Abstract

Background and Purpose: Moyamoya is a progressive steno-occlusive arteriopathy. Magnetic resonance imaging assessment of cerebrovascular reactivity (CVR) can be performed by measuring blood oxygen level dependent (BOLD)-CVR response to vasoactive stimuli. Our objective was to determine whether negative BOLD-CVR status is predictive of ischemic events in childhood moyamoya.

Material and Methods: We conducted a retrospective study of a consecutive cohort of children with moyamoya who underwent BOLD-CVR assessment. The charts of consented patient were reviewed for the occurrence of: arterial ischemic stroke, transient ischemic attack, or silent infarct(s). We used logistic regression to calculate the OR and 95% CI for ischemic events based on steal status. Hazard ratios (HR) for ischemic events based on age at BOLD-CVR imaging, sex, and moyamoya etiology were calculated using Cox hazard models.

Results: Thirty-seven children (21 female, median age 10.7, interquartile range [IQR: 7.5-14.7] years) were followed for a median of 28.8 months (IQR: 13.7-84.1). Eleven (30%) had ischemic events, 82% of which were TIA without infarcts. Steal was present in 15 out of 16 (93.8%) hemispheres in which ischemic events occurred versus 25 out of 58 (43.1%) ischemic-free hemispheres (OR= 19.8; 95% CI: 2.5-160, p=0.005). Children with idiopathic moyamoya were at significantly greater risk of ischemic events (HR=3.71, 95% CI 1.1-12.8, p=0.037).

Conclusions: Our study demonstrates that idiopathic moyamoya and the presence of steal are independently associated with ischemic events. The use of BOLD-CVR could potentially assist in the selection of patients for revascularization surgery and the direction of therapies in children with moyamoya.
**Key words:** moyamoya; stroke; childhood; magnetic resonance imaging; cerebrovascular reactivity; risk

**Abbreviation key:** AIS= arterial ischemic stroke; BOLD= blood oxygen level–dependent; CVR= cerebrovascular reactivity; HR= hazard ratio; IQR= interquartile range; NA= not applicable; NF1= neurofibromatosis type 1
Introduction

Moyamoya is a chronic progressive steno-occlusive arteriopathy, which typically involves the distal internal carotid artery and/or the proximal anterior cerebral and middle cerebral arteries of the circle of Willis, leading to the development of a compensatory vascular network at the base of the brain.\(^1\)\(^2\) In childhood, moyamoya is associated with a greater risk of recurrent ischemic strokes and poor neurological outcomes that result in a substantial and sustained economic burden to the family and society.\(^3\)\(^4\) There is no cure for the disease and medical therapeutic strategies are thus far inadequate at preventing the adverse outcomes associated with moyamoya. Surgical revascularization, the mainstay of treatment, has been shown to be effective in improving cerebral blood flow and reducing ischemic risk in children with moyamoya.\(^5\)

However, multiple factors need to be considered when determining the appropriateness and timing of surgical interventions including disease severity, risk of ischemic events, peri-operative risk, technical aspects of vascular surgery and anesthetic risk.\(^6\)-\(^9\)

Cerebrovascular reactivity (CVR) is defined as the measurement of vessel reactivity in response to a vasoactive stimulus such as carbon dioxide. It is an important marker of cerebrovascular reserve and the autoregulation through which cerebral blood flow is maintained under physiologic conditions of stress such as hypotension and anemia.\(^10\)-\(^12\)

Harnessing the paramagnetic properties of deoxygenated hemoglobin, blood oxygen level dependent (BOLD) MRI can be used to perform \textit{in vivo} assessment of cerebrovascular reactivity and reserve by measuring the change in BOLD-MRI signal in response to a hypercapnic-vasoactive challenge.\(^13\)-\(^15\) Negative BOLD-CVR, referred to as “vascular steal”, occurs when blood flow redistributes away from the corresponding vascular territory during the global vasodilatory stimulus. Impairment of CVR and negative BOLD reactivity or steal in adults with
Arteriopathy is an independent predictor of ischemic risk including stroke and TIA.\textsuperscript{16-18} Hence, the demonstration of steal is used to identify adult moyamoya patients who might benefit from revascularization surgery.\textsuperscript{19,20} However, any association between steal and ischemic risk has not been demonstrated in children. Early diagnosis of children with moyamoya prior to symptomatic ischemic presentation now occurs as a result of increased syndrome-specific MRI screening protocols. The incidence of ischemic events is reported to peak between 5 - 10 years, and the risk of recurrent ischemic events after the first ischemic presentation is high.\textsuperscript{21-23} The need for improved risk-stratification for the direction of care forms the basis of the compelling need for a clinically useful tool for the prediction of ischemic risk in children with moyamoya. An MRI-based biomarker of ischemic risk using standard MR sequences has the potential to be such a tool, and to provide a non-invasive, individualized approach to the selection of pediatric patients for revascularization surgery.

We hypothesized that negative BOLD-CVR status or steal is a predictor of ischemic risk in children with moyamoya.

**Materials and Methods**

**Population and Study Definitions**

We conducted a retrospective study of a consecutive cohort of children with moyamoya who underwent BOLD-CVR assessment and were followed in our clinic between November 2000 and September 2017. We included children aged 1-18 years, diagnosed according to Fukui criteria and confirmed by catheter angiography.\textsuperscript{24} Children with unilateral moyamoya and collaterals were included in the study. Children without a comorbid condition were diagnosed as having idiopathic moyamoya. Children with comorbid neurofibromatosis Type 1, Sickle Cell
Disease, Trisomy 21, other chromosomal conditions, or radiation vasculopathy, were diagnosed as having moyamoya syndrome. Demographic data, clinical characteristics and treatment modalities were reviewed for all eligible patients.

Ethical permission was obtained from the institutional Research Ethics Board and written informed consent was obtained from all study participants.

**Study Outcomes**

Our primary outcome was the occurrence or recurrence of ipsilateral ischemic event(s) following BOLD-CVR imaging evaluation. Patient charts were reviewed for the occurrence of any of the following: arterial ischemic stroke (AIS), TIA, or silent infarct(s). AIS was defined as the occurrence of a focal neurological deficit with radiological evidence of new focal area(s) of infarction on neuroimaging within a vascular territory. TIA was defined as the occurrence of transient focal neurological deficits, lasting less than 24 hours, without radiological evidence of new focal area(s) of infarction and which were not clinically seizures or migraine. Silent infarcts were defined as the presence of new focal area(s) of infarction on neuroimaging in the absence of a clinically evident focal neurological deficit.

**Magnetic Resonance Imaging Acquisition**

MR imaging was performed on a 1.5 or 3.0 Tesla scanner (Philips Healthcare, Netherlands). Anatomical imaging included standard fluid-attenuated inversion recovery, diffusion weighted imaging and three-dimensional time-of-flight MRA. High-resolution 3D T1-weighted structural images [160 slices; voxel size = (0.86-1)×(0.86-1)×(1-2) mm³; FOV=22-26 cm] were acquired for tissue classification and co-registration of the CVR maps.

**Cerebrovascular Reactivity Imaging Acquisition**
Vasoactive stimulation was achieved by hypercapnic challenge using breath-hold or targeted controlled-delivery of carbon dioxide in children > 7 years, and ventilator-assisted delivery of carbon dioxide under general anesthetic in children < 7 years during CVR acquisition. CVR data were acquired using a T2*-weighted single-shot echo planar imaging gradient echo sequence (25 slices, echo time 30-40 milliseconds, repetition time 2000 ms, flip angle 90°, FOV=22-26 cm, matrix = 64x64, slice thickness = 5mm, dynamics = 180 - 240).

Cerebrovascular Reactivity Post-Processing

Blood oxygen level dependent MRI processing and the generation of CVR maps was conducted using Analysis of Functional NeuroImages (AFNI), FMRIB Software Library (FSL), and custom scripts. The first two volumes were dropped for scanner stabilization, and the data slice-time and motion corrected. The maximum displacement of each volume was calculated as the maximum distance any voxel within the brain shifted during motion correction. The maximum distance signal was regressed from the data, and volumes with a maximum distance exceeding 1.5mm were censored. Data were smoothed using a 7mm FWHM Gaussian Kernel, normalized to a mean intensity of 10,000, and temporally filtered between 0.001 and 0.2 Hz. Patients’ functional data were registered to the MNI space using each patient high-resolution T1 image. Signal contributions from the CSF, along with the six motion parameters, were regressed from the data as covariates in a generalized linear model.

For CVR maps, the patient's BOLD time series in each voxel of the brain was subjected to generalized linear model analysis, using the corresponding averaged cerebellar time courses as a regressor. The regression coefficients (or the beta weights) were then calculated for each voxel. Negative beta weights describing an inverse relationship with the regressor are the markers of ‘steal’. CVR maps consisting of voxel-wise negative and positive beta weights (describing a
negative and positive relationship with the regressor respectively) were co-registered to the high-resolution T1 images in the native space for visualization.  

Visual inspection of the BOLD-CVR maps for hemispheric negative reactivity/steal was conducted by study neurologists blinded to the clinical information (Figure 1). The inter-rater reliability for the hemispheric scoring by visual inspection was substantial (weighted kappa of 1 for the left side and 0.83 for the right side).  

**Statistical Analysis**

Continuous variables were presented as median and interquartile ranges (IQR). Qualitative variables were described using frequency distributions and proportions. Patients' characteristics were compared using Mann–Whitney U test or Fisher’s exact test, as appropriate.

The evaluation of the ischemic risk as a function of steal status was conducted per hemisphere. In children who had multiple BOLD-CVR assessments during the study period, the BOLD-CVR study prior to the occurrence of ischemic event(s) or end of study follow-up was considered. We used logistic regression to calculate the OR and 95% CI for ischemic risk based on BOLD-CVR steal status. In order to control for the effects of surgical interventions, we used multivariable logistic models that controlled for procedures undertaken in the corresponding hemispheres.

Hazard ratios (HR) and the corresponding 95% CI for ischemic events at the patient level (i.e., occurring in any of the two hemispheres) as function of age at initial BOLD-CVR imaging (dichotomized into ≤8 and >8 years), sex, and moyamoya etiology were calculated using Cox proportional hazard models. The compliance with the proportional hazards assumption was assessed using the scaled Schoenfeld residuals and by visual inspection of the log (minus log)
curves for the different Cox models. P<0.05 was considered to be statistically significant.

Statistical analyses were conducted using R Statistical Software, version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

*Population Description*

Thirty-seven children (21 females; median age 10.7 years, IQR: 7.5, 14.7 years) were included in the study (Table 1). The median age at moyamoya diagnosis was 9.9 years (IQR: 6.3-11.8). Twelve (32%) presented with AIS, eight (22%) TIA (without infarction), six (16%) were asymptomatic, eight (21.6%) headaches only and three (8%) seizures. Twenty-eight children (76%) were treated with Aspirin; four children were on chronic blood transfusion; one child had a bone marrow transplant and another received radiotherapy and chemotherapy during the study period. Twenty-one children had revascularization surgery prior to (7 [19%]) or following (14 [38%]) enrollment and prior to the study endpoint.

*Steal Status and Baseline Clinical and Demographic Characteristics*

Twenty-five children had steal in at least one hemisphere on BOLD-CVR imaging. Thirty-seven out of 74 hemispheres had steal: 17 (23%) left and 20 (27%) right hemispheres. Comparisons of clinical and demographic characteristics of patients with steal in at least one hemisphere versus those with no steal are summarized in Table 2. Patients with steal were more likely to experience ischemic events compared to those with no steal (36% versus 16.7%). They were more likely to be female (64% versus 41.7%) and be diagnosed with idiopathic moyamoya (40% versus 33.3%) (Table 2).

*Predictors of Ischemic Events*
During a median follow-up of 28.8 (IQR: 13.7-84.1) months, ischemic events were documented in 11 children: one with AIS, nine with TIA without infarcts, and one with asymptomatic silent infarction. Five children had bilateral, four had left-sided, and two had right-sided ischemic events. No significant differences in clinical and demographic characteristics were found between children who had ischemic events and those who did not (Table 2).

Between groups comparisons of hemispheric steal-status by ipsilateral hemispheric ischemic event-status demonstrated the presence of steal in 15 out of 16 (93.8%) hemispheres in which ischemic events occurred versus 25 out of 58 (43.1%) ischemic-free hemispheres (OR = 19.8; 95% CI: 2.5-160, p=0.005). When adjusted for surgical interventions in the corresponding hemisphere, the odds for ischemic events remained significantly higher among hemispheres with steal (OR = 19.9; 95% CI: 2.45-161, p=0.005).

Univariable analysis using the Cox proportional hazard model demonstrated that children with idiopathic moyamoya were at significantly greater risk of ischemic events (HR = 3.71, 95% CI: 1.1-12.8, p=0.03) (Figure 2). Age as a continuous variable was not predictive of ischemic events. Older age (>8 years) and male sex were suggestive of lower risk of ischemic events although statistical significance was not reached (Figure 2). Upon controlling for age and sex, the association of ischemic risk with idiopathic moyamoya remained statistically significant (HR = 3.95, 95% CI: 1.12, 13.9, p=0.03). There were no violations of the proportional hazards assumption in any of these models.

Discussion

Our study suggests an association between BOLD-CVR steal status, idiopathic moyamoya and an increased risk of ischemic events in childhood moyamoya. Almost two-thirds of the children...
with moyamoya had steal. Children with steal were more likely to be female, diagnosed with idiopathic moyamoya, and experience ischemic events. The presence of steal was associated with an increased risk of ischemic events in the corresponding hemisphere, which is similar to studies in adults with arteriopathy.\textsuperscript{17, 18} To our knowledge this is the first study to investigate the association between steal status and ischemic risk in children with arteriopathy.

In a large single-center study of asymptomatic children with syndromic moyamoya, radiographic progression occurred in the majority, and typically heralded clinical progression.\textsuperscript{41} Children with Sickle Cell Disease had a higher risk of radiographic and clinical progression than children with neurofibromatosis Type 1, and children with unilateral moyamoya had the lowest overall rate of progression. In our study there were no differences in clinical characteristics between the steal and no-steal, nor the ischemic and no ischemic events groups, highlighting the limitations of current clinical approaches to the assessment of ischemic risk in this population. Our study showed that children with steal had significantly higher ipsilateral ischemic risk. The odds for ischemic events remained significantly elevated for children with steal after controlling for revascularization surgery conducted in the respective hemispheres.

Current understanding of the natural history and stroke risk profile of idiopathic moyamoya is mostly derived from studies in Asian populations which describe a bi-modal stroke risk profile of ischemic stroke typically occurring in the first decade of childhood, and hemorrhagic syndromes dominating in adulthood.\textsuperscript{24} In a recently published cross-sectional study of a large international cohort of children with predominantly syndromic moyamoya, older age was also linked to lower ischemic risk.\textsuperscript{42} Similarly, in our study, older children had lower ischemic risk but these results did not reach statistical significance. While no significant differences in the ischemic risk between patients with idiopathic or syndromic moyamoya were reported, our
longitudinal analysis using Cox regression models demonstrated significantly higher ischemic risk associated with a diagnosis of idiopathic moyamoya.

Hence, BOLD-CVR studies using standard T2* gradient-echo sequences could potentially allow for quantifiable clinical assessment of ischemic risk and the subsequent prediction of future ischemic events in children with moyamoya. The clinical correlates of BOLD-CVR detected steal are pertinent to and important for an improved individualized model of care for children with moyamoya.

Limitations of our study include the small sample size, limiting our statistical analysis. However, to our knowledge this is the largest single-center North American study examining a functional MRI technique for the prediction of ischemic risk in childhood moyamoya. BOLD-CVR studies were systematically conducted at predetermined time-points according to institutional practice guidelines in the majority of study participants. Consequently, we were unable to determine the temporal relationship between sub-clinical ischemic MRI changes and changes in steal status. However, this reflects real-world clinical practice. With the wider acceptance and implementation of BOLD-CVR studies in the longitudinal follow-up of children with moyamoya, future directions will include qualitative and quantitative predictive analysis of a larger prospective cohort. However, the purpose of this study was to evaluate whether qualitative analysis of BOLD-CVR maps could be used as a biomarker of ischemic risk in childhood moyamoya, and thus be translatable for clinical use.

Conclusions

Our study demonstrated that the presence of steal was associated with significantly greater odds for developing ipsilateral ischemic events. Furthermore, idiopathic moyamoya etiology was
predictive of ischemic events. The use of hypercapnic challenge BOLD-CVR in combination with other clinical predictors in children with moyamoya represents a promising model for the clinical assessment of ischemic risk and patient selection for revascularization surgery. Larger prospective clinical studies are warranted to adequately elucidate the clinical utility of BOLD-CVR in predicting ischemic risk in this high risk population.

Disclosures

None.
Table 1. Baseline clinical and demographic characteristics

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Total sample (n= 37)</th>
</tr>
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<tbody>
<tr>
<td>Female, n (%)</td>
<td>21 (56.8)</td>
</tr>
<tr>
<td>Age at moyamoya diagnosis, years, median (IQR 25-75)</td>
<td>10 (6.4-11.9)</td>
</tr>
<tr>
<td>Age at initial CVR, years, median (IQR 25-75)</td>
<td>10.7 (7.5-14.7)</td>
</tr>
<tr>
<td>Time to follow-up, months, median (IQR 25-75)</td>
<td>20.8 (7.6-60)</td>
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<table>
<thead>
<tr>
<th>Moyamoya classification</th>
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<tbody>
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<td>Idiopathic</td>
<td>14 (37.8)</td>
</tr>
<tr>
<td>Syndromic</td>
<td>23 (62.2)</td>
</tr>
<tr>
<td>NFI</td>
<td>9 (24.3)</td>
</tr>
<tr>
<td>Trisomy 21/other chromosomal disorders</td>
<td>7 (18.9)</td>
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<tr>
<td>Sickle cell disease</td>
<td>5 (13.5)</td>
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<tr>
<td>Post-radiation vasculopathy</td>
<td>2 (5.4)</td>
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<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Stroke, n (%)</td>
<td>12 (32.4)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>Right</td>
<td>6 (16.2)</td>
</tr>
<tr>
<td>Left</td>
<td>4 (10.8)</td>
</tr>
<tr>
<td>TIA, n (%)</td>
<td>8 (21.6)</td>
</tr>
<tr>
<td>Seizure, n (%)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Headaches, n (%)</td>
<td>8 (21.6)</td>
</tr>
<tr>
<td>Asymptomatic, n (%)</td>
<td>6 (16.2)</td>
</tr>
</tbody>
</table>
Other, n (%) | 2 (5.4)
---|---
**Radiographic findings, n (%)**

<table>
<thead>
<tr>
<th>Subcategory</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Parenchymal</td>
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<tr>
<td>Not ischemic</td>
<td>8 (21.6)</td>
</tr>
<tr>
<td>Watershed</td>
<td>12 (32.4)</td>
</tr>
<tr>
<td>Deep white matter</td>
<td>1 (2.7)</td>
</tr>
<tr>
<td>Cortical</td>
<td>12 (32.4)</td>
</tr>
<tr>
<td>Cortical</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>Cortical ischemic and watershed</td>
<td>14 (37.8)</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Moyamoya laterality, n (%)</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>8 (21.6)</td>
</tr>
<tr>
<td>Right</td>
<td>6 (16.2)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>23 (62.2)</td>
</tr>
<tr>
<td>Grade of Stenosis, n (%)</td>
<td></td>
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<tr>
<td>50-74% occlusion</td>
<td>5 (13.5)</td>
</tr>
<tr>
<td>≥75% occlusion</td>
<td>32 (86.5)</td>
</tr>
</tbody>
</table>

IQR: interquartile rage; CVR: cerebrovascular reactivity; NF1: neurofibromatosis type 1; TIA: transient ischemic attack
Table 2. Comparison of clinical and demographic characteristics based on Steal status* and ischemic events

<table>
<thead>
<tr>
<th></th>
<th>No-Steal</th>
<th>Steal</th>
<th>P-value</th>
<th>Ischemic Events</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at baseline CVR, years, median (IQR 25-75)</strong></td>
<td>9.3 (5.6-14.5)</td>
<td>10.8 (8.3-15)</td>
<td>0.28</td>
<td>10.9 (8.3-15)</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>5 (41.7)</td>
<td>16 (64)</td>
<td>0.29</td>
<td>14 (53.9)</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td><strong>Moyamoya classification, n (%)</strong></td>
<td>0.69</td>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td><em>Idiopathic</em></td>
<td>4 (33.3)</td>
<td>10 (40)</td>
<td>7 (26.9)</td>
<td>7 (63.6)</td>
<td></td>
</tr>
<tr>
<td><em>Syndromic</em></td>
<td>8 (66.7)</td>
<td>15 (60)</td>
<td>19 (73.1)</td>
<td>4 (36.4)</td>
<td></td>
</tr>
<tr>
<td><em>NF1</em></td>
<td>2 (16.7)</td>
<td>7 (28)</td>
<td>7 (26.9)</td>
<td>2 (18.2)</td>
<td></td>
</tr>
<tr>
<td><em>Trisomy 21/other chromosomal disorders</em></td>
<td>3 (25)</td>
<td>4 (16)</td>
<td>6 (23.1)</td>
<td>1 (9.1)</td>
<td></td>
</tr>
<tr>
<td><em>Sickle cell disease</em></td>
<td>1 (8.3)</td>
<td>4 (16)</td>
<td>4 (15.4)</td>
<td>1 (9.1)</td>
<td></td>
</tr>
<tr>
<td><em>Post-radiation vasculopathy</em></td>
<td>2 (16.7)</td>
<td>0</td>
<td>2 (7.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>4 (33.3)</td>
<td>8 (32)</td>
<td>1</td>
<td>11 (42.3)</td>
<td>1 (9.1)</td>
</tr>
</tbody>
</table>
TIA, n (%)  |  2 (16.7) |  6 (24) |  1 |  5 (19.2) |  3 (27.3) |  0.67  
Seizure, n (%) |  2 (16.7) |  1 (4) |  0.24 |  2 (7.7) |  1 (9.1) |  1  
Headaches, n (%) |  3 (25) |  5 (20) |  1 |  6 (23.1) |  2 (18.2) |  1  
Asymptomatic, n (%) |  2 (16.7) |  4 (16) |  1 |  3 (11.5) |  3 (27.3) |  0.33  
Others, n (%) |  0 |  2 (8.3) |  0.54 |  0 |  2 (18.2) |  0.08  
Moyamoya laterality, n (%) |  |  |  | 0.77 |  | 0.78  

Left | 3 (25) | 5 (20) | 6 (23.1) | 2 (18.2)  
Right | 1 (8.3) | 5 (20) | 5 (19.2) | 1 (9.1)  
Bilateral | 8 (66.7) | 15 (60) | 15 (57.7) | 8 (72.7)  

*Steal status prior to ischemic event occurrence or end of follow-up
1 Comorbidities falling under syndromic moyamoya are shown for informative purposes only and were not included in the inferential analysis.
IQR: interquartile range; CVR: cerebrovascular reactivity; NA: not applicable; NF1: neurofibromatosis type 1; TIA: transient ischemic attack
FIGURE LEGENDS
(See separate files for figures)

**Figure 1.** Representative BOLD-CVR parametric maps demonstrating A) Normal (positive) reactivity, B) Abnormal (negative) reactivity (see arrow).

**Figure 2.** Direct adjusted survival curves for ischemic-free survival in function of the (A) moyamoya comorbidities (Hazard ratio [HR] for idiopathic moyamoya: 3.71, 95% CI: 1.1-12.8, p=0.03), (B) sex (HR for males: 0.65; 95% CI: 0.19-2.23, p=0.49), and (C) age group (HR for >8 years: 0.62; 95% CI: 0.18-2.1, p=0.44). Age as a continuous variable was not predictive of ischemic events.

F: Female; M: Male; Age is presented in years.