase of blood flow of the cerebellum after ACZ is 30%, but in the MCA territory only 10%), usually revascularization was indicated. If the further course was uneventful, CO₂ BOLD MRI and a conventional angiography were performed approximately 1 year after surgery in all patients. If no surgery was required, follow-up examinations were scheduled individually, usually within 6–12 months.

Main inclusion criteria were angiographically proven moyamoya angiopathy and the availability of a minimum of 2 CO₂ BOLD MRI examinations at least 3 months apart. Ethical approval was obtained from the local ethics committee. General patient data were obtained from the patients' clinical files, and all imaging data were stored and analyzed in the hospital's PACS system.

MR Data Acquisition

All patients underwent MR imaging on a standard 3T MR scanner (Magnetom Skyra, Siemens, Erlangen, Germany). Using a 20-channel head coil, a T2*-weighted EPI sequence was measured with the following imaging parameters: TR = 3,000 ms, TE = 36 ms, matrix size, 96 × 96, slice thickness = 3 mm, slices =

Table 1. General patient data

Patients, <i>n</i>	18
CO ₂ BOLD MRI included	39
F/M ratio	14F/4M
Mean age (range)	43 (17–66)
Stroke/TIA/incidental/hemorrhage [#]	8/6/3/1
Unilateral angiopathy	5
Bilateral disease	13
Affected territories (mean; range)	51 (2.8; 1–4)
Patients with follow-up without revascularization*	7
Patients with surgical revascularization*	11
Revascularized territories* (mean; range)	20 (1.8; 1–4)

[#] Symptoms at initial diagnosis (patients). * In between 2 MRI examinations.

34, and FOV = 256. The paradigm consisted of 5 cycles of 9-s breath-holds in expiration, each followed by 60 s of normal breathing. The start of the paradigm always was a period of 60 s of normal breathing.

All breathing instructions were cued visually using a coil-mounted mirror and a wall-mounted display. All instructions were scanner triggered and generated by Presentations V20.1 (Neurobehavioral Systems, Berkeley, CA, USA).

MR Data Processing

MR data processing and calculation of MR maps and response curves were performed by using a method previously validated and described [9]. In brief, MR data were converted to nifty format using SPM12 (the Wellcome Dept. of Imaging Neuroscience, London; www.fil.ion.ucl.ac.uk/spm). After slice timing correction, realignment, and normalization, all data were smoothed using a 12-mm full width at half maximum filter. Using a script programmed in MATLAB R2019b (MathWorks, Inc., Natick, MA, USA; <http://www.mathworks.com>), curves of each of the 5 breath-hold cycles were displayed for a cerebellar region of interest. If data quality or patients cooperation was insufficient, one or more cycles were excluded from further analysis [9].

Using the arterial transit time-based flow atlas, averaged and detrended signal curves for the perfusion territories of the ACA (left and right), MCA (left and right), and PCA (left and right) as well as the cerebellar territory were calculated and displayed [18]. For calculation of response maps, the signal curve of each voxel was divided by its baseline to eliminate differences of baseline signal intensity. Then, the data were sampled up for each voxel and averaged over time for the previously determined start and end points of the positive cerebellar response.

MR Data Analysis

CVR was determined as the average of the maximum BOLD signal change (absolute numbers in %) within all included breath-hold cycles for each vascular territory. These values were then normalized to the signal change of the cerebellum. Data of follow-up examinations were used for comparison with the first available CO₂ BOLD MRI (Fig. 1).

Fig. 2. Scatter plot of results of group 1. All values are the signal quotient normalized to the cerebellum. ICC = 0.784, $p < 0.001$, linear $R^2 = 0.615$. x axis = first examination; y axis = second examination. ICC, intraclass correlation coefficient.

Definition of 2 Groups for the Analysis

Conventional angiographies were reviewed for all territories included in this analysis before evaluation of the MRI data. Two groups have been defined for analysis of the data.

Group 1 only included territories with no disease affection (therefore also no territories with surgical revascularization in between the 2 MRI examinations were included). Territories without disease affection but change of collateral flow after surgical revascularization in another territory caused by collateral flow through A-comm, P-comm, or leptomeningeal collaterals were also excluded. Group 2 included all vascular territories (angiographically affected and nonaffected) in patients with no surgical intervention for any territory in between the CO₂ BOLD MRI examinations.

Statistical Analysis

Data were analyzed using SPSS (IBM SPSS Statistics for Windows, Version 26.0; IBM Corp., Armonk, NY). Categorical data were presented as frequencies. Reliability was calculated with intraclass correlation coefficients (ICC) (two-way random) [19]. The grade of correlation calculated with ICC was defined as <0.41 as “poor,” values between 0.41 and 0.59 as “fair,” values between 0.60 and 0.74 as “good,” and values >0.74 as “excellent.” [20]. A p value was accepted to be significant at $p \leq 0.05$.

Results

Eighteen moyamoya patients with 39 CO₂ BOLD MRI examinations fulfilled the inclusion criteria. General clinical data can be found in Table 1. Median time between 2 MRI examinations was 12.5 months (range: 4–29). Fifteen patients had 1 follow-up, and 3 patients underwent 2 follow-up MRI examinations. All MRI examinations were of good quality and therefore used for further analysis.

Intraindividual Correlation Analysis for Group 1

The angiography review of all patients revealed 106 territories (14 × ACA, 20 × MCA, and 72 × PCA) eligible for the analysis of group 1. The change of the BOLD signal (normalized to the cerebellum) was analyzed for all 106 territories pairwise. Median follow-up between the MRI examinations was 12 months (range 4–29 months). Statistical analysis of signal change revealed excellent correlation ($ICC = 0.784$, $p < 0.001$) for the territories analyzed (Fig. 2).

Intraindividual Correlation Analysis for Group 2

Fourteen CO₂ BOLD MRI control examinations of 7 patients without surgical treatment in between were analyzed to correlate the comparability of all supratentorial territories, independent of a possible angiographic disease affection. Median follow-up between the MRI examinations in this group was 17.5 months (range 5–28 months). For these 84 territories, an excellent correlation with $ICC = 0.899$, $p < 0.001$, was seen (Fig. 3). Despite this excellent correlation, in 2 patients/3 territories, relevant change with worsening of CVR was seen.

Analysis of Revascularized Territories

Analysis of all 20 surgically revascularized territories was performed separately. Four of them were revascularized by indirect and 16 by direct bypass. Median follow-up was 12 months (range 7–20 months). The mean change of the BOLD signal (normalized to the cerebellum) between the examinations was 0.455 (range –0.31 to 1.76). The BOLD signal increased in all but 4 patients. Two of these showed a stable result with a signal decrease of <0.1 . One patient showed a rapid disease progression with small silent hemodynamic strokes perioperatively which might have caused the worsened signal. The fourth patient did have an angiographically proven patent bypass, with an overall increase of the BOLD signal in the revascularized territory. However, due to a response curve with 2 peaks (instead of only one), the calculated signal change was lower than the preoperative one.

Clinical Relevance of Imaging Results in Revascularized and Nonrevascularized Territories

After review of all available imaging (PET-CT, angiography, and CO₂ BOLD MRI), each patient's vascular territories were judged if surgical revascularization was needed. If indicated, revascularization was planned, and if not, follow-up examinations were scheduled which was the case in 7 patients. Two of these patients did show relevant worsening of CVR (>30 – 40% signal change nor-

Fig. 3. Scatter plot of results of group 2. All values are the signal quotient normalized to the cerebellum. $ICC = 0.899$, $p < 0.0001$, linear $R^2 = 0.812$. x axis = first examination; y axis = second examination. ICC, intraclass correlation coefficient.

malized to the cerebellum) in a total of 3 territories after 24 months. For these patients, revascularization surgery was recommended for the respective territories. Within the total follow-up duration of these patients (140 patient months), none of the patients experienced a new stroke. All bypasses were patent as judged in the last available imaging (MR-TOF and/or angiography) of each patient. An exemplary case can be found in Figure 4.

Discussion

The evaluation of follow-up is of importance as moyamoya can progress over time resulting in decrease of cerebral perfusion thereby necessitating cerebral revascularization. Breath-hold CO₂ BOLD MRI has currently been used as a supplemental tool in addition to H₂¹⁵O PET-CT [2, 9]. The final indication for surgical revascularization should primarily be supported by an initial H₂¹⁵O PET-CT with ACZ challenge. We always perform the initial H₂¹⁵O PET-CT and the first CO₂ BOLD MRI within 1–3 months. The results of a good intraindividual correlation of BOLD MRI values for both groups 1 and 2 over time in this current longitudinal analysis show that CO₂ BOLD MRI may be a reliable alternative technique to perform follow-up hemodynamic monitoring over time in place of PET-CT. BOLD MRI hence might be used for further follow-up examinations, and changes can be correlated with the initial H₂¹⁵O PET-CT. This resolves the need for further H₂¹⁵O PET-CTs and reduces costs

Fig. 4. Exemplary case of a 26-year-old female patient with unilateral moyamoya angiopathy with angiographically proven subtotal occlusion of the right terminal internal carotid artery and collateral flow from the left internal carotid artery into both ACA and the right MCA territories (images not shown). Upper row, preoperative; lower row, 1-year postoperative (after direct STA-MCA bypass on the right side) images. *x* axis shows time course of the examination in seconds. *y* axis shows the BOLD signal change in percent. **a, c** Color scale on the right side shows BOLD signal change for anatomical maps in %. **b, d** Note the decrease of the

signal of the right MCA territory can be interpreted as a steal phenomenon. One-year postoperative improvement can be seen, although normal vasoreactivity cannot be seen yet. Slight affection of the right ACA and right PCA curves can be explained by collateral supply from these territories into the MCA territory. The preoperative angiography images of the right ICA and ECA (**e**). The respective postoperative ones after 1 year (**f**). ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.

and radiation exposure. If worsening of vasoreactivity is seen in BOLD MRI, revascularization surgery may be indicated. However, a clear BOLD MRI-based cutoff to indicate bypass surgery in follow-up examinations is not defined. In our opinion, it is very important to evaluate the cerebral perfusion for each territory according to all available imaging data, the patients' clinical condition, and the timely course of BOLD signal changes. Yet, in our experience, a vasoreactivity of <50% compared to the cerebellum is usually a good benchmark when revascularization should be indicated.

Furthermore, several controversies still exist in defining the best stimulus to induce hypercapnia in measuring the CVR by changes of the BOLD signal [9, 12]. Our approach with 5 repetitive cycles of 9 s of breath-hold each proved to work well. This also fits to the report of Lipp et al. [20], who were able to show that breath-hold CO₂ BOLD MRI shows excellent repeatability of vascular reactivity in healthy volunteers and seems to be advantageous compared to resting-state MRI with a CO₂ trigger. The described need for at least 3 cycles of breath-hold is in strong agreement with our

experiences. Within the 5 cycles performed in each patient in our protocol, occasionally one or 2 measurements need to be discarded due to divergent response curves, most likely caused by insufficient patient cooperation or unknown differences in physiology. However, this can be seen and selected easily by visual inspection in each case as described and published before [9]. This helps to minimize doubts of mis-cooperation or differences in patients' physiology, as only cycles with a clear and comprehensible vasoreactivity response are included in the final analysis.

Limitations

This is a retrospective analysis with a limited number of patients. Seven of 18 patients underwent meticulous follow-up without surgery between the 2 MRI examinations. This high number of conservatively treated patients is caused by the fact that these patients did get more frequent follow-up exams than the surgical group. However, patients without surgical treatment in between the MRI examinations were of importance for this analysis as all territories could be analyzed. Within this group, disease progression was seen in 3 territories, and revascularization surgery was recommended. The progression certainly did influence the results of this analysis, and one might discuss if these territories should have been excluded. On the other hand, exclusion of these territories might have resulted in even further increase of ICC. In patients with surgery in between 2 BOLD MRI examinations, we did exclude territories with direct disease affection or changes of blood flow after revascularization as judged in conventional angiography (see description of groups 1 and 2).

Breath-hold BOLD MRI might be criticized as dependent on the cooperation of patients. However, our pattern of a post hoc analysis of the BOLD response curves with a possible exclusion of individual breath-hold cycles makes this technique reliable for the clinical use, as also shown in other studies [9, 21]. All values analyzed in this study were semiquantitative and normalized to the cerebellum. In our opinion, normalization to the cerebellum should always be performed for CVR mapping examinations, as this can minimize the variabilities in intraindividual physiological responses occurring per se or as a result of differences in the respective cooperation of patients. Due to the small simple size, no further covariables (such as time in between examinations and comorbidities) have been taken into consideration for this analysis.

Conclusions

The longitudinal use of breath-hold CO₂ BOLD MRI in moyamoya patients shows an excellent correlation for individual cerebral vascular territories. Therefore, this technique might be used for longitudinal follow-up examinations in patients with moyamoya angiopathy to detect possible disease progression over time. Prospective studies with larger cohorts are needed to verify these findings and for a better understanding of CVR changes after surgical revascularization.

Statement of Ethics

Approval of this study has been obtained at the University of Tübingen's Ethics Committee (282/2020BO2). As to the retrospective design of this study, no informed consent was required.

Conflict of Interest Statement

There are no conflicts of interest to be declared.

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Author Contributions

C.R.: study concept, patient and data acquisition, data analysis, statistics, and writing of the paper. U.K.: technical conception of imaging, imaging data processing, analysis of imaging data, and proof reading. H.H.: patient and data acquisition, patient data management, statistics, and proof reading. C.B.: imaging data acquisition, imaging data processing, statistics, and proof reading. M.T. and U.E.: conception of the study, interpretation of data, and proof reading. N.K.: study concept, clinical patient management, data analysis, and writing of the paper. T.K.H.: study concept, patient and imaging data acquisition, data analysis, statistics, and writing of the paper.

Submission Statement

All authors have read and approved the submitted manuscript, and the manuscript has not been submitted elsewhere nor published elsewhere in whole or in part.

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