
The University Of Sheffield.

**PhD Thesis**

# MOYAMOYA DISEASE IN THE WESTERN POPULATION AFTER EXTRACRANIAL-INTRACRANIAL BYPASS AND DEVELOPMENT OF PREDICTIVE MODELLING FOR PERIOPERATIVE STROKE RISK

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**Thesis submitted for the degree of Doctor of Philosophy**

**The University of Sheffield**

**2022**

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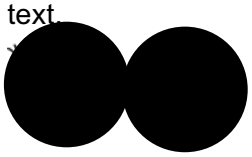
Signature:  Date: 10 February 2022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**To**

**Chih Mun, Kieran, Caleb and Mum**

**ACKNOWLEDGEMENTS**

This dissertation is the result of 7-years part time research work on moyamoya disease, which include 2 years while working as a clinical fellow and clinical instructor at Stanford University, California, USA, and 5 years as a consultant neurosurgeon at Bristol Institute of Clinical Neuroscience, UK.

Too many people have helped me along the way. Though some names might not be mentioned here, I wish to acknowledge that every single help and support that I received, is always deeply appreciated.

I would like to thank my supervisor, Professor Gary Steinberg for his very thoughtful supervision throughout the course of this work, for his constant support, advice in preparing this thesis and manuscripts for peer reviewed publications.

My appreciation also extends to Venkatesh Madhugiri, Jeremiah Johnson, Sunil Furtado, Kumar Abhinav, my co-fellows (at different period) at Stanford University for all the brainstorm sessions and research ideas. Although the Stanford moyamoya database was maintained by Jeanne Gu, for this project, additional clinical information was collected, and help were provided by Dr Eric Sussman, Dr Tej Deepak Azad, Dr Rohaid Ali, Dr Rogelio Esparza, Dr Michael Zhang, Dr Arjun Pendakar, Dr Zack Medress, Dr Alan Ho, Dr Adi Iyer, medical students and residents at the Stanford department of neurosurgery. For the data (2015-2018) to validate the newly proposed Stanford-Berlin moyamoya grade, Dr Yi Ping Li (cerebrovascular fellow 2017-2018) assessed and provided the scores designed. Neuroradiology input for the various grading scales was supported by Dr Kaneko, Professor Marks, Professor Do, Professor Dodd.

While working in Stanford University, California, we have a yearly moyamoya picnic, attended by patients and their family. Jill MacInnes and her family have always dedicated their time to support the event and the moyamoya community, and together with Teresa Bell-Stephens, were instrumental in coordinating the long term questionnaire outcome study presented in this thesis.

I am indebted for the statistical support by Dr Tej Deepak Azad (Johns Hopkins University Hospital, on R software, predictive modelling development), Dr John Zhang (National University of Singapore, on R software meta-analysis), IT support provided by Jessica Huang, basic science data analysis by Michelle Cheng, moyamoya blood methylome work by Dr Masaki Ito.

After the confirmation review in 2018, valuable advice was given by Professor Arshad Majid and Professor Newell-Price. The Nottingham systematic review course 2020 was invaluable to improve my understanding on systematic review and meta-analysis. This work would not have been possible without the help of Richard Kielb from the Medical Library at the University of Bristol for giving us invaluable advice on our search strategy; and Keng Siang Lee (Bristol Medical School, UK), Dr John Zhang (Yong Loo Lin School of Medicine, National University of Singapore) for data extraction and some of the data analysis.

Over the last 2 years, covid pandemic has made our clinical work extremely challenging, with constant bed pressure, additional work to try to cope with ever increasing NHS waiting list. I am so indebted to Professor Richard Ross for his pearls of wisdom over the years, keeping me on track to complete this postgraduate study despite the various challenges.

I am also very grateful to the Bristol neurosurgery team for their support over the last 5 years in my clinical role, and my secretaries (Nikki and Sheila) for keeping my clinical work well organised while supporting my additional endeavours.

Last but not least, a very big thanks to my beloved family for their encouragement and understanding, sacrifices for the weekends and late nights working on this PhD.

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## Summary

Moyamoya disease (MMD), steno-occlusive disease affecting terminal ICAs, typically affects children and young adults, causing strokes. However due the rarity in the western world, access to best medical advice and management can be limited. Furthermore, very little is known about the long term treatment outcome, functional status in terms of employment, education, family life, and what prognostic factors are predictive of good or poor outcome for these patients.

Stanford in California, USA has the largest experience treating moyamoya patients in the western world, with over 1500 extracranial to intracranial bypasses performed since 1990s. This thesis tests the hypothesis that:

1. Selective subgroups of patients with moyamoya disease in the western world are symptomatically and functionally cured after extracranial-intracranial bypasses.

2. Robust and means tested scoring system could be designed to identify subgroups with good and poor outcome, and thereby help with decision making process.

In Chapter 3, we performed a systematic review and meta-analysis comparing direct and combined versus indirect bypass for MMD patients. We showed that both direct and indirect bypasses have similar rates of perioperative complications in pediatric and adult patients, however there was no comparative data to report long term (>5 years) stroke risk, angiographic revascularization between direct/combined bypass and indirect bypass. We also summarized the findings of 10 published meta-analyses on MMD addressing different aspects of the management and surgical treatment.

In Chapter 4, the short and long term outcome of western patients with MMD post revascularisation is presented, analysed and potential risk factors for perioperative stroke identified. In this surgical series, 96% and 73% of the adults and paediatric cohort respectively had direct revascularisation, with 7.3% per procedure 30-days

stroke risk, and 0.6% per patient year long term stroke risk. Combining the outcome from questionnaires, clinical reviews, and radiological findings, we found 80% of MMD patients post revascularization have excellent long-term physical, social, functional wellbeing, with up to 26 years of follow-up (mean 7.3 years). The estimated stroke free interval is 20 years or more for patients younger than 60 years old, while it is 10 years for those 60 or older (as this cohort of older patients are also prone to atherosclerotic strokes).

In Chapter 5, existing MMD Berlin symptomatology grading system is validated, and we showed that the proposed grading system that took into account of DSA, MRI and CVRC findings correlated well with symptoms occurrence. We showed that the MMD Berlin grading system could correlate with postoperative radiological stroke risks. However, several limitations with the grading system were identified, including the hemispheres were assessed individually (while patients should be assessed globally), non-statistical significant correlation with postoperative clinical stroke risk, and identified risk factors from this thesis was not accountable in the Berlin grading system. Therefore, together with the perioperative stroke risk factors identified from Chapter 4, we proposed the Stanford Berlin Moyamoya grading system, and a new moyamoya predictive modelling for assessing postoperative stroke risk (Chapter 8).

Small group of patients needed repeat revascularisation due to persistent or new symptoms secondary to inadequate collateralization post initial bypass surgery. These 57 patients (identified from a prospective moyamoya database) were studied in details, and presented in Chapter 6. We showed that patients with previous indirect bypass have a higher rate of repeat revascularization. Furthermore, over 50% of repeat revascularizations could be achieved with direct procedures, however, the choice of procedure depends on the operative findings and the status of donor and recipient vessels.

It is generally accepted that patients with moyamoya syndrome (MMS) have worse outcome compared to classical moyamoya disease. The comparative study was presented in Chapter 7, and patients with primordial dwarfism were studied in details. MMS is more common in the paediatric age group, has fewer Asian, with more seizure

presentations compared to patients with classical MMD. However, their underlying radiological characteristics, 30-days postoperative risk, and long term stroke risk did not differ significantly compared to patients with classical MMD.

In Chapter 8, we developed the newly proposed Stanford Berlin Grading system, taking into account the factors identified as statistically significant on the logistic regression analysis: A) age category, B) DSA score, C) modified MRI score, D) haemodynamic reserve (HDR) score; and validated the grading system using another cohort of MMD patients treated at Stanford University from 2015-2018. We also used machine learning algorithm to develop a predictive modelling for post revascularisation stroke risk, with 93% accuracy. Further work is ongoing, combining the expertise from INSIGNEO Institute to improve the accuracy of the predictive modelling.

With all this work and knowledge, I set up a UK moyamoya national service, developed a multidisciplinary team and accepted referrals from different parts of the UK, created a website for patient information, and performed several ECIC bypasses for UK patients with good outcome so far. This work also helped me to counsel and consent my patients accordingly, with results presented in Chapter 9.

# List of original publications

## PEER REVIEWED PUBLICATIONS

**Teo M**, Furtado S, Kaneko OF, Azad TD, Madhugiri V, Do HM, Steinberg GK. Validation and application for the Berlin grading system of moyamoya disease in adult patients. *Neurosurgery* 2020; 86(2): 203-212.

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**Teo M,** Johnson JN, Steinberg GK. Strategies for and outcome of repeat revascularization surgery for moyamoya disease: an American institutional series. *Neurosurgery* 2017 Nov 1; 81: 852-859.

**Teo M**, Johnson JN, Bell-Stephens TE, Marks MP, Do HM, Dodd RL, Bober MB, Steinberg GK. Surgical outcomes of Majewski osteodysplastic primordial dwarfism Type II with intracranial vascular anomalies. *J Neurosurg Pediatr*. 2016; 25:717-723.

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following revascularization surgery for moyamoya disease. *J Neurosurg* 2018 Dec 14:1-7.

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## BOOK CHAPTERS

**Teo MK**, Johnson JN, Steinberg GK. "Direct Superficial Temporal Artery to Middle Cerebral Artery Bypass" In: Operative Cranial Neurosurgical Anatomy, F Gagliardi, P Mortini, C Gragnaniello, A Caputy Eds. Thieme 2019.

**Teo MK**, Johnson JN, Steinberg GK. "Pediatric Moyamoya Disease – Indirect Revascularization" In: Pediatric vascular neurosurgery: A comprehensive guide to pediatric neurosurgical disorders and its management. G Britz Eds. Springer-Verlag 2016.

**Teo MK**, Steinberg GK. "Surgical Aspects of Moyamoya Disease" In: Primer on Cerebrovascular Diseases, 2nd Edition. LR Caplan, J Biller, M Leary, A Thomas, E Lo, M Yenari, JH Zhang Eds. Academic Press 2017. San Diego

**Teo MK**, Madhugiri V Steinberg GK. "Adult Moyamoya Disease." In: Decision Making in Cerebrovascular Diseases, Rangel-Castilla, Nakaji, Siddiqui, Spetzler, and Levy Eds. Taylor & Francis 2018.

**Teo MK**, Johnson JN, Steinberg GK. "Rescue Strategies for Repeat Surgery-Omentum Transposition" In: Surgical Techniques for Revascularization in Moyamoya Disease, P. Vajkoczy Eds. Thieme, 2019.

**Teo MK**, Johnson JN, Steinberg GK. “Rescue Strategies for Repeat Surgery- Occipital Artery to Middle or Posterior Cerebral Artery Bypass” In: Surgical Techniques for Revascularization in Moyamoya Disease, P. Vajkoczy Eds. Thieme, 2019.

## ABSTRACTS AND PRESENTATIONS

**Teo M,** Azad TD, Li YP, Wang AR, Madhugiri V, Abhinav K, Zhang M, Steinberg GK (2022). Development and Validation of Stanford-Berlin Moyamoya grading system and Development of Predictive Modelling for Perioperative Stroke. British Neurovascular Group Meeting, 29 March 2022. Cardiff, UK

**Teo M**, Lee KS, Nelson RJ (2020). Brain Bypass practice in early career neurosurgeon in current NHS. British Neurovascular Group Meeting 6-7 Feb 2020. Stoke-on-Trent, UK

**Teo M**, Abhinav K, Madhugiri V, Bell-Stephens T, Sussman E, Azad TD, Ali R, Zhang M, Steinberg GK (2019). Comparative study of moyamoya syndrome and moyamoya disease. WFNS Special World Congress, 9-12 Sept 2019, Beijing, China

Spaul R, Holmes R, Bradley M, Smallbone T, **Teo M,** Edwards RJ, Mallick AA (2019). Same-day split bolus acetazolamide challenge brain perfusion SPECT in paediatric neurovascular practice. European Paediatric Neurology Society Congress, 17-21 Sept 2019, Athens, Greece

**Teo M**, Madhugiri V, Abhinav K, Bell-Stephens T, Sussman E, Azad TD, Ali R, Zhang M, Steinberg GK (2018) How can we reduce STA-MCA risk? WFNS meeting, 15-19 Aug 2018. Kuala Lumpur, Malaysia.

Narayanamurthy H, Edwards R, Mallick A, Bradley M, Mortimer A, Renowden S, Holmes R, Porter DG, Nelson RJ, **Teo M** (2018). Moyamoya disease in the UK: Development of an Integrated Service and Registry. Society of British Neurological Surgeons Meeting, 11-13 April 2018. Torquay, UK.

Ito M, Cheng MY, Lee AG, **Teo M**, Shoemaker LD, Steinberg GK (2018). Analysis of genome-wide blood DNA methylation profile in moyamoya disease. International Stroke Conference, 24-26 Jan 2018. Los Angeles Convention Center, Los Angeles, California, USA.

**Teo M**, Bell-Stephens T, Madhugiri V, Sussman E, Azad TD, Ali R, Esparza R, Zhang M, Steinberg GK (2017). Long term physical and functional outcome of Western moyamoya patients post bypasses. XVI World Congress of Neurosurgery of World Federation of Neurosurgical Societies (WFNS), 20-25 Aug 2017. Istanbul Congress Center, Istanbul, Turkey.

**Teo M**, Johnson J, Steinberg GK. Comparative study of repeat revascularization surgery for moyamoya patients after previous indirect or direct bypass. Congress of Neurological Surgeons Meeting, 24-28 Sept 2016. San Diego, California, USA.

**Teo M**, Bell-Stephens T, Madhugiri VS, Sussman E, Azad TD, Ali R, Esparza R, Zhang M, Steinberg GK. Long term outcome of moyamoya patients post revascularization surgery. 84$^{th}$ AANS Annual Scientific Meeting, 30 Apr – 4 May 2016. Chicago, Illinois, USA

Madhugiri VS, Furtado S, **Teo M**, Steinberg GK. Acute symptomatic contralateral ICA occlusion after direct EC-IC bypass in patients with bilateral moyamoya disease. 84$^{th}$ AANS Annual Scientific Meeting, 30 Apr – 4 May 2016. Chicago, Illinois, USA.

**Teo M**, Furtado S, Kaneko OF, Azad TD, Johnson JN, Do HM, Steinberg GK. Validation and application of a new grading system of moyamoya disease in adult patients. 4$^{th}$ International Moyamoya Meeting, 2-4 July 2015. Berlin, Germany.

**Teo MK**, Johnson JN, Steinberg GK, "Rescue Strategies for Repeat Surgery-Omentum Transposition". 4$^{th}$ International Moyamoya Meeting, 2-4 July 2015. Berlin, Germany.

**Teo MK**, Johnson JN, Steinberg GK, "Rescue Strategies for Repeat Surgery- Occipital Artery to Middle or Posterior Cerebral Artery Bypass". 4th International Moyamoya Meeting, 2-4 July 2015. Berlin, Germany.

**Teo M,** Johnson JN, Steinberg GK (2015). Outcome of repeat revascularization surgery for moyamoya disease. Congress of Neurological Surgeons Meeting, 26-30 Sept 2015. New Orleans, Louisiana, USA.

**Teo M**, Johnson JN, Bell-Stephens T, Marks MP, Do HM, Dodd RL, Bober MB, Gary K. Steinberg GK (2015). Surgical Outcomes of Majewski Osteodysplastic Primordial Dwarfism Type II (MOPD II) with Intracranial Vascular Anomalies. 83rd American Association of Neurological Surgeons AANS Annual Scientific Meeting. 2-6 May 2015. The Walter E. Washington Convention Center, Washington D.C, USA.

## INVITED SPEAKER

Development of predictive modelling for postbypass stroke risk
Brain Interventional Group meeting, 4-5 March 2022, Cotswolds, UK

Moyamoya Disease – Multidisciplinary approach and State of the Art update
National Congress of Modern Neurosciences, 12-16 October 2021, Iasi, Romania

Moyamoya – Therapeutics and Development of a National Registry
UK Neurointerventional Group (UKNG) Meeting, 9-10 June 2017, Bristol, UK

Moyamoya Disease – The Final Frontier for Brain Bypass Surgery?
The British Neurovascular Group 8th Annual Meeting, 2-3 Feb 2017, Glasgow, UK

# ABBREVIATIONS

| | |
|---|---|
| ACA: | Anterior Cerebral Artery |
| AP: | Anterior – Posterior projection |
| AUC: | Area Under the Curve |
| Avrg: | Average |
| BEGPS: | Bilateral EncephaloGaleoPeriosteosynangiosis |
| CBF: | Cerebral Blood Flow |
| CCA: | Common Carotid Artery |
| CENTRAL: | Cochrane Central Register of Controlled Trials |
| CB: | Combined Bypass |
| CI: | Confidence Interval |
| Cons: | Conservative Management |
| CT: | Computed Tomography |
| CVRC: | Cerebrovascular Reserve Capacity |
| DB: | Direct Bypass |
| Diff: | Difference |
| DSA: | Digital Subtraction Angiography |
| DWI +ve: | Diffusion Weighted Image positive |
| ECA: | External Carotid Artery |
| ECIC: | ExtraCranial-IntraCranial |
| EDAGS: | EncephaloDuroArterioGaleoSynangiosis |
| EDAMS: | EncephaloDuroArterioMyoSynangiosis |
| EDAS: | EncephaloDuroArterioSynangiosis |
| EEG: | Electroencephalography |
| EMS: | EncephaloMyosynangiosis |
| EMAS: | EncephaloMyoArterioSynangiosis |
| EGPS: | EncephaloGaleoPeriosteosynangiosis |
| FHx: | Family History |
| F.U: | Follow-Up |
| GBM: | Gradient Boosted Machine |
| Haem: | Haemorrhagic |
| Hx: | History |

| | |
|---|---|
| HDR: | Haemodynamic Reserve |
| IB: | Indirect Bypass |
| ICA: | Internal Carotid Artery |
| ICH: | Intracerebral Haemorrhage |
| ICIC: | IntraCranial-IntraCranial bypass |
| IRB: | Institutional Review Board |
| IVH: | Intraventricular Haemorrhage |
| JBI: | Joanna Briggs Institute |
| JNS: | Journal of Neurosurgery |
| kNN: | K Nearest Neighbour algorithm |
| LASSO: | Least Absolute Shrinkage and Selection Operator |
| LT: | Long term |
| MAP: | Mean Arterial Pressure |
| MBH: | Multiple Burr Holes |
| MCA: | Middle Cerebral Artery |
| M4: | Distal Middle Cerebral Artery |
| MMD: | Moyamoya Disease |
| MMS: | Moyamoya Syndrome |
| MOPD: | Majewski Osteodysplastic Primordial Dwarfism |
| MRI: | Magnetic Resonance Imaging |
| mCVRC: | modifield CVRC score |
| mMRI: | modifield MRI score |
| mRS: | modified Rankin Score |
| mSS: | modified Suzuki Score |
| Mx: | Management |
| NA: | Not Available |
| ND: | Neurological Deficit |
| NF1: | Neurofibromatosis type 1 |
| NF2: | Neurofibromatosis type 2 |
| OA: | Occipital Artery |
| OR: | Odd Ratio |
| PACS: | Picture Archiving and Communication System |
| PCA: | Posterior Cerebral Artery |
| PET: | Positron Emission Tomography |

PIRAMD: Prior Infarcts, Reactivity and Angiography in Moyamoya Disease
PMHx: Past Medical History
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
RCT: Randomised Controlled Trial
REDCap: Research Electronic Data Capture
ROC: Receiver operating characteristic curve
ROI: Region of Interest
RR: Relative risk
SAH: Subarachnoid Haemorrhage
SBMG: Stanford Berlin Moyamoya Grade
SBMS: Stanford Berlin Moyamoya Score
SD: Standard Deviation
SPECT: Single Photon Emission Computed Tomography
STA: Superficial Temporal Artery
STAMCA: Superficial temporal artery to middle cerebral artery direct bypass
Sx: Surgery
TIA: Transient Ischaemic Attack
TNE: Transient Neurological Episodes
WNS: World Neurosurgery
Xe-CT: Xenon-enhanced Computed Tomography

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# CHAPTER ONE

# INTRODUCTION

## 1.1 Moyamoya Disease

Moyamoya disease (MMD), an idiopathic, chronic, steno-occlusive cerebrovascular disease that involves distal ICAs or proximal MCA/ACA, and the development of basal collateral channels, including hypertrophy of the lenticulostriate and thalamoperforating arteries, resulting in the characteristic “moyamoya vessels.” This disease was first described by Takeuchi in 1957 (Takeuchi and Shimizu, 1957), and Suzuki named it “moyamoya disease,” meaning “puff of smoke” in Japanese in 1969 (Suzuki and Takaku, 1969, Gooderham and Steinberg, 2015).

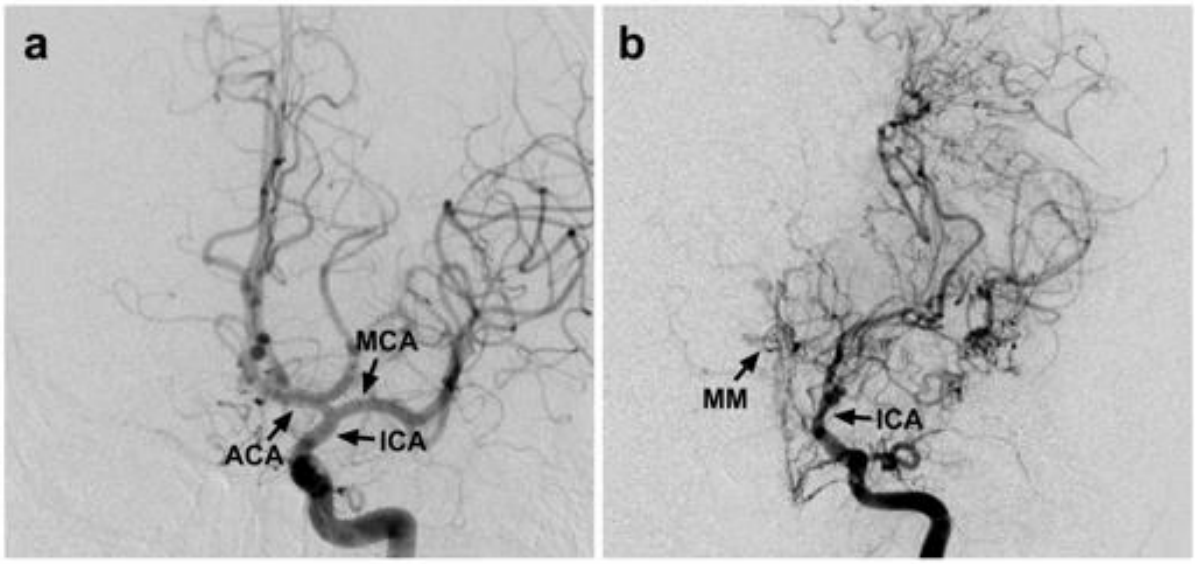


**Figure 1.1** Comparison of (a) normal intracranial cerebral vasculature with (b) moyamoya disease where steno-occlusion of distal ICA led to basal channels collateralisation (moyamoya MM vessels), and non-visualisation of ACA and MCA.

Several syndromes and conditions are associated with or can cause MMD, and these cases are termed the Moyamoya syndrome or atypical MMD - however, such distinctions are probably no longer relevant. The various conditions associated with MMD include prior radiotherapy to the head and neck or brain, Down’s syndrome, neurofibromatosis type 1, tuberous sclerosis, Majewski osteodysplastic primordial dwarfism (MOPD), Fanconi’s anemia, sickle cell disease, autoimmune disorders (Grave’s disease), Marfan’s syndrome, renal artery stenosis and infections (tuberculous meningitis, leptospirosis) (Scott and Smith, 2009, Smith, 2009, Bober et al., 2010, Teo et al., 2016).

### 1.1.1 Epidemiology

Although initially described and more prevalent in Asian populations, it is now increasingly recognised to affect people of various ethnicities – Europeans, Americans, Japanese, Chinese, Africans, with the highest reported incidence of 0.54–0.94 per 100,000 and prevalence of 6.03 per 100,000 in the Japanese population (Baba et al., 2008, Kuriyama et al., 2008). In Europe and North America, current estimated incidence is 0.086 per 100,000 population (Cook et al., 2015). The true incidence may be higher, due to underdiagnosis or misdiagnosis of MMD, as shown by a recent 2012 study from USA that reported the incidence of 0.57/100,000 (Starke et al., 2012).

Two peaks exist in the age distribution of moyamoya disease, with the first peak in the paediatric population (age 5-9 years), and second in the mid-adulthood (40-50 years). There is an equal gender distribution between males and females in the first decade of life, but subsequently female predominate with a ratio of 2-3:1 (Gooderham and Steinberg, 2015).

### 1.1.2 Presentation

Patients commonly present with cerebral ischemia (TIAs, or stroke) or intracranial (intracerebral, intraventricular or subarachnoid) haemorrhage from rupture of the fragile moyamoya vessels. In medically treated or untreated patients, progression of the underlying arteriopathy or bleeding from the moyamoya vessels almost inevitably led to clinical events with ongoing follow up. According to Hallemeier et al, of 20 patients managed conservatively at Washington University, the 5-year risk of recurrent ipsilateral stroke after symptoms onset and angiographic diagnosis, was 65% and 27% respectively (Hallemeier et al., 2006b). Furthermore, they also showed that ischaemic MMD patients with bilateral ICA involvements were at the highest risk of subsequent stroke (82% 5-year stroke risk)(Hallemeier et al., 2006b). For patients with haemorrhagic MMD, early natural history study showed that nearly 20% died of the initial intracranial haemorrhage, and 38% suffered further rebleed with a mean follow-up of 7 years (Yoshida et al., 1999).

Medical treatments to reverse or inhibit the progression of the arterial occlusion are not currently available, hence neurosurgical intervention in the form of direct or indirect revascularisation procedures to reduce the risk of strokes remained the mainstay of treatment for these patients.

## 1.2 Surgical Revascularisation

There are two main types of surgical revascularization for the treatment of MMD: direct and indirect extracranial to intracranial bypass. The two strategies rely on different principles of cerebral reperfusion. In the direct methods (most commonly direct STA-MCA bypass), anastomosis of scalp arteries to intracranial arteries is performed to perfuse affected cerebral territories (Figure 1.2, Figure 1.3); indirect methods depend on the development of a new vascular network over time due to the underlying brain angioplasticity (Figure 1.4, Figure 1.5). This can be achieved by using adjacent tissues (galea, muscle, scalp arteries, dura) or distant graft (omentum) to cover the brain surface to promote indirect collateralization. Indirect procedures include encephalomyosynangiosis (EMS), encephalogaleo[periosteo]synangiosis (EGPS), encephaloduroarteriosynangiosis (EDAS), encephaloduroarteriomyosynangiosis (EDAMS), pial synangiosis, multiple burr holes (MBH), and omental transposition (encephalo-omental synangiosis).

Patients who are potential candidates for operative cerebral revascularization procedures have a thorough medical, cardiac and baseline neurologic evaluation. In addition, routine preoperative labs and radiologic studies which include a formal 6-vessel cerebral angiogram, MRI brain, and cerebral perfusion imaging with and without Diamox (PET, MR perfusion, SPECT, or TCDs) are performed prior to surgery.

### 1.2.1 Direct STA-MCA bypass

Direct STA-MCA bypass was first described by Yasargil in 1970 (Yasargil et al., 1970) for atherosclerotic stroke, however with the advancement of medical and

endovascular stroke therapy, direct bypass is rarely required (The EC/IC Bypass Study Group, 1985, Powers et al., 2011, Berkhemer et al., 2015, Campbell et al., 2015, Goyal et al., 2015, Goyal et al., 2016). In modern neurosurgical practice, direct STA-MCA bypass is rarely performed as the indications are very limited. There are 2 broad categories where direct bypasses are employed to prevent ischemia. One setting is to replace native cerebral blood flow, such as when an intracranial vessel sacrifice is necessary as in the setting of complex or giant ICA or proximal MCA aneurysms. The second is to supplement cerebral blood flow in the setting of ongoing poor cerebral perfusion secondary to intracranial vasculopathy like MMD. At Stanford University Medical Centre, due to the large volume of MMD referrals, direct STA-MCA bypass is performed regularly.

#### 1.2.1.1 Direct STA-MCA bypass – operative nuances

During surgery under general anesthesia and mild hypothermia to about 33°C, the patient is positioned supine with the head turned lateral and fixed in a Mayfield clamp (so the operative field is parallel to the floor). The most suitable STA branch (frontal vs. parietal branch) is chosen as the donor based on the preoperative angiogram. In most cases the parietal branch is selected as it is behind the hairline, has a straighter course, and there is less risk of damage to the frontalis nerve branches during dissection (Figure 1.2). Using a handheld Doppler probe, 9 cm of the donor STA branch is transduced above the zygoma and harvested along its course under microscopic magnification. The frontal branch of STA is generally preserved for a potential subsequent revascularization procedure; small distal branches are coagulated and divided to mobilize the STA trunk. Papaverine is intermittently applied to the dissected STA to alleviate spasm, and a Doppler probe used to ensure the patency during STA dissection.

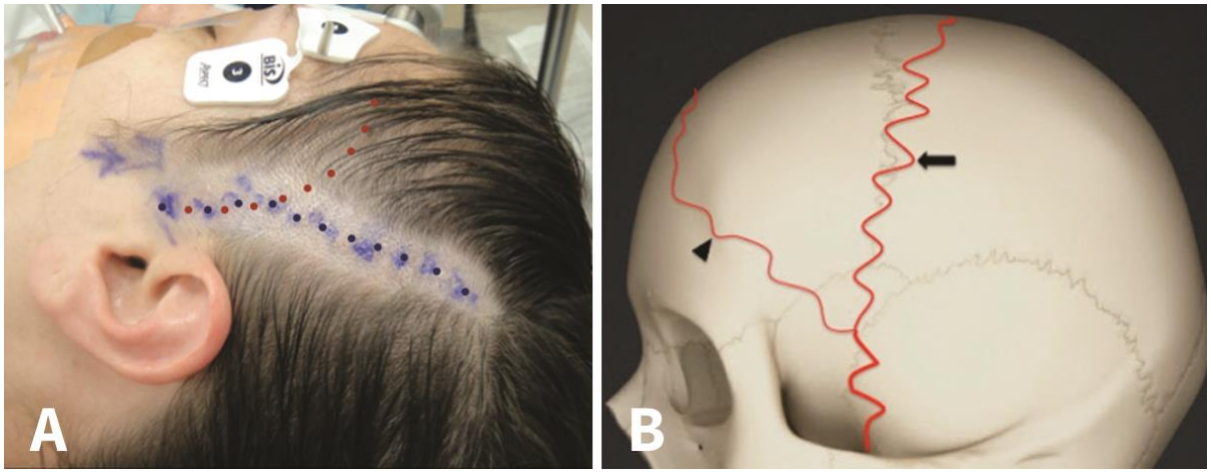


**Figure 1.2**. (A) Patient positioned supine with the operative field parallel to the floor. The STA branches are marked (parietal branch in blue, frontal branch in red). (B) The configuration of the frontal (arrowhead) and parietal (arrow) STA branch on the skull model. Adopted from Teo MK, Johnson JN, Steinberg GK. "Direct Superficial Temporal Artery to Middle Cerebral Artery Bypass" In: Operative Cranial Neurosurgical Anatomy, F Gagliardi, P Mortini, C Gragnaniello, A Caputy Eds. Thieme 2017. (Teo et al., 2017b)

After harvesting the STA vessel off the temporalis fascia, the temporalis muscle is cut and retracted and a craniotomy approximately 6 cm in diameter is performed. Under maximal magnification, 1-2 cm of the distal STA is dissected free of the surrounding tissue and skeletonized using fine micro scissors. Similarly, a short length of the proximal STA is dissected from its surrounding soft tissue cuff to create a site for placement of a proximal temporary clip. The ideal site for temporary clipping is distal to the take-off of the unused frontal branch of the STA; this allows continued flow through the STA into the unoccluded branch, reducing stagnant flow and the risk of thrombosis proximal to the temporary clip.

The dura is then opened in a stellate fashion, and the microscope is used to find a suitable recipient cortical MCA branch. The most important considerations are size of the donor and recipient vessels (0.9 mm or greater is optimal), location of the recipient M4 branch of the MCA (away from the craniotomy edges is preferred) and orientation of the vessels (to avoid an acute angulation between the donor and recipient vessels, and facilitate suturing both walls of the recipient artery).

The arachnoid over the potential recipient vessel is opened; the MCA M4 branch is prepared for anastomosis by placing a high visibility background material underneath the vessel. Larger perforators can be spared by including their origin from the MCA segment in the temporary vessel clips. Before temporary clipping, blood flow is measured in the MCA branch and the cut STA using a Transonics, Charbel ultrasonic flow probe. After the temporary clip is applied to the proximal STA, the STA is cut at a 45° angle to create a fish mouth. The cut STA segment is then flushed with heparinized saline.

MAP is gently raised to over 90 mmHg. Burst suppression is achieved using propofol. Specially designed Anspach-Lazic temporary mini-clips are placed proximally and distally on the recipient vessel. An arteriotomy is then made over the recipient MCA using microscissors, and the lumen flushed with heparinized saline. Indigo-carmine dye (or a sterile marking pen) is used to stain the walls of the donor and recipient vessel and allow the lumen to be seen more easily and facilitate the microanastomosis. 10-0 sutures are first placed to anchor the apices of the arteriotomy (toe stitch, followed by heel stitch). Sutures should be passed from outside the donor artery to inside the recipient artery, and then tied on the outer surface of the anastomosis. Once the donor STA has been anchored, interrupted sutures are place on each side of the anastomosis at close intervals, making sure not to catch the back wall of the vessel. Once the anastomosis is complete, the temporary clips on the recipient artery are released, followed by opening of the clip on the proximal STA (Figure 1.3). Occasionally additional sutures are needed to seal the anastomosis. Blood flow in the STA, proximal MCA and distal MCA to the anastomosis is then measured with the Transonics Charbel flowmeter, and intraoperative indocyanine green (ICG) as well as intraoperative Doppler are performed to confirm patency and quantitative function of the bypass graft (Figure 1.3). During closure, the dura is loosely replaced, the inferior burr hole enlarged to accommodate the entering STA graft, the bone is replaced avoiding any kinking or pressure on the vessel, the temporalis muscle is approximated, and the skin is closed with care. The patency of the STA trunk is verified with a Doppler probe at the end of the procedure.

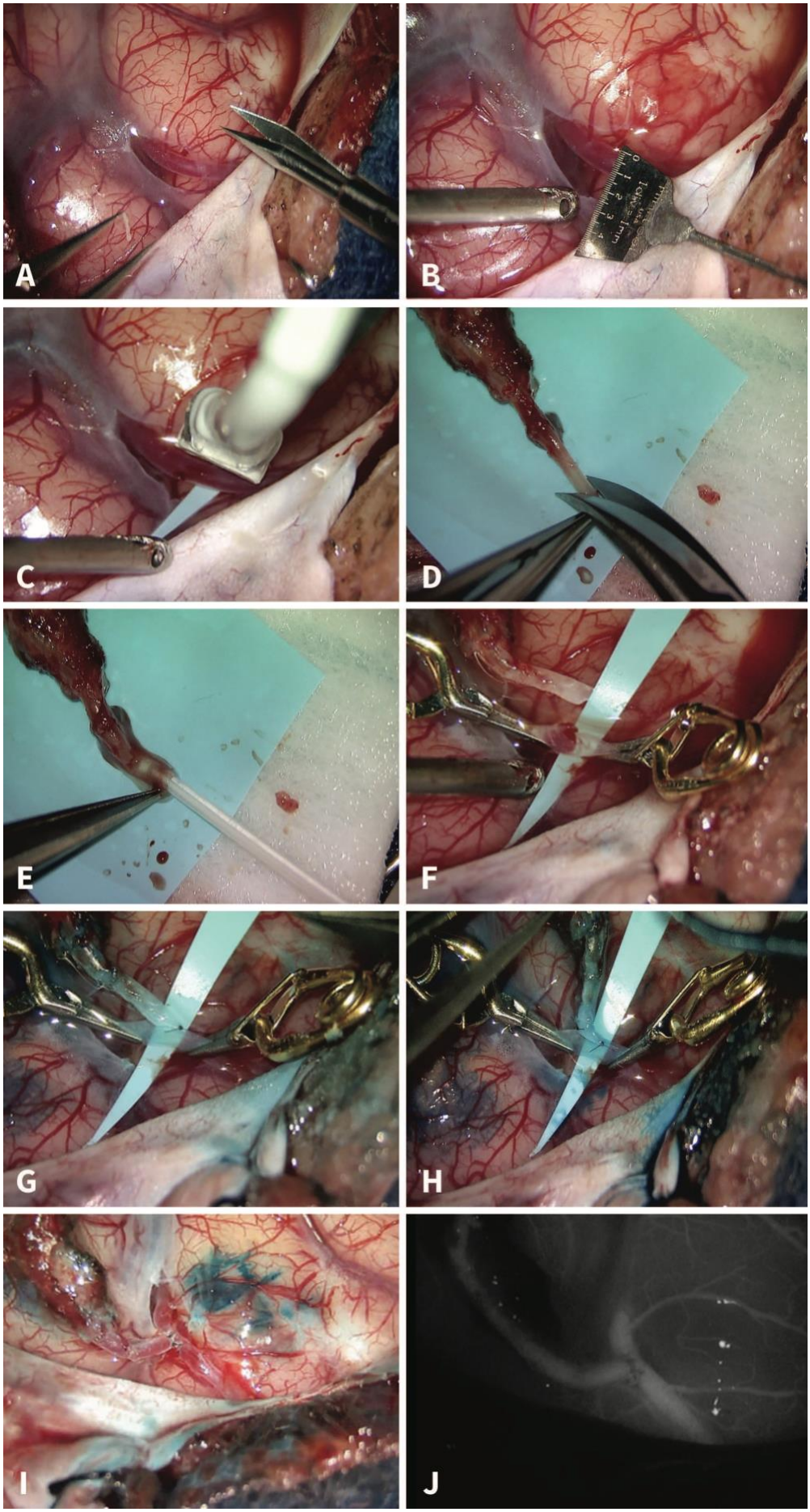
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**Figure 1.3**. Intradural stage of direct STA-MCA bypass.
(A) Opening of the arachnoid over the potential recipient MCA vessel, exposing 7mm of M4 branch.
(B) Measurement of the diameter for the recipient vessel.
(C) High visibility background material is passed beneath the recipient vessel, and blood flow is measured using a Charbel Transonics ultrasonic flow probe.
(D) The distal STA is divided at a 45-degree angle,
(E) The cut STA segment flushed with heparinized saline
(F) After temporary clips are applied to MCA vessel, an arteriotomy is made and the lumen is flushed with heparinized saline.
(G) The donor and recipient vessels are tinted with indigo-carmine or a marking pen to better visualize the microanastomosis. Monofilament sutures (10-0) are used to anchor the apices of the incision, toe stitch first, (H) followed by the heel stitch.
(I) The side walls of the anastomosis are sutured in an interrupted fashion, also using 10-0 monofilament sutures. Once the anastomosis is complete, the temporary clips on the recipient artery are released, and then the proximal clip on the STA is removed.
(J) Blood flow in the STA, and proximal and distal MCA to the anastomosis is measured with a flow probe, and intraoperative ICG angiogram is performed to confirm patency and function of the bypass graft.
Adopted from Teo MK, Johnson JN, Steinberg GK. “Direct Superficial Temporal Artery to Middle Cerebral Artery Bypass” In: Operative Cranial Neurosurgical Anatomy, F Gagliardi, P Mortini, C Gragnaniello, A Caputy Eds. Thieme 2017.

### 1.2.2 Indirect Bypass

#### *1.2.2.1 Encephalomyosynangiosis (EMS)*

EMS was first applied to MMD by Karasawa and associates (Karasawa et al., 1977) in the late 1970s and has now been widely used as an initial surgical intervention (Irikura et al., 2000, Kono et al., 1997, Takeuchi et al., 1983, Tu et al., 1997, Yoshioka and Tominaga, 1998).

The principle is to place vascularized muscle on the brain cortical surface. It usually involves frontotemporal craniotomy with transposition of the temporalis muscle, due to its anatomical location, rich blood supply and potential for dense vascular collateralization.

For frontotemporal craniotomy, a linear incision is used overlying the temporalis muscle, where the muscle is dissected from the bone. After craniotomy, dura is opened, muscle placed on the brain and sutured to the dural edges. Hemostasis is obtained to avoid postoperative hemorrhage in the subdural and epidural space. The bone edges are removed, bone flap thinned prior to securing down to prevent compression of the muscle on the brain and skull edges.

#### *1.2.2.2 Encephalogaleoperiostealsynangiosis (EGPS)*

For ischemia of the anterior cerebral artery territory, bifrontal EGPS is recommended, preserving the STA branches for future procedures. Galea tissue with or without periosteum is placed on each side of the frontal area. A curvilinear scalp incision and bifrontal craniotomy crossing midline is performed. The posterior margin of the craniotomy is placed at the coronal sutures, to avoid disruption of large draining parasagittal veins during dural opening.

The galea tissue is harvested using anterior, posterior and midline incisions (H pattern). Some reflect and place the periosteum with galea as one layer, while others insert the galeal tissue only and leave the periosteum in situ. For very young children with very thin scalp, leaving the vascularized periosteum in situ may be help to avoid the complication of postoperative ischemic scalp necrosis.

The dura mater is incised separately in both hemispheres, and arachnoid fenestration performed. The previously created dural flaps are inserted into each hemispheric fissure, and the galeoperiosteal flap sutured to the margin of the dura. This technique is well documented and illustrated by Park et al (Park et al., 2007) and Kim et al (Kim et al., 2002).

### *1.2.2.3 Encephaloduroarteriosynangiosis (EDAS)*

EDAS was first developed by Matsushima and colleagues (Matsushima et al., 1981a) in 1980s and is our preferred technique for indirect revascularization in pediatric MMD. It is probably the most commonly performed indirect procedure for MMD, and many variants were developed which include the following: EDAS + pial synangiosis, EDAS + split dural technique.

One of the three main branch arteries of the scalp (frontal or parietal superficial temporal artery branch, or the occipital artery) is used, based on the area of ischemia, and the vessels configuration. The artery is traced out using Doppler, and skin incision made either over the artery or as a scalp flap behind the hairline to harvest the vessel. The galea is cut with a fine tip monopolar electrocoagulator parallel to but 5-7mm from the artery so that the artery is dissected with a strip of galea from the underlying muscle and periosteum. It is then mobilized, carefully retracted so that temporalis muscle incision and craniotomy performed underneath.

Two burrholes are made for craniotomy, proximal and distal to the ends of the skeletonized artery so that when the bone flap is replaced, the artery can enter and exit through these burrholes. Cruciate dura opening is performed, with care taken not to transect major meningeal arteries, and arachnoid layer fenestrated at multiple sites. The scalp vessel is then placed on the pia-arachnoid surface (Figure 1.4). The dura is then approximated over the vessel, bone flap replaced, and multilayer scalp closure performed ensuring the patency of the bypass graft.

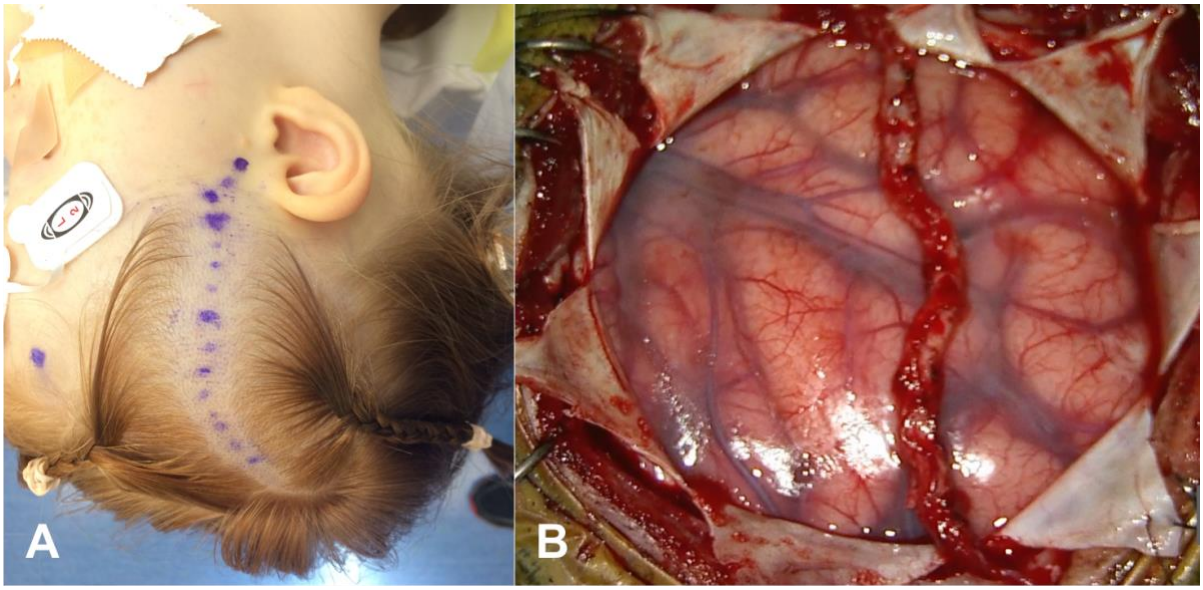


**Figure 1.4**. EDAS indirect bypass. (A) Scalp incision with minimal hair shave along the parietal STA branch as tranduced using a hand-held Doppler. (B) Harvested parietal STA branch is laid on the pia-arachnoid brain parenchymal surface to allow for neoangiogenesis from the perivascular tissue after multiple fenestration of the arachnoid lining. Variations of the technique include suturing the STA perivascular cuff to the pia (pia synangiosis), or split the dural folds, infold the inner dural layer to allow for neovascularization to the underlying parenchyma, while suture the outer layer to allow for dural opposition (split dural technique).

#### *1.2.2.4 Modified EDAS + Pial synangiosis*

Slight modification to the techniques for EDAS was made by the Boston group (Scott et al., 2004). After cruciate dural opening, the arachnoid layer is incised under surgical microscope to allow wide access to the pia. The superficial temporal artery is then placed on the pial surface and sutured to the pia using 10-0 monofilament sutures. This creates the synangiosis of the artery and the brain. As many sutures as possible are placed to encourage tight approximation of the artery to the brain surface. Hemostasis is obtained by gentle irrigation or judicious bipolar coagulation. The rest of the closure is as described for EDAS.

#### *1.2.2.5 Modified EDAS + Split-dural technique*

This technique was described by Kashiwagi and colleagues ((Kashiwagi et al., 1997), with similar approach taken for EDAS until bone flap removal. The dural incision is made carefully through the outer layer of the dura, preserving major MMA. The outer layer of the dura is split from the inner layer, the inner layer is then incised along the same configuration and folded over into the subdural space so that this split surface is attached to the cortical surface. The outer dural layer is then approximated after STA vessel is laid on the cortical surface. Ideally bleeding from dural incision or split surface should be controlled with minimal coagulation to maintain the dural blood supply.

#### *1.2.2.6 Encephaloduroarteriomyosynangiosis (EDAMS)*

Another variation is the combination of both EDAS and EMS, where EDAMS (Kinugasa et al., 1993) was developed with the hypothesis that increased neovascularization from the temporalis muscle, STA and dura would be more likely to fully perfuse the affected area. This procedure also requires the creation of dural flaps that are folded into the subdural/epiarachnoid space to allow MMA participation in angiogenesis.

#### *1.2.2.7 Multiple burrholes (MBH)*

This less technically challenging technique was developed after vasculogenesis was observed in patients with ventriculostomies requiring cranial burrholes ((Sainte-Rose et al., 2006b). Thus strategically placed burrholes in areas of cerebral hypoperfusion might aid in stimulating vascular formation between underlying cortex and dura matter, effectively providing an arterial supply to hypoxic brain areas.

#### *1.2.2.8 Omental-cranial transposition*

Karasawa and associates ((Karasawa et al., 1993) dissected omental tissue with gastroepiploic artery and vein for transplantation to the MCA and ACA territories of the brain. They concluded that this procedure may be appropriate for MMD in ACA or PCA

territory, however it is technically challenging as it required harvesting of omental tissue via laparotomy, large craniotomy to overlay the omental tissue on the cortical surface, and vessels grafted to the external carotid artery. In our own experience, although the revascularization obtained is quite effective, it has been infrequently performed owing to its associated morbidity with laparotomy and numerous graft complications including torsion, necrosis and mass effect on the brain. We have since introduced modifications to the omental-cranial transposition technique in children, and found it especially effective in children with progressive neurological symptoms despite previous revascularization procedures (Navarro et al., 2014). The omentum is harvested in a minimally invasive way by a pediatric general surgery team with laparoscopic expertise, which helps minimize the morbidity of the procedure. The right gastroepiploic artery is preserved to maintain the vascular pedicle to the omentum. Once the omentum is maximally mobilized, it is brought to the surface at the midepigastric level using a 3-4cm incision for inspection ensuring the patency of its blood supply. The omentum was carefully divided between the epiploic arcades with step cuts, which then create a thin, homogeneous omental flap that would be long enough to reach the contralateral cerebral hemisphere as required. A subcutaneous channel is then created between the craniotomy wound and midepigastric incision using blunt dissection, then omental flap is then thoroughly irrigated and lubricated with KY jelly to facilitate its tunneling to the cranial region (Figure 1.5). Vascular patency is checked at the cranial end by direct inspection and use of a Doppler probe.

While the pediatric surgery team harvested the omentum, the neurosurgery team worked on the craniotomy, designing the incision and bone flap away from the previous surgery to avoid damage to previous revascularization. The bone flap is fashioned to allow for wide area of brain revascularisation (Figure 1.4), then the inner table drilled off to prevent strangulation of the flap and its vasculature, and to reduce mass effect on the brain while bone flap is replaced. Two layers scalp closure and abdominal wound incision is then performed.

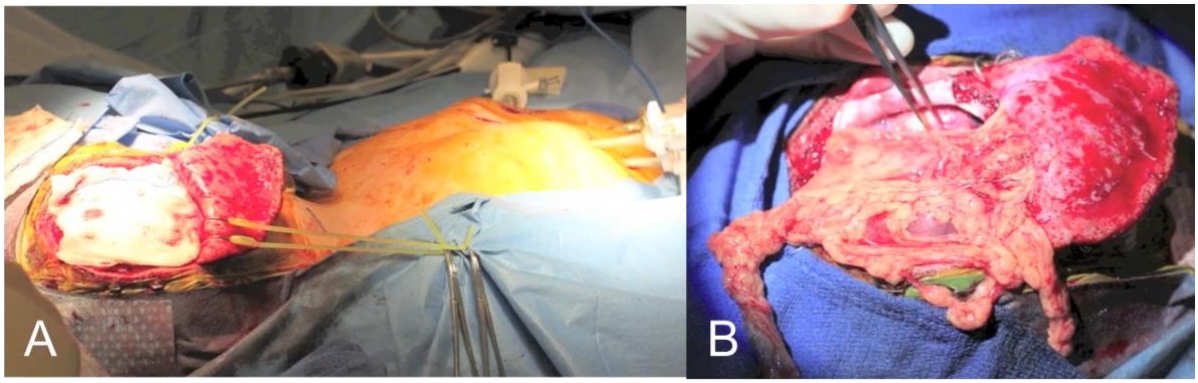


**Figure 1.5**. Omental transposition indirect bypass. (A) Modifications made with laparoscopic harvest of the vascularized pedicled omentum, subcutaneous tunnel created to allow for smooth delivery of the omental flap to the cranial wound. (B) Craniotomy with dural opening to allow for wide area of brain revascularization using omental flap.

#### *1.2.2.9 Gracilis Muscle- Cranial Transplantation*

Touho et al (Touho et al., 1995) described a technique for cerebral revascularization with gracilis muscle transplantation used in children who continued to suffer symptoms of ischemia in the territory of the ACA or PCA territory after omental transposition. Although technically feasible, it is very rarely performed in contemporary neurosurgical practice, and we have not found the need to do so in our own experience.

#### 1.2.2.10 Combined Indirect Techniques

Multiple combined indirect procedures use many of the previously mentioned techniques to obtain the widest coverage of brain parenchyma to allow optimal revascularization. The commonly described techniques are EDAS plus bifrontal EGPS (Kim et al., 2002), EDAS plus EMS plus EMAS ((Miyamoto et al., 1988), EDAS plus EMS (Matsushima et al., 1997), multiple burrholes plus EMS ((Pandey and Steinberg, 2011). The results for these procedures are variable depending on specific technique combinations.

### 1.2.3 Combined Indirect and Direct Procedures

Of the indirect/ direct procedure combinations, the most common is the STA-MCA anastomosis with an EMS using the same craniotomy. Other combinations included STA-MCA anastomosis with EDAS, MMA-MCA anastomosis with EDAS, STA-MCA anastomosis with EDAMS ((Matsushima et al., 1998, Shrestha et al., 2008, Houkin et al., 2001).

### 1.2.4 Comparative Studies between Direct and Indirect bypass

Comparative studies between direct and indirect bypass for MMD were searched using pubmed. Currently there is no randomized controlled trial (RCT) that determine either direct or indirect revascularization is superior to the other in the management of moyamoya disease. The findings in current literature are showing mixed results, and some of the literatures on this topic are suggesting that direct bypass is superior (Kazumata et al., 2014b, Nakashima et al., 1997, Houkin et al., 1996). The main advantages of direct anastomosis are the establishment of augmented flow immediately following surgery, a more consistent and higher extent of angiographic collateralization (Arias et al., 2015a, Matsushima et al., 1998), superiority in restoring cerebrovascular reserve capacity post-bypass (Czabanka et al., 2011a), more patients with symptomatic improvement, less recurrent ischemic risk and more patients with stroke-free survival (Kazumata et al., 2014b, Bang et al., 2012, Houkin et al., 2000).

Indirect procedures are very popular, especially in the paediatric population, as they are technically less demanding, are highly effective due to children's robust potential for angiogenesis, and believed to have lower short-term complication rates (Fujimura et al., 2009b, Fung et al., 2005a, Houkin et al., 2000, Irikura et al., 2000, Isono et al., 2002, Karasawa et al., 1993, Kim et al., 2007, Kim et al., 2002, Komotar et al., 2009, Matsushima et al., 1989, Ross et al., 1994, Sainte-Rose et al., 2006b, Scott et al., 2004, Veeravagu et al., 2008), the efficacy in adults is still controversial. A summary of the literatures comparing direct and indirect bypasses in the adult and paediatric cohort are shown in Table 1.1 and Table 1.2.

| Author | Year | Journal | Country | No. of pts | Comments |
|---|---|---|---|---|---|
| *Adult series* | | | | | |
| Arias et al | 2015 | J Stroke Cerebrovas Dis | USA, Missouri | 15 pts | Direct bypass provides more consistent & complete cerebral revascularization |
| Kazumata K et al | 2014 | JNS 121: 432-440 | Japan, Sapporo | 2032 direct, 4171 indirect systematic review | Direct bypass: higher extent of angiographic revascularization<br>Comparable postop stroke risk in direct and indirect group<br>Recurrent stroke risk is higher in indirect bypass group |
| Abla et al | 2013 | NeuroSx 73: 430-439 | USA, BNI | 39 indirect<br>29 direct | Direct bypass: significantly greater improvement in symptoms.<br>Both direct and indirect bypass can be equally effective in preventing stroke. |
| Bang et al | 2012 | NeuroSx 70: 625-633 | Korea, Seoul | 65 pts, 75 bypasses | Direct bypass: higher extent of angiographic revascularization at 6mths |
| Czabanka et al | 2011 | Cerebrovasc Dis 32: 361-369 | Germany, Berlin | 24 patients<br>24 direct, 24 indirect | STA-mca/EMS: superior to single EMS in restoring CVRC<br>Better angiographic collateralization |
| Kawaguchi S et al | 2000 | JNS 93: 397-401 | Japan, Nara | 22 patients<br>11 cons, 6 direct bypass, 5 EDAS | Direct bypass significantly reduce the risk of recurrent hemorrhage<br>Direct bypass significantly reduce the risk of recurrent ischemic events |
| Houkin et al | 2000 | Acta Neurochir 142: 269-276 | Japan, Sapporo | 85 pts<br>22 sides in adult cases assessed | Direct bypass useful in over 90% of adult cases<br>Poorer rate of neo-angiogenesis by indirect bypass in adults |

| Author | **Year** | **Journal** | **Country** | **No. of pts** | **Comments** |
|---|---|---|---|---|---|
| *Paediatrics series* | | | | | |
| Abla et al | 2013 | NeuroSx 73: 430-439 | USA, BNI | 20 indirect<br>4 direct | Due to children's robust potential for angiogenesis, despite predominantly indirect bypass, outcome is similar to adult direct bypass group. |
| Czabanka et al | 2011 | Cerebrovasc Dis 32: 361-369 | Germany, Berlin | 7 patients<br>7 direct, 7 indirect | Indirect (EMS): provide adequate collateralization, perhaps young patient has stronger angiogenesis inducing potential |
| Houkin et al | 2000 | Acta Neurochir 142: 269-276 | Japan, Sapporo | 85 pts<br>34 sides in peds cases assessed | Direct bypass graft remained patent in 53% of peds cases at 3mths<br>Excellent rate of neo-angiogenesis by indirect bypass in peds |
| Matsushima et al | 1998 | Neurosurg Focus 5 | Japan, Fukuoka | 50 pts | Direct: best postop vessel collateralisation<br>Direct: best clinical improvement<br>Indirect: less postop complication |

**Table 1.1**

A summary of the literatures comparing direct and indirect bypasses in the adult and paediaric series.

**Table 1.2**

Comparison of direct and indirect bypasses, advantages, disadvantages, post-operative and 5-years stroke risk, including comparison from western series.

| | Direct bypass | Indirect bypass | |
|---|---|---|---|
| | | | |
| Advantages | Immediate & significant improvement of CBF | Technically easier | |
| | More symptomatic improvement | Allow wide cortical revascularization | |
| | More stroke free survival | Very efficient in children | |
| | Less recurrent hemorrhagic risk | | |
| | More superior in restoring CVRC | | |
| | Better extent of angiographic revascularization | | |
| | Lower rate of repeat revascularization | | |
| | | | |
| Disadvantages | Technically more challenging | Delayed effect | |
| | Feasibility limited in children due to size | Less impact on hemorrhagic risk | |
| | | Less certain response in adults | |
| | | | |
| Surgical risks (combined risk from literatures) | | | |
| Postop stroke | 5.4% (3.4% - 7.5%) | 5.5% (3.7% - 7.3%) | Kazumata et al, JNS 2014 |
| Postop ischemic stroke | 4.1% (2.4% - 5.9%) | 5.2% (3.5% - 7.0%) | |
| Postop hemorrhagic stroke | 1.3% (0.3% - 2.3%) | 0.3% (0% - 0.8%) | |
| Long term recurrent stroke risk | 3.5% (95% CI 1.0% - 6.0%) | 11.2% (CI 3.5% - 18.9%) | |
| | | | |

| | | | |
|---|---|---|---|
| Surgical risks (USA series comparison) | | | |
| Postop death | 0.4% | 0% | Direct series: Guzman et al ; JNS2009 |
| Postop stroke | 3.5% | 3.1% | Indirect series: Dusick et al; NeuroSx 2011 |
| postop ischemic stroke | 1.7% | 3.1% | |
| Postop hemorrhagic stroke | 1.8% | | |
| | | | |
| 5 years recurrent stroke risk | | | |
| Overall stroke | 1.7% | 14.3% | Bang et al 2012, 5yrs mean F.U |
| Hemorrhage | 0% | 7.1% | |
| Ischemic stroke | 1.7% | 7.1% | |
| | | | |
| Stroke free interval | 8.5 +/- 1.5 yrs | 4.0 +/- 1.5 yrs | Kawaguchi et al JNS 2000, 8yrs mean F.U |

A recent meta-analysis included 16 studies of randomized controlled trials, prospective controlled cohort studies and retrospective case-controlled studies comparing the treatment efficacy of symptomatic moyamoya disease. It concluded that the long term stroke risk was significantly reduced with surgical treatment when compared to medical therapy (OR of 0.17, 95% CI, 0.12–0.26, p<0.01), especially for haemorrhagic MMD (OR of 0.23, 95% CI, 0.15–0.38, p<0.01). Furthermore, when comparing the different bypass techniques, the secondary stroke risk reduction was lower with indirect bypass compared to direct bypass (OR of 1.79, 95% CI, 1.14 – 2.82, p=0.01), with no significant detectable difference for perioperative complications (Qian et al., 2015).

### 1.2.5 Endovascular treatment

Despite attempts to dilate the stenotic vessels in MMD using endoluminal therapy (balloon angioplasty with or without stenting) no long-term success has been achieved, most likely due to the progressive steno-occlusive nature of the affected vessels. Although no prospective trials were conducted to examine this therapy, in a small series of 5 patients who underwent angioplasty or stenting, treatment failure was observed in all 5 patients within a year of treatment (Khan et al., 2011).

### 1.2.6 Randomised Controlled Trial (RCT) in MMD

Since about one half the adult Asian MMD presented with intracranial haemorrhage, and no medical therapy was available to reduce rebleeding risk, the Japan Adult Moyamoya (JAM) Trial was conducted in 2001, with 22 recruiting institutes, and final follow-up completed in 2013 for all enrolled patients (Miyamoto et al., 2014a).

The multicentered, prospective, controlled trial randomized 80 haemorrhagic MMD patients (16-65 years of age) into direct surgical revascularization versus medical management, and with 5 years follow up, the rebleed rate was 2.7% per year in the surgical group versus 7.6% per year in the medical group (p=0.042). Furthermore, when all recorded morbidity was compared between the surgical and medical group, it was 3.2%/year versus 8.2%/year respectively (p=0.048). Therefore, although

statistically marginal, they concluded that direct revascularization led to a reduction in stroke and intracranial haemorrhage in these patients as opposed to medical or conservative management (Miyamoto et al., 2014a).

For ischaemic MMD, no RCT was conducted comparing the outcome of revascularisation and medical management, but generally many groups observed that the long term stroke risks reduced after surgical revascularisation, compared to the natural history of MMD as reported in the literature. One of the largest controlled cohort study which included 98 ischaemic MMD patients, 89 patients had surgical revascularisation, and 9 patients managed medically, recurrent strokes occurred in 17/89 (19%) compared to 6/9 (67%) of surgical and medical patients, respectively (p=0.0013), with patients who underwent direct or combined bypass having the lowest recurrent stroke risks (7%) (Lee et al., 2012a).

## 1.3 Comparison between MMD in the east and the west

### 1.3.1 Presentations

In children, the most common presentation is cerebral ischemia. In a North American study (Scott et al., 2004) of 143 pediatric patients with MMD, nearly all presented with either stroke or TIA; similar findings were also found in European studies (Khan et al., 2003b, Sainte-Rose et al., 2006b). In a large Asian population study, 40% of those younger than 10 years of age presented with TIA and nearly 30% with cerebral infarction (Kim et al., 2002). Hemorrhagic presentation occurred in 3 to 9% of pediatric patients in both Asian and North American series (Han et al., 2000, Scott et al., 2004). Other less common presentations include seizures, movement disorders, learning difficulties and developmental delays.

In adults, nearly 50% presented with intracranial hemorrhage in the Asian series (Miyamoto et al., 2014a, Hung et al., 1997, Miao et al., 2010). In the North American cohort, adult MMD still largely presented with cerebral ischemia (about 80%) (Guzman et al., 2009b). A recent systematic review which included 8 studies (three from Japan,

one each from Taiwan and China and three from the USA) that met the predetermined inclusion criteria also showed such regional differences in presenting symptoms (Kleinloog et al., 2012).

### 1.3.2 Genetics

5-15% of MMD occurs in patients with positive family history, which supports a genetic basis to disease predisposition (Kuriyama et al., 2008). Recent genome-wide and locus-specific association studies identified RNF213 gene as an important susceptibility gene of MMD for east Asian population (Liu et al., 2011). RNF213 was found to be mutated in 95% of Japanese familial MMD, 73% of nonfamilial MMD and only 1.4% of controls (Kamada et al., 2011). Furthermore, the RNF213 p.R4810L variant was shown to segregate with disease in Asian families, but not in Europeans (Kamada et al., 2011, Cecchi et al., 2014).

## 1.4 Long term outcome of MMD post revascularisation

Since MMD primarily affected the children and young adults, the long term risk of late cerebrovascular events following surgical revascularization is important. Most of the studies on long term outcome after MMD revascularization were from the east (Table 1.3). Only 6 studies in the paediatric series (Rashad et al., 2016, Liu et al., 2016a, Funaki et al., 2014, Mukawa et al., 2012, Ulrich and Januschek, 2011, Scott et al., 2004), and 4 in the adult series (Ozaki et al., 2016, Liu et al., 2016b, Cho et al., 2014, Bao et al., 2012) reported patients mean outcome of 5 years or longer.

In the children series, with one of the longest follow-up reported in the literature, Funaki et al reported on their experience of 58 paediatric MMD with a mean follow up of 18 years. The incidence of late cerebrovascular events were 0.41% per year (95% C.I. 0.15-1.08); furthermore 10-year, 20-year, and 30-year cumulative incidences were 1.8%, 7.3%, and 13.1%, respectively (Funaki et al., 2014).

**Table 1.3**

A summary of the published literatures on the long term outcome (mean 5 years or longer) of MMD adult and paediatric patients treated with revascularization.

Paediatric Series

| Authors | Country of Origin | Time Period | No. of patients (Sex) | Mean age (yr) | Demographics & Surgery Types | Mean F/U (yrs), F/U rate | Long term stroke risk and outcome |
|---|---|---|---|---|---|---|---|
| Rashad et al | Japan | 2004-2015 | 23<br>26F, 7M | 9.4<br>(2-16) | Ischaemic stroke/TIAs<br>combined STA-MCA/EDMS | 6.41 | none<br>All stabilised or improved, 87% (20/23) mRS 0-1 |
| Liu et al | China | 2004-2012 | 30<br>20F, 10M | <18 | Haemorrhagic MMD<br>EDAS | 6.4 | 1 died of recurrent haemorrhagic stroke<br>83% (25/30) mRS 0-1 |
| Funaki et al | Japan | 1978-2003 | 58<br>34F, 24M | 6<br>(0-15) | Mostly ischaemic MMD<br>Direct bypass | 18.1<br>(9-33.7)<br>96.6% | 0.41% (95% CI 0.15-1.08) per year |
| Mukawa et al | Japan | 1979-2010 | 208<br>NA | 8.5<br>(1-18) | NA<br>Indirect (EDAS, EDPS, EGS) | 14.3<br>(3-32)<br>83% | cumulative late onset stroke: 0.8%, 6.3%, 10% by 10, 20, 30 years postop, respectively.<br>80.2% (138/172) mRS 0-2 |
| Ulrich et al | Germany | 1984-2009 | 19<br>13F, 6M | 8<br>(1-18) | Ischaemic stroke/TIAs, seizures<br>Indirect (EDAS, EMS) or combined | 17.3<br>(2-25)<br>89% | 94% no ischaemic symptoms |
| Scott et al | Boston, USA | NA | 143<br>89F, 54M | 7.1<br>(0.5-21) | 66 idiopathic MMD, 16 Asians<br>pial synangiosis | 5.1<br>(0.3-17)<br>88% | 5.5% (7/126), 1% per year.<br>71% (90/126) mRS 0-1, 10% (13/126) mRS 2 |

Adult Series

| Authors | **Country of Origin** | **Time Period** | **No. of patients (Sex)** | **Mean age (yr)** | **Demographics & Surgery Types** | **Mean F/U (yrs)** | **Long term stroke risk** |
|---|---|---|---|---|---|---|---|
| Ozaki et al | Japan | NA | 26<br>NA | NA | NA | 14.3<br>(5.5-25.6) | 1.14% haemorrhagic risk per year |
| Liu et al | China | NA | 145<br>76F, 69M | 36<br>(19-65) | Haemorrhagic MMD<br>EDAS | 6.33 | 6.5% haemorrhagic risk, 1% per yr |
| Cho et al | Korea | 2004-2008 | 60<br>41F, 19M | 37<br>(18-56) | Ischaemic MMD<br>combined STA-MCA/EDGS | 5.92 (5-8.7) | 0.4% and 0.2%, annual risks of symptomatic haemorrhage and infarction, respectively |
| Bao et al | China | NA | 470<br>239F, 231M | 36.8<br>(18-59) | Mostly ischaemic MMD<br>EDAS | 5 | 13% in 5 yrs, 2.6% annual risk<br>73% mRS 0-2 |

The longest reported outcome from a western paediatric cohort was by Ulrich et al, who reported on 19 patients aged 1-18, mainly with seizure or ischaemic presentations. They underwent indirect or combined bypasses, and with 89% follow-up rate (2 lost to follow up), mean follow-up of 17 years, over 90% of patients were free from ischaemic symptoms (Ulrich and Januschek, 2011), however the quality of life for these patients were not discussed. Scott et al reported on 143 paediatric MMD who underwent indirect bypass (pial synangiosis) at Boston Children Hospital, followed up for a mean of 5.1 years and showed a 5.5% (7/126) long term stroke risk (i.e. 1% per year). The long term functional outcome (mRS, Table 1.4) of these patients were also assessed, with 71% (90/126) mRS 0-1, 10% (13/126) mRS 2 (Scott et al., 2004).

Table 1.4 Modified Rankin Scale (mRS) (Rankin J 1957, Bonita et al 1988)

| Score | Description |
|---|---|
| 0 | No symptoms at all |
| 1 | No significant disability despite symptoms; able to carry out all usual duties and activities |
| 2 | Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance |
| 3 | Moderate disability; requiring some help, but able to walk without assistance |
| 4 | Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance |
| 5 | Severe disability; bedridden, incontinent and requiring constant nursing care and attention |
| 6 | Dead |

In the adult series that reported long term outcome, none of the studies were from the western population. Of the 4 studies published, Bao et al reported the largest cohort with 470 symptomatic adult MMD patients who underwent indirect bypass (EDAS), and the postoperative stroke risk (ischaemic events or haemorrhage) was 5.9% per procedure, 9.8% per patient. With a mean follow-up of 5 years, the long term stroke risk was 13% (i.e. 2.5% annual stroke risk), and 73% of patients had independent living with no significant or slight disability (mRS 0-2) (Bao et al., 2012). Only 1 study reported the long term outcome beyond 10 years for adult MMD (Ozaki et al., 2016) in 26 patients, but the article was published in Japanese.

A lot can be learnt from the long term studies with large patient cohort from the Eastern population, however in view of the differences in MMD in the east and west, the result might not be directly applicable to our patient cohort from the western hemisphere.

Mesiwala et al reported on a series of 39 MMD patients treated surgically (65 procedures) at the University of Washington from 1990 to 2004, with mean follow up of 3.5years (0.5 to 8.3 years). 3 patients died (4.6% mortality per procedure), 8 experienced postoperative complications (12.3% procedure related morbidity), and 6 patients had further ischemic events with the follow up reported, an observation which might indicate a lower event rate compared with the natural history, however the mean follow up was very short. Furthermore, cerebral perfusion dynamics improved postoperatively in all 36 surviving patients (Mesiwala et al., 2008b), but longer term data is still not available.

Guzman et al reported on the revascularisation outcome of 272 adults and 96 paediatric MMD patients (96.6% of adult and 67.2% of paediatric patients underwent direct bypass). Postoperative significant neurological deficit occurred in 15 patients undergoing 16 procedures (3.5% of procedures or 5.6% of patients). With a mean follow up of 4.9 years, the overall cumulative risk of stroke or haemorrhage was 5.5% (Guzman et al., 2009b).

Since there were only very few studies with small patient cohort that reported the long term outcome of MMD in the western population, and none with over 5 years outcome in the adult MMD population, more knowledge in this field is important. With increasing awareness, and studies suggesting an increasing prevalence of MMD in the west (Starke et al., 2012), the long term result of MMD is crucial for both clinicians and patients, in order to have a fully informed decision making process.

## 1.5 Scoring system for MMD

The original MMD grading scale by Suzuki et al in 1969, which later adopted by the Japanese Ministry of Health and Welfare (Fukui, 1997) was based solely on the DSA findings, and were highly complicated with multiple stages (Table 1.5). Furthermore, they do not correlate with clinical symptoms or with surgical treatment risks.

Table 1.5. Suzuki Classification – 6 angiographic stages of MMD

| **Stage** | **Finding** |
|---|---|
| **1** | stenosis of supraclinoid ICA, usually bilateral |
| **2** | development of moyamoya vessels at base of brain |
| **3** | increasing ICA stenosis & prominence of moyamoya vessels |
| **4** | entire circle of Willis and PCA occluded, extracranial collaterals start to appear, moyamoya vessels begin to diminish |
| **5** | further progression of stage 4 |
| **6** | complete absence of moyamoya vessels and major cerebral arteries |

The Berlin group (Czabanka et al., 2011c) (Table 1.6) first developed a new MMD grading system incorporating DSA, MRI and CVRC (Cerebrovascular Reserve Capacity) using Xenon-CT. They used a simplified angiographic classification, and regarded intracranial compensation mechanisms (for example, leptomeningeal anastomosis and pericallosal anastomosis) as a result of hemodynamic compromise and therefore as a marker of advanced disease (assigned 2 points). The development of extra-intracranial collaterals was regarded as indicator for the most severe angiographic form of MMD, as the recruitment of extracranial compensation is supposed to be the result of long- standing and severe hemodynamic compromise (Grubb et al., 1998) (assigned 3 points).

Table 1.6. New proposed grading scale by Czabanka et al 2013.

| Variable | Characteristics | Points |
|---|---|---|
| DSA | Steno-occlusive lesion + Moyamoya vessels | 1 |
| | Steno-occlusive lesion + Moyamoya vessels + intracranial compensation routes | 2 |
| | Steno-occlusive lesion + extra-intracranial compensation routes | 3 |
| MRI | No signs of ischemia/hemorrhage/atrophy | 0 |
| | Signs of ischemia/hemorrhage/atrophy | 1 |
| CVRC | No steal phenomenon (> –5%) | 0 |
| | Steal phenomenon (< –5%) | 2 |

MRI was identified as the second important variable for grading MMD. The presence of acute or chronic ischemic lesions provided important information about structural damage and historical disease severity (Horn et al., 2005). In 20% of MMD patients clinically silent infarctions have been reported, emphasizing the importance of MRI for estimating the clinical severity of the disease (Kuroda et al., 2007). Increasing evidence are showing that previous radiological ischemia detected on MRI are associated with postoperative stroke risk and outcome. In a large Korean series of 410 pediatric MMD patients, Kim et al showed that preoperative clinical infarct (OR 4.33, 95% CI 2.55-7.36, p<0.001) and radiological infarct (OR 4.14, 95% CI 2.45-7.01, p<0.001) were associated with unfavorable clinical outcome postoperatively (Kim et al., 2010). However, normal-appearing white matter on MRI might still be associated with impaired cerebrovascular reserve capacity (CVRC) (Conklin et al., 2010).

Therefore, CVRC is another key variable identified. Currently, there are different techniques available to quantify the hemodynamic compromise in MMD, which include PET, SPECT, xenon-enhanced CT, dynamic perfusion CT, MR imaging with dynamic susceptibility contrast and with arterial spin labeling, and Doppler ultrasonography (Lee et al., 2009). Xenon-CT has been the workhorse for measuring and quantifying rCBF in MMD patients and it has

been shown that reduced CVRC assessed by xenon-CT is a predictor of stroke in patients with occlusive cerebrovascular disease (Webster et al., 1995, Horowitz et al., 1995, McAuley et al., 2004, Nambu et al., 1995, Suzuki et al., 1996).

In order to take into account of patients' cerebrovascular reserve and those with chronic cerebral ischemia due to cerebrovascular hemodynamic insufficiency, new grading scale was proposed (Table 1.6, Table 1.8). The original article (Czabanka et al., 2011c) was designed to stratify for clinical symptoms in MMD patients, using 40 patients (80 hemispheres) and assigned scores to the 3 components (DSA, MRI, CVRC) with final stratification to mild (grade1, score1-2), moderate (grade 2, score 3-4), severe (grade 3, score 5-6). Fourteen hemispheres were graded as mild (grade I), 35 as moderate (grade II) and 31 as severe (grade III); 21% of grade I, 63% of grade II and 93% of grade III hemispheres were clinically symptomatic. The same group subsequently applied the same scoring system and showed that it can be used to stratify for ischaemic complications in MMD patients post revascularization in only a very small group of 37 patients. No postop stroke was found in grade I patients, compared to 16% of grade III patients (Czabanka et al., 2016).

Another similar preoperative symptomatology scoring system was recently proposed that take into account of Prior Infarcts, Reactivity and Angiography in Moyamoya Disease (PIRAMD) based on 11 healthy control and 25 patients. For each hemisphere, 1 point was assigned for prior infarct, 3 points for reduced CVR, 3 points for a modied Suzuki Score ≥ Grade II, and 3 points for flow impairment in ≥ 2 of 7 predetermined vascular territories (Table 1.7, Table 1.8). Hemispheres were divided into 3 severity grades based on total PIRAMD score, as follows: Grade 1, 0–5 points; Grade 2, 6–9 points; and Grade 3, 10 points. They showed increasing proportion of symptomatic hemispheres with increasing PIRAMD grade (0% (0/8), 55.6% (10/18), 90% (18/20) of Grade 1, 2 and 3 hemispheres respectively) (Ladner et al., 2016).

Despite these new proposed scoring systems, they have not been validated in a larger, separate cohort of patients. Several limitations still occur with the

currently proposed scoring system, as they concentrate on determining preoperative symptomatology. Furthermore, it is crucial that a scoring system has wide clinical applicability, especially if it can be used in predicting the radiological and clinical outcome after surgical revascularization, which would be crucial for clinical decision making. Other risk factors (female sex (Khan et al., 2012), presence of an acute infarct on preop MRI, impaired CVRC (Antonucci et al., 2016), unstable MMD (Funaki et al., 2015), associated conditions (Koss et al., 2013)) have also been identified from recent studies that could be predictive of postoperative ischemic events, and not accountable in the current proposed scoring systems (Czabanka et al., 2011c, Czabanka et al., 2016, Ladner et al., 2016). With my current study, these added risk factors would be analysed, and we aim to propose a grading system that is clinically applicable, robust, and tested.

Table 1.7. Modified Suzuki Scoring

| Score | Description of Classification |
|---|---|
| 0 | No evidence of disease |
| I | Mild-to-moderate stenosis around ICA bifurcation w/ absent or slightly developed ICA MMD |
| II | Severe stenosis around the ICA bifurcation or occlusion of either proximal anterior or MCA branches w/ well-developed ICA MMD |
| III | Occlusion of both anterior & MCA branches w/ well-developed ICA MMD (only a few of anterior or MCA branches or both are faintly opacified in antegrade fashion through meshwork of ICA MMD) |
| IV | Complete occlusion of both anterior & MCA branches w/ absent or small amount of ICA MMD (w/o opacification of either anterior or MCA branches in antegrade fashion) |

Table 1.8. The PIRAMD Scoring system

| Variable | Characteristics | Points |
|---|---|---|
| MRI | Prior infarct | 1 |
| CVR | Decreased | 3 |
| mSS | ≥ Grade II | 3 |
| Collaterals | ≥ 2 territories impaired | 3 |

## 1.6 Research Direction and Hypothesis

Very little is known about MMD in the west, especially on the long term treatment outcome, functional status in terms of employment, education, family life, and what prognostic factors are predictive of good or poor outcome.

Stanford in California, USA has the largest experience treating moyamoya patients in the western world, with now over 1000 patients, and over 1500 extracranial to intracranial bypasses performed since 1990s. Some of the earlier patients have been followed up for over 20 years. As a neurosurgeon having completed my neurosurgical training in the UK, and now subspecialise in vascular neurosurgery with fellowship training in Stanford University, USA, I am pursuing a consultant neurosurgeon career with special interest in vascular neurosurgery and academia. According to the Hippocratic Oath: “First, Do no Harm”. Extracranial to intracranial bypasses are relatively high risk procedure for some patients, and are now rarely performed in the UK. With this work, I would be able to help select the suitable patients, to minimise the postoperative stroke risks and to inform my patient group their long-term outcome after cranial bypasses.

### 1.6.1 Hypothesis of the research

1. Selective subgroups of patients with moyamoya disease in the western world are symptomatically and functionally cured after extracranial-intracranial bypasses.

2. Robust and means tested scoring system could be designed to identify subgroups with good and poor outcome, and thereby help with decision making process.

## 1.7 Aims of the study

To determine the short and long term outcome of MMD patients post revascularisation in the western world, and identify the risk factors associated that could be incorporated into a predictive modelling for postoperative stroke risks.

To validate the proposed moyamoya Berlin symptomatology grading system.

To study the strategies and outcome of repeat revascularisation surgery for MMD patients who have persistent or new neurological symptoms due to inadequate collateralisation post initial bypass surgery.

To compare and contrast the patients with moyamoya syndrome and classical MMD.

To develop and validate a newly proposed Stanford Berlin Moyamoya Grading system.

To develop a predictive modelling using machine learning algorithm for postoperative stroke risk in MMD patients, in order to help with patient counselling, consent process, and decision making.

# CHAPTER TWO

# MATERIALS AND METHODS

## 2.1 Study Designs

Each individual chapters have the materials and methods described in details. The contribution from collaborative authors are included in the acknowledgements.

Chapter 3: Direct and combined revascularization versus indirect revascularization in the treatment of moyamoya disease: a systematic review and meta-analysis
Chapter 4. Short and long-term outcome of moyamoya disease post revascularisation.
Chapter 5: Validation and application of Berlin grading system of moyamoya disease in adult
Chapter 6: Comparative study of repeat revascularisation for moyamoya disease
Chapter 7: Moyamoya syndrome and clinical outcome
Chapter 8: Development and validation of Stanford Berlin Moyamoya Grading System and Development of Predictive Modelling for Perioperative Stroke
Chapter 9: Moyamoya disease in the UK: Personal Experience, Development of an Integrated Service and Registry

Overall, patients' demographics (age, sex, ethnicity, date and types of surgery) were prospectively collected in the Stanford University moyamoya database since 1990s. With institutional review board (IRB) approval, retrospective chart reviews were carried out to verify their comorbidity, family history, presentations, preoperative Suzuki stage, MRI brain findings, cerebrovascular reserve. The following clinico-radiological outcomes were analysed and correlated at different time interval after cranial revascularisations, including the latest follow up to date.

A) Postoperative stroke, death, complications
B) mRS clinical outcome
C) Functional outcome in terms of employment, education, family life
D) Symptomatic outcome, whether suffering with ongoing ischemia
E) Cerebral angiogram to assess the bypass patency, extent of

collateralization, changes to moyamoya fragile vessels

F) MRI findings: evidence of new ischemic changes
G) MR perfusion study with/without Diamox to assess cerebrovascular reserve.

## 2.2 Systematic Review and Meta-Analysis

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.(Moher et al., 2009a, Moher et al., 2009b) The protocol was registered on the PROSPERO international prospective register of systematic reviews (registration number CRD42020169426).

Searches of the following three electronic databases were undertaken: Ovid Medline, Ovid Embase, and Cochrane Central Register of Controlled Trials (CENTRAL).

Searches were performed in each database from its inception until 4th January 2020. The search strategy was developed in consultation with a research librarian/ information specialist. The concepts of “moyamoya disease” and “revascularization” were used in addition to synonyms and related terms. Examples of the search strategy used are presented in Supplementary Table 1. Reference lists of publications included in the full review were searched to identify further studies for inclusion.

Articles were selected based on predetermined inclusion and exclusion criteria. For inclusion, the studies were a primary research written in English on revascularization in MMD: randomized and observational studies and case series excluding case reports. The review included studies on patients of all ages who met all the following criteria: diagnosed MMD treated by bypass surgery (direct, indirect, combined). Patients were included regardless of gender and ethnicity, presence of symptoms or neurological deficits on presentation.

The primary outcome included any perioperative complications were defined as any major adverse events within 30 days after bypass surgery, including any symptomatic stroke (ischaemic and haemorrhagic), death, or neurologic deficit. Secondary outcomes include long term follow up study (> 5 years) and the degree of angiographic revascularization.

A pro forma was developed to extract data on the following variables to ensure standardization and consistency in this process: study details; study design; patient, disease and types of revascularization; study methods and results which included rates of perioperative complications (hemorrhage, ischemia, permanent neurologic deficit death) and measures of long-term outcomes (> 5 years) – degree of angiographic revascularization, modified Rankin (mRS), long-term stroke risk. The meta-analyses were performed using R software version 3.4.3 (R Foundation for Statistical Computing, 2016).

### 2.3 Patient population (1990-2014)

Stanford University in California, USA has the largest database of patients with moyamoya disease in the western world. From 1990 to 2014, 769 patients with 1250 extracranial-intracranial bypasses were performed, and this is the study sample of my thesis.

IRB approval was obtained (protocol number: 36691) from the Stanford University School of Medicine (appendix 12.1). A study template of the clinical and radiological information to be collected was designed using Research Electronic Data Capture (REDCap) (appendix 12.2), supported by the Stanford University IT department. REDCap is a secure, web-based application designed to support data capture for research studies, providing an intuitive interface for validated data entry; audit trails for tracking data manipulation and export procedures; and automated export procedures for seamless data downloads to common statistical packages. (Harris et al., 2009).

Patients' name, demographics, dates of surgery was available from the Stanford MMD database. Other clinical and radiological information (including patients' comorbidity, postoperative results and complications) required was obtained from retrospective chart review using electronic medical records (e-portal Stanford), radiological imaging reviews (Picture Archiving and Communication System PACS), and paper records for the patients without electronic records.

Data collection on the latest clinical and radiological outcome of patients was obtained by electronic medical chart reviews, radiological imaging reviews (including MR brain, CVRS, 6-vessel angiogram at 6 months, 3 year, 10 year, 20 years postoperatively), patient questionnaires (local Institutional Review Board approval obtained), and latest clinical consultation. Paper medical chart review was also performed when appropriate.

### 2.4 Questionnaire Study

In order to study the long term physical, functional and social well-being of MMD patients post revascularisation, a questionnaire study (focusing on symptoms, blood pressure management, social situation, Figure 2.1) was designed and sent to all patients.

**Please circle the best answer to questions below:**

Did you have headaches before surgery for your moyamoya? Yes No

How are your headaches since your moyamoya surgery? Better worse unchanged

Did you have high blood pressure before surgery for your moyamoya? Yes No

Were you on blood pressure medication before surgery for your moyamoya? Yes No

Are you on blood pressure medication after your moyamoya surgery? Yes No

Did your blood pressure medication dose go down after moyamoya surgery? Yes No

Did your blood pressure medication dose go up after moyamoya surgery? Yes No

Do you work outside of the home? Yes No

Do you attend school? Yes No

Do you manage all of your own finances/legal affairs if over 18? Yes No

Do you provide all of your own care? Yes No

Do you have any recurrent stroke like symptoms since your moyamoya surgery? Yes No

If yes, when was your last stroke like symptom? Date: ___/___/____
If yes, how often do you have stroke like symptoms?

Did you have any other symptoms before your moyamoya surgery that are still present? If so, please list them below:

**Figure 2.1** Questionnaire study used to for long term physical, functional and social outcome.

### 2.5 Statistical Analyses

The following are the statistical tests that are common to many of the chapters.

#### 2.5.1 Chi-squared test

The chi-squared test is used to determine if there is an association between categorical variables. The test calculates the frequencies that would be

expected if there were no association, and compares them to the observed numbers in each category in the table. If the observed numbers are significantly different to the expected numbers, this suggests there is an association. The greater the difference, the larger the chi- squared value. It then gives a P value based on the chi squared distribution formula with n degree of freedom where n is given by (number of rows -1) x (number of columns-1).

The test requires large sample size and less than 20% of the expected frequencies to be less than 5 and none less than 1. If that assumption does not hold, Fisher's exact test would be used.

### 2.5.2 Cox regression

Cox regression, also known as proportional hazards regression, is commonly used to analyse survival time data in medical research. It also allows assessment of the effects of various predictor variables on the time-to-event outcomes. The predictor variables can be continuous, binary, or categorical data. A regression coefficient is given to represent the relationship between each predictor variable and the time-to- event outcome, after adjusting for all other variables in the model.

### 2.5.3 Mann-Whitney U-test or t-test

Mann-Whitney U-test or t-test was used to compare continuous variables between groups, assuming that the continuous data is normally distributed within groups.

### 2.5.4 Kaplan-Meier curves

Kaplan-Meier curves display probabilities of survival or stroke-free interval over the follow-up duration on a graph. The x-axis is the length of follow-up duration, and the y-axis is the cumulative probability of survival or stroke-free interval. The curve is stepped due to the occurrence of an event e.g. stroke or death.

### 2.5.5 Logrank test

Survival curves which consist of two groups or more on one graph require a statistical method that will compare the entire curve for each category. This is done with the logrank test by utilising all the survival data from the entire curve. It is only a significance test giving a P value but not mortality estimate.

### 2.5.6 Statistical software

Analyses were performed using SPSS version 22 (Chicago, IL, USA) unless otherwise stated.

### 2.5.7 Statistical significance

P-value of less than 0.05 is considered statistically significant unless specified otherwise.

## 2.6 Development, Validation of Stanford Berlin Moyamoya Grade and Development of Predictive Modelling for Perioperative Stroke

Further predictive modelling studies based on the identified risk factors associated with good and poor postoperative outcome was conducted.

A separate patient cohort (264 patients) managed at Stanford University Medical Centre from 2015-2018 was used to validate the Stanford Berlin Moyamoya grade proposed.

To design a clinical tool applicable to daily clinical use for 30-day major stroke risk post bypass, predictive modelling using R Statistical package was developed combining the entire dataset from 1990-2018. The data was divided into train and test sets, with 70/30 split in order to allocate the 30-day stroke events proportionally.

### 2.6.1 kNN Algorithm

Missing data imputation was carried out using K nearest neighbours (KNN) approach (Altman, 1992, Moraleda, 2008), whereby KNN function uses data from other variable with similar non-missing values in the dataset to predict missing values.

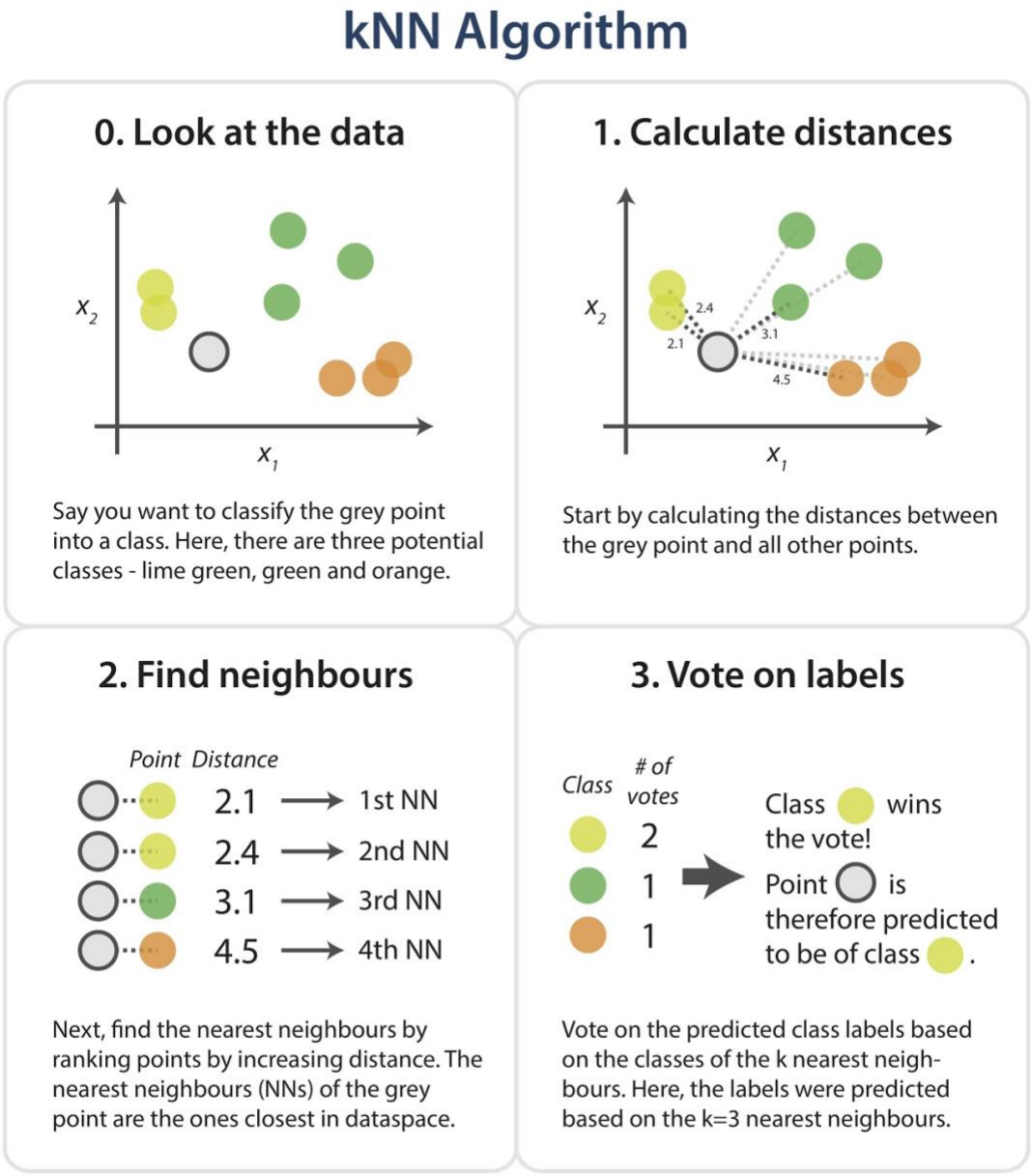


**Figure 2.2** K Nearest Neighbour (KNN algorithm). (Adopted from Cambridge Coding Academy)

Given the relatively small number of strokes and large number of variables studied, dimensionality reduction was carried out. In the predictive modelling, two training models were used.

### 2.6.2 LASSO Regression

“LASSO” stands for Least Absolute Shrinkage and Selection Operator. In statistical and machine learning, LASSO is a regression analysis method that perfoms both variable selection and regularization in order to enhance the prediction accuracy and interpretability of the resulting statistical model.

Regularization is a concept to avoid overfitting of data, especially when the trained and test data are much varying. Therefore, LASSO regression using “shrinkage”, a statistical technique where data values are shrunk towards a central point as the mean. (Tibshirani, 1996, Tibshirani, 1997)

### 2.6.3 Gradient Boosting Machine (GBM) regression.

Gradient boosted machines (GBMs) are an extremely popular machine learning algorithm that have proven successful across many domains and is one of the leading methods. It is built in a stage-wise fashion as shown in Figure 2.3.


**Figure 2.3** Sequential ensemble approach in Gradient Boosting Machine (GBM). (Adopted from https://uc-r.github.io/gbm_regression)

Whereas Random forest models build an ensemble of deep independent trees, GBMs build an ensemble of shallow and weak successive trees with each tree learning and improving on the previous. When combined, these many weak successive trees produce a powerful “committee” that are often hard to beat with other algorithms (https://uc-r.github.io/gbm_regression). (Hastie et al., 2009, Boehmke and Greenwell, 2019)

Although the method is more computationally demanding compared to other machine learning algorithms, they are often first-in-class with predictive accuracy. (Boehmke and Greenwell, 2019, Hastie et al., 2009)

# CHAPTER THREE

# DIRECT AND COMBINED REVASCULARIZATION VERSUS INDIRECT REVASCULARIZATION IN THE TREATMENT OF MOYAMOYA DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

## 3.1 Introduction

Moyamoya disease (MMD) refers to an abnormal progressive steno-occlusive disorder of unknown etiologies at the distal internal carotid artery (ICA) or proximal middle cerebral artery (MCA).(Suzuki and Takaku, 1969) Over time, compensatory collateral vasculature develops in the basal brain, which is commonly seen on angiography as a 'puff of smoke', which is literally what moyamoya means in Japanese.

Surgical revascularization provides better outcomes for these patients than medical treatment alone.(Hallemeier et al., 2006a, Duan et al., 2012) The current goal in the surgical management of moyamoya angiopathy is to augment cerebral blood flow in patients with an ischemic presentation and to prevent intracranial hemorrhage by decreasing hemodynamic stress in patients with a hemorrhagic presentation.(Kim and Jeon, 2014) Surgical revascularization methods can be direct, indirect, or a combination of the two bypass approaches. Direct bypass is accomplished by anastomosing extracranial vessels to intracranial vessels (EC-IC bypass), most often the superficial temporal artery (STA) to the middle cerebral artery (MCA) (STA-MCA bypass).(Karasawa et al., 1978) Indirect bypass has many variations but is generally accomplished by incorporating well-vascularized tissue – temporal artery, temporalis muscle, omentum and galea – onto the surface of the brain to promote angiogenesis, rather than by direct anastomosis.(Karasawa et al., 1980, Kawamoto et al., 2000, Matsushima et al., 1981b) Unlike the direct method, indirect bypass begins to alter the cerebral blood flow only after angiogenesis has taken place, which may take a few months to a year.(Matsushima et al., 1991) A combined bypass uses both direct and indirect approaches simultaneously to maximize the effect of revascularization.

In the pediatric population, the efficacy of direct or combined bypass is not significantly different from the efficacy of indirect bypass.(Fung et al., 2005b) The best choice of bypass method is still controversial. There is currently no definite consensus regarding the surgical treatment of adult MMD, although surgical benefits of direct bypass have been increasingly reported.(Bang et al.,

2012, Miyamoto et al., 2014b) Conducting a randomized controlled trial (RCT) in patients with a rare progressive disease such as MMD is very difficult. To date, there has been only one RCT published assessing the efficacy of the direct bypass procedure but it was with regard to conservative treatment.(Miyamoto et al., 2014b)

Therefore, the aim of this meta-analysis was to directly compare published studies of direct, indirect and combined bypasses with regard to perioperative complications and long-term angiographic revascularization, stroke risks in pediatric and adult patients with MMD.

### 3.2 Methods

The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.(Moher et al., 2009a, Moher et al., 2009b) The protocol was registered on the PROSPERO international prospective register of systematic reviews (registration number CRD42020169426).

#### 3.2.1 Search strategy

Searches of the following three electronic databases were undertaken: Ovid Medline, Ovid Embase, and Cochrane Central Register of Controlled Trials (CENTRAL).

Searches were performed in each database from its inception until 4$^{th}$ January 2020. The search strategy was developed in consultation with a research librarian/ information specialist. The concepts of “moyamoya disease” and “revascularization” were used in addition to synonyms and related terms. Examples of the search strategy used are presented in Supplementary Table 12.1. Reference lists of publications included in the full review were searched to identify further studies for inclusion.

### 3.2.2 Eligibility criteria

Articles were selected for inclusion if they were a primary research written in English on revascularization in MMD were eligible for inclusion: randomized and observational studies and case series excluding case reports. The review included studies on patients of all ages who met all the following criteria: diagnosed MMD treated by bypass surgery (direct, indirect, combined). Patients were included regardless of gender and ethnicity, presence of symptoms or neurological deficits on presentation.

### 3.2.3 Exclusion criteria

The review excluded narrative and systematic reviews, editorials, commentaries, opinion papers, letters, education papers, conference abstracts, protocols, reports, theses or book chapters as they were unlikely to contain sufficient detail about the effectiveness of the different revascularization surgeries. Articles in languages other than English were also excluded.

Articles were also excluded if they did not distinguish pediatric from adult patient, or if they did not distinguish the revascularization approaches. Studies were excluded if they reported the use of different revascularization surgeries but had an intervention arm < 10, or if they did not describe and report outcomes of our interest.

### 3.2.4 Study selection

All titles and abstracts were screened against a set of pre-defined eligibility criteria developed independently by two reviewers (MKT and KSL). Potentially eligible studies following title and abstract screening were then selected for full-text analysis. In the event of multiple publications analyzing the same cohort, the most recent paper was used for evaluation. A full list of inclusion and exclusion criteria of studies are stated in Table 3.1.

Table 3.1. Inclusion and exclusion criteria used to select studies for the review

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Primary interventional or observational studies assessing revascularization surgeries in moyamoya angiopathy | • Not written in English<br>• Systematic reviews and meta-analysis, editorials, commentaries, opinion papers, letters, education papers, conference abstracts, protocols, reports, theses or book chapters<br>• Not exclusively about MMD (either not about MMD at all, or about MMD within a heterogenous cerebrovascular disease population)<br>• Interventions not tested in the clinical setting (e.g. lab based rather than clinical practice)<br>• Non-human subjects (e.g. murine, porcine studies)<br>• Comparing direct/combined versus indirect revascularization but did not split their results according to pediatric and adult patients<br>• Non-comparative (e.g. revascularization versus conservative treatment) studies<br>• Overlapping populations<br>• Arm < 10 patients |

Studies of small sample sizes were included following recommendations by the Cochrane Statistical Methods Group to not exclude studies purely on the basis of sample size.(Grainge) Nonetheless, case reports were excluded to reduce the likelihood of publication bias. A minimum sample size arm of 10 patients was implemented in accordance with methodologies of a previously published

meta-analysis.(Ravindran et al., 2019) The quality of included studies was assessed using the Joanna Briggs Institute (JBI) checklist for prevalence studies and the JBI checklist for case series.

### 3.2.5 Reliability of study selection

At each stage, MKT and KSL reviewed 100% of the screened studies for inclusion to ensure reliability of study selection. Disagreements were resolved by consensus and where agreement could not be reached, the senior reviewer (GKS) assisted with decision making. Agreement among the reviewers on study inclusion was evaluated using Cohen's kappa.(Cohen, 1960)

### 3.2.6 Outcomes

The primary outcome included any perioperative complications were defined as any major adverse events within 30 days after bypass surgery, including any symptomatic stroke (ischaemic and haemorrhagic), death, or neurologic deficit. The definition of a perioperative period varied among studies. In some studies, only complications that occurred during the same hospitalization as the revascularization were considered perioperative complications. However, in many studies, perioperative outcomes were counted if they occurred within 30 days of revascularization regardless of discharge status. Hence to unify the studies, we considered any complications that occurred within 30 days of bypass to be perioperative complications.

Secondary outcomes include long term follow up study (> 5 years) and the degree of angiographic revascularization. The degree of revascularization was dichotomized into "good or fair revascularization" or "poor revascularization." When angiographic assessment was used according to a 2-grade classification (poor or good),(Kawaguchi et al., 2000a) 3-grade classification (poor, moderate, or good),(Lee et al., 2012b) or 4-grade classification (none, poor, medium, or extensive),(Czabanka et al., 2011b) we classified "moderate," "medium," "good," and "extensive" as "good or fair revascularization" and "poor" or "none" as "poor revascularization." Revascularized areas covering less than

30% of the affected hemisphere were categorized as “poor” in the study by Bang et al.(Bang et al., 2012) Other secondary outcomes were the modified Rankin score (mRS) and long term stroke risk.

### 3.2.7 Data extraction

A pro forma was developed to extract data on the following variables to ensure standardization and consistency in this process: study details; study design; patient, disease and types of revascularization; study methods and results which included rates of perioperative complications (hemorrhage, ischemia, permanent neurologic deficit death) and measures of long-term outcomes (> 5 years) – degree of angiographic revascularization, modified Rankin (mRS), long-term stroke risk. Two reviewers (MKT and KSL) independently and blindly extracted 100% of the data each to ensure reliability. Discrepancies or disagreements about extracted material were resolved by discussion and when agreement could not be reached, consensus was achieved after consulting the senior reviewer (GKS).

### 3.2.8 Statistical Analysis

We analyzed both direct and combined approaches as a single cohort compared with the indirect approach. The rationale is that in combined procedures, patients undergo a direct and an indirect component of the revascularization in the same setting. The direct component would afford an immediate increase in cerebral perfusion, while the indirect collateralization would take months to a year to form.(Matsushima et al., 1991) Therefore, in our opinion, a suitable analysis would be to include the direct and combined groups as a single group to compare with the indirect group, which is in accordance to the opinion of other authors.(Kazumata et al., 2014a, Teo et al., 2017c)

The outcome measures (perioperative stroke, perioperative mortality and perioperative neurological deficits) were compared between the direct/combined bypass group and the indirect bypass group. For each outcome, the overall odds ratio (OR) and its 95% confidence interval (CI)

comparing the groups across relevant studies were summarized using a meta-analysis of binary outcomes.

The meta-analysis for each comparison included only studies in which the outcomes of 2 approaches of interest were both reported and then a weighted analysis of ORs from each individual study was conducted. Meta-analyses of proportions were done for each outcome measure to provide a pooled overall estimate. For both types of meta-analysis, the random effects model was used to account for study heterogeneity, with the overall pooled estimate computed using the inverse variance method. Pooled proportions were computed with the inverse variance method using the variance-stabilizing Freeman-Tukey double arcsine transformation.(Nyaga et al., 2014) Confidence intervals (CI) for individual studies were calculated using the Wilson Score confidence interval method with continuity correction. The $I^2$ statistic was used to present between-study heterogeneity, where $I^2 \leq 30\%$, between 30% and 50%, between 50% and 75%, and $\geq 75\%$ were considered to indicate low, moderate, substantial, and considerable heterogeneity, respectively.(Higgins JPT, 2011) P values for the $I^2$ statistic were derived from the chi-squared distribution of Cochran Q test. No studies were excluded because of bias, but possible sources of publication bias were evaluated using funnel plots when 5 or more articles were included. Quantitative analyses of funnel plot asymmetry was done using Egger's regression test, based on a weighted linear regression of the treatment effect (expressed as a Freeman-Tukey double arcsine transformed proportion) on its standard error.(Egger et al., 1997)

All statistical analyses were performed using R software version 3.4.3 (R Foundation for Statistical Computing, 2016). P-values less than 0.05 were considered statistically significant.

## 3.3 Results

### 3.3.1 Study selection and characteristics

Figure 3.1 presents the PRISMA flow diagram illustrating the number of reviews screened and selected for inclusion. Using the designated search terms, a total of 2490 articles were retrieved. A total of 20 studies reporting 2982 patients were included in our analysis (Yu et al., 2019c, Zhao et al., 2018, Zheng et al., 2019, Deng et al., 2017, Jang et al., 2016, Teo et al., 2017a, Czabanka et al., 2016, Sadashiva et al., 2016, Liu et al., 2015, Abla et al., 2013, Gross and Du, 2013a, Bang et al., 2012, Choi et al., 2012, Kim et al., 2012, Lee et al., 2012a, Ng et al., 2012, Hyun et al., 2010, Guzman et al., 2009b, Matsushima et al., 1998, Ishikawa et al., 1997).

Figure 3.1 showed the PRISMA diagram for number of studies screened and reasons for exclusion at each stage. Reliability of study selection between observers was substantial at both the title and abstract screening stage (Cohen's $\kappa = 0.75$) and the full-text review stage (Cohen's $\kappa = 0.71$).(Cohen, 1960)

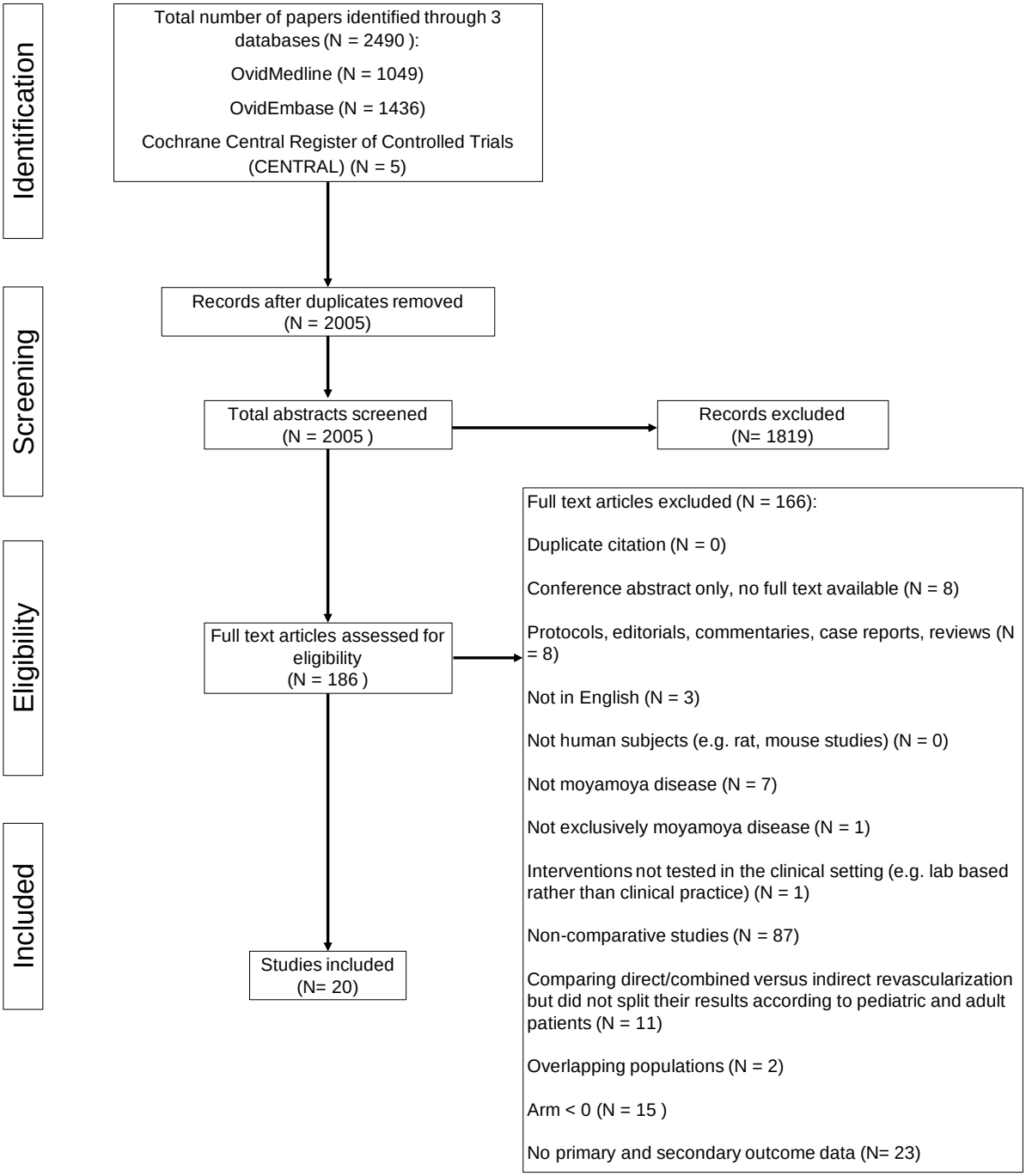


Figure 3.1. PRISMA flow diagram for study selection.

A total of 20 studies reporting 2982 patients were included in our analysis. All included studies were retrospective observational comparative studies. There were 2341 adult patients (78.5%) and 641 pediatric patients (21.5%). Among the adults, a total of 2979 revascularization procedures were performed. 1376 (46.2%) were direct bypass, 427 (14.3%) were combined bypass and 1176 (39.5%) were indirect bypass. Among the pediatric patients, a total of 1010 revascularizations were performed. 325 (32.2%) were direct bypass, 179

(17.7%) were combined bypass and 506 (50.1%) were indirect bypass. 9 studies reported the mean and standard deviation (SD) of patients' age. Pooled mean age was 37.5 years (95% CI: 33.5 – 41.5) and 7.4 years (95% CI: 4.1 – 10.7) in adult and pediatric patients, respectively. Study heterogeneity was considerable ($I^2$ = 97.9% [95% CI: 97.1 – 98.5], $p < 0.001$) for adults and $I^2$ = 96.6% [95% CI: 91.0 – 98.8], $p < 0.001$ for pediatric patients).

Table 3.2 Baseline characteristics of all patients included in this systematic review and meta-analysis.

| First Author (Year) | Patient type | No. pediatric in DB/CB | No. pediatric in IB | Age (years) | No. adult in DB/CB | No. adult in IB | Age (years) | Types of DB/CB | Type of IB |
|---|---|---|---|---|---|---|---|---|---|
| **Yu (2019)** | Paediatric and adult | 79 | 24 | 9.09 ± 4.319 | 221 | 44 | 35.58 ± 9.023 | STAMCA | NA |
| **Zhao (2019)** | Adult | NA | NA | NA | 411 | 199 | 37.5 ± 9.4 | STAMCA | EDAS, multiple burr holes |
| **Zheng (2019)** | Paediatric | 96 | 219 | 9.4 | NA | NA | NA | STAMCA, STAMCA + EDAS | EDAS, EMAS |
| **Deng (2017)** | Adult | NA | NA | NA | 70 | 70 | NA | STAMCA | EDAS and multiple burr holes |
| **Jang (2017)** | Adult | NA | NA | NA | 111 | 101 | 39.8 ± 10.7 | STAMCA | EDAS, EDAGS, EDAMS, EMS, inverted EDAS, inverted EDAGS |
| **Teo (2017)** | Adult | NA | NA | NA | 33 | 23 | NA | STAMCA, OAMCA, saphenous vein MCA | NA |
| **Czabanka (2016)** | Adult | NA | NA | NA | 40 | 34 | 44 ± 9 | STAMCA + EMS | EMS |
| **Sadashiva (2016)** | Peadiatric and adult | 41 | 44 | 13.8 | NA | NA | NA | STAMCA + EDAMS | EDAMS |
| **Liu (2015)** | Adult | NA | NA | NA | 227 | 194 | 26 ± 13 | STAMCA | EDAS, multiple burr holes and carotid artery adventitial |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Abla (2013)** | Adult | NA | NA | NA | 40 | 59 | 43.6 ± 11.5 | STAMCA | EDAS |
| **Gross (2013)** | Adult | NA | NA | NA | 35 | 18 | 39.2 ± 12.2 | STAMCA | Pial synangiosis |
| **Bang (2012)** | Adult | NA | NA | NA | 61 | 14 | 35.06 ± 12.4 | STAMCA, STAMCA + EMS, STAMCA + EDAS, STAMCA + EDAMS | EDAS |
| **Choi (2012)** | Adult | NA | NA | NA | 25 | 33 | NA | STAMCA, STAMCA + EDAGS, STAMCA + EDAMS | EDAMS, EDAGS, EDAMS + BEGPS, EDAGS + BEGPS |
| **Kim (2012)** | Adult | NA | NA | NA | 72 | 62 | NA | STAMCA + EDAGS + DP, STAMCA + inverted EDAGS | EDAGS + DPI, inverted EDAGS |
| **Lee (2012)** | Adult | NA | NA | NA | 69 | 78 | NA | STAMCA, STAMCA + EDAGS | EDAGS, EDAMS, EMS |
| **Ng (2011)** | Pediatric | 49 | 85 | NA | NA | NA | NA | STAMCA | Pial synangiosis, EDAS, EDMS |
| **Hyun (2010)** | Adult | NA | NA | NA | 12 | 234 | NA | STAMCA | EDAS, EDAMS |
| **Guzman (2009)** | Pediatric and adult | 113 | 55 | NA | 376 | 13 | NA | STAMCA | EDAS |
| **Matsushima (1998)** | Pediatric | 54 | 18 | NA | NA | NA | NA | STAMCA +EMS, EDAS + EMS + EMAS | EDAS |
| **Ishikawa (1997)** | Pediatric | 48 | 16 | 5.7 ± 2.8 | NA | NA | NA | STAMCA + EDAMS | EDAMS, EDAS |

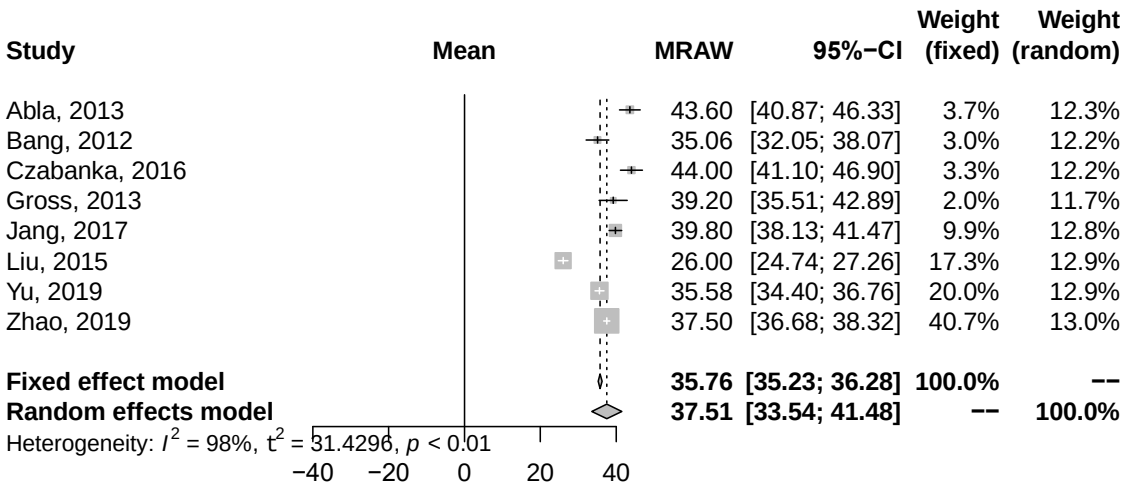


Figure 3.2. Forest plot for pooled percentage of age of included adult patients.

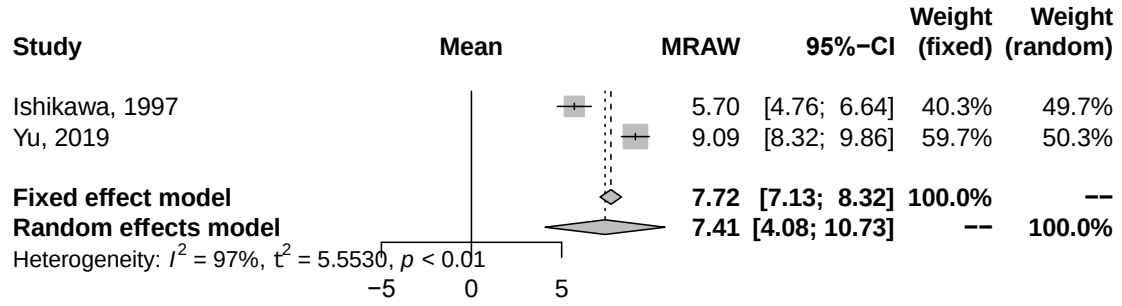


Figure 3.3. Forest plot for pooled percentage of age of included pediatric patients.

Using the JBI checklist for prevalence studies, 19 studies attained a full score of 9 and one study attained a score of 8 [Supplementary Table 12.2]. Using the JBI checklist for case series, 18 studies attained a full score of 10, one study attained a score of 9, and one study attained a score of 8 [Supplementary Table 12.3].

### 3.3.2 Perioperative stroke

15 studies reported overall rate of perioperative stroke. For adult patients, pooled overall percentage of perioperative stroke was 8.8% (95% CI: 5.4 – 12.9). Study heterogeneity was considerable ($I^2$ = 90.2% [95% CI: 85.1 – 93.6], p < 0.001). Perioperative stroke rate was comparable between direct/combined bypass and indirect bypass (OR = 1.26 [95% CI: 0.81 – 1.96], p = 0.300 for indirect bypass). There was no evidence of publication bias for adult perioperative stroke rates (p = 0.149).

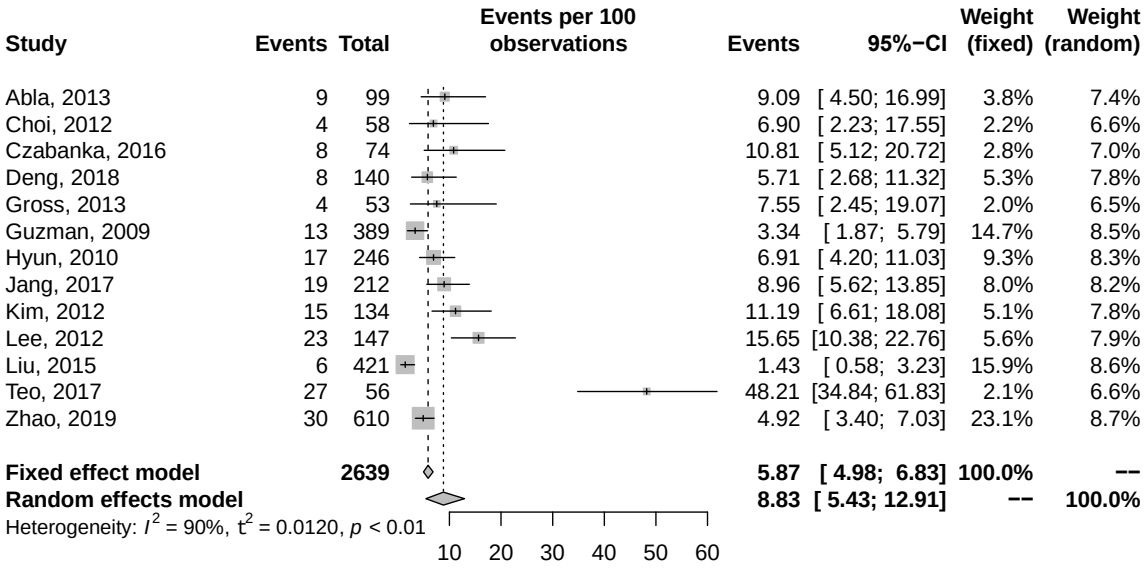


Figure 3.4. Forest plot for pooled percentage of overall perioperative stroke rate of included adult patients.

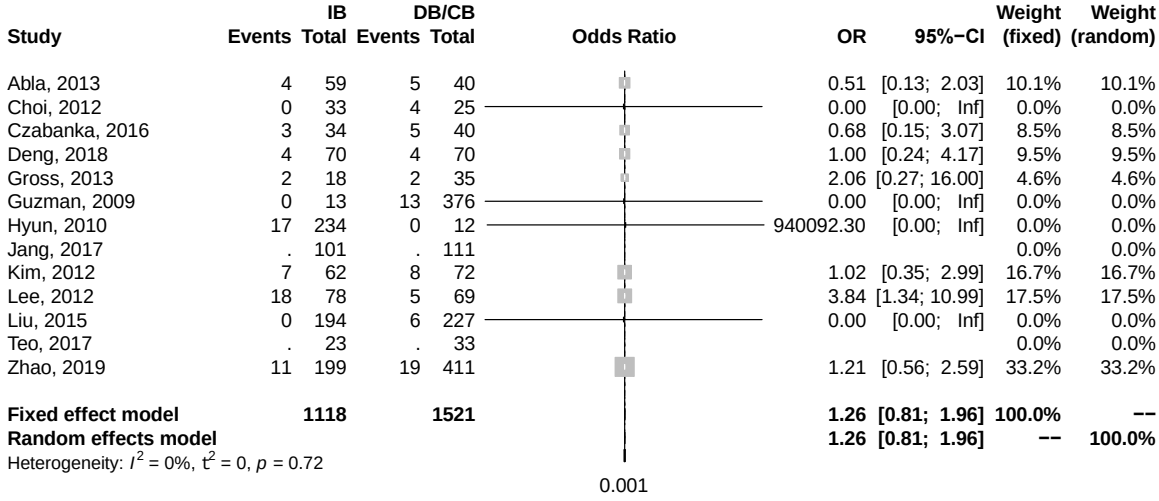


Figure 3.5. Forest plot for perioperative stroke rate of indirect bypass and direct/combined bypass revascularizations in adult patients.

For pediatric patients, pooled overall percentage of perioperative stroke was 7.5% (95% CI: 0.0 – 28.8). Study heterogeneity was considerable ($I^2$ = 93.6% [95% CI: 79.4 – 98.0], p < 0.001). Perioperative stroke rate was comparable between direct/combined bypass and indirect bypass (OR = 2.43 [95% CI: 0.74 – 7.94], p = 0.143 for indirect bypass).

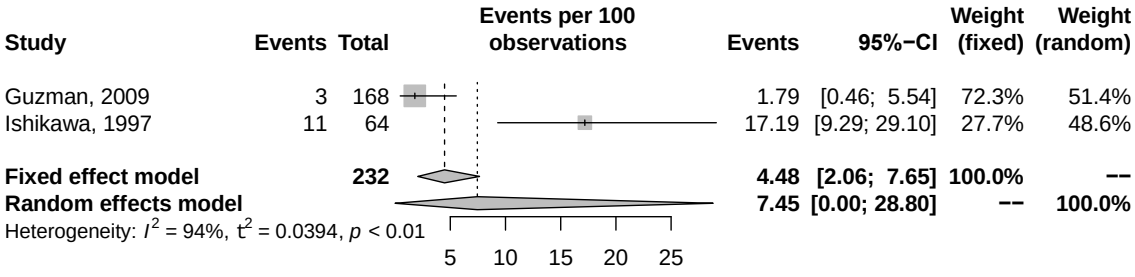


Figure 3.6. Forest plot for pooled percentage of overall perioperative stroke rate of included pediatric patients.

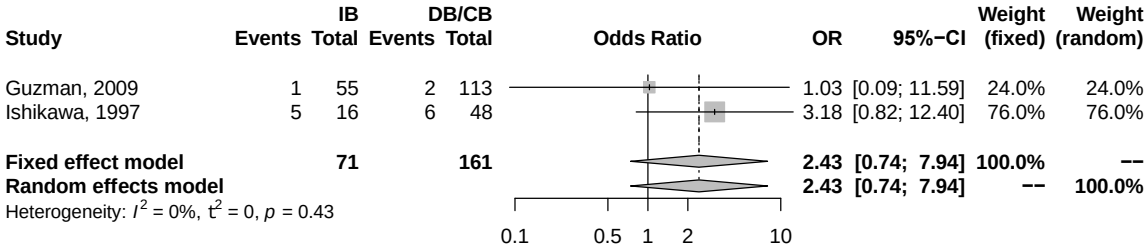


Figure 3.7. Forest plot for perioperative stroke rate of indirect bypass and direct/ combined bypass revascularizations in pediatric patients.

### 3.3.3 Perioperative mortality

10 studies reported perioperative mortality rate. For adult patients, pooled overall perioperative mortality rate was 0.3% (95% CI: 0.0 – 1.1). Study heterogeneity was substantial ($I^2$ = 57.3% [95% CI: 1.0 – 81.6], p = 0.029). No difference was found in perioperative mortality between direct/combined bypass and indirect bypass for adult patients (OR = 1.16 [95% CI: 0.07 – 19.00], p = 0.915 for indirect bypass). There was no evidence of publication bias for adult perioperative mortality rates (p = 0.067).

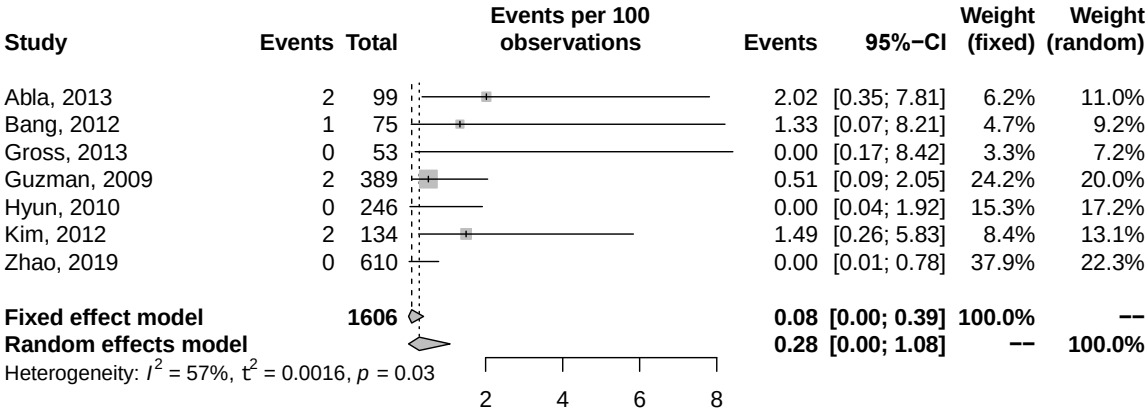


Figure 3.8. Forest plot for pooled percentage of overall perioperative mortality rate of included adult patients.

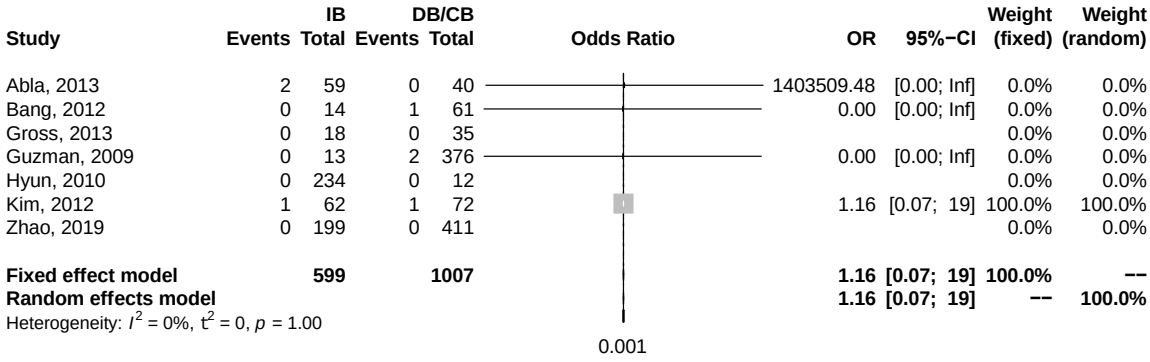


Figure 3.9. Forest plot for perioperative mortality rate of indirect bypass and direct/combined bypass revascularizations in adult patients.

For pediatric patients, pooled overall mortality rate was 0.1% (95% CI: 0.0 – 0.8). Study heterogeneity was low and insignificant ($I^2$ = 18.9% [95% CI: 0.0 – 87.6], p = 0.296). There was no difference in perioperative mortality between direct/combined bypass and indirect bypass (OR = 1.39 [95% CI: 0 – Inf], p = 1.00 for indirect bypass).

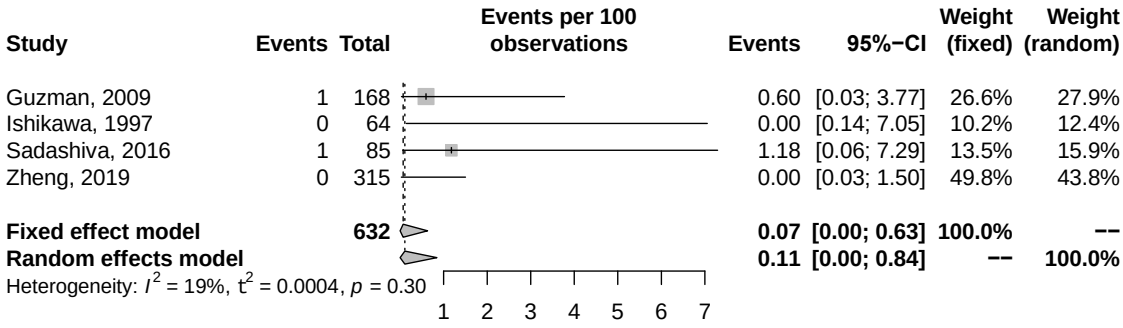


Figure 3.10. Forest plot for pooled percentage of overall perioperative mortality rate of included pediatric patients.

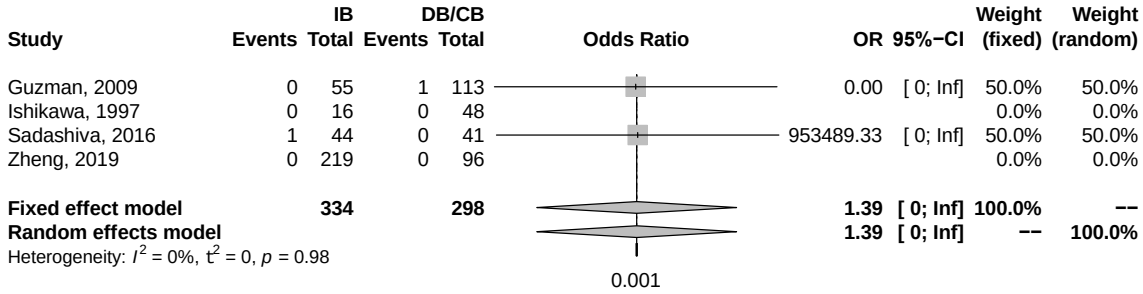


Figure 3.11 Forest plot for perioperative mortality rate of indirect bypass and direct/combined bypass revascularizations in pediatric patients.

### 3.3.4 Perioperative neurological deficit

6 studies reported perioperative neurological deficit rate in adults, and these are likely linked to TNE. Pooled overall rate of neurological deficit was 20.0% (95% CI: 10.2 – 32.0). Study heterogeneity was considerable ($I^2$ = 94.5% [95% CI: 90.5 – 96.8], p < 0.001). There was no significant difference in perioperative neurological deficit rates between direct/combined bypass and indirect bypass (OR = 1.27 [95% CI: 0.68 – 2.39], p = 0.451 for indirect bypass). There was significant evidence of publication bias for adult perioperative neurological deficit rates (p < 0.001). None of the included studies reported perioperative neurological deficit rates for pediatric patients.

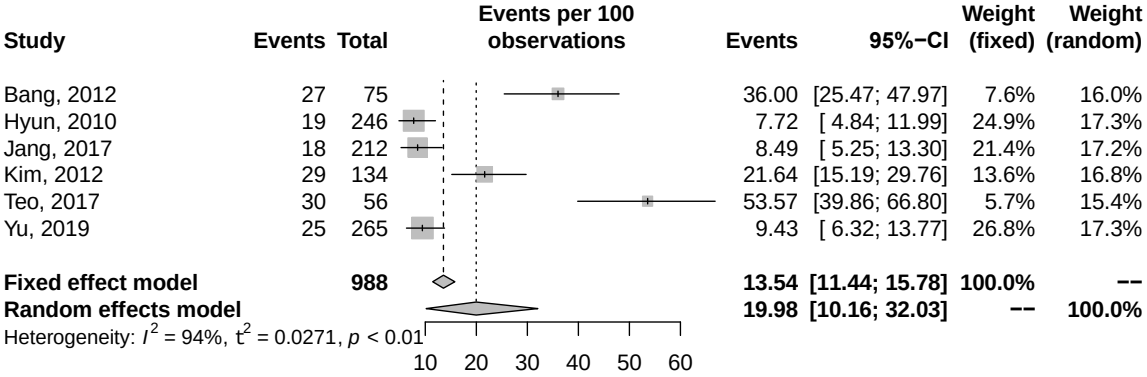


Figure 3.12. Forest plot for pooled percentage of overall perioperative neurological deficit of included adult patients.

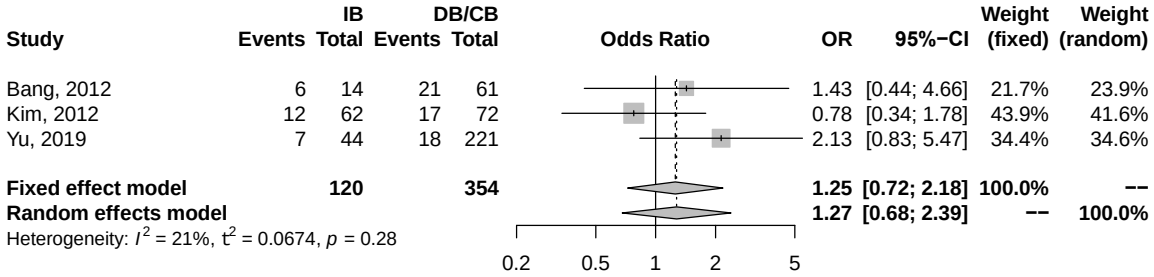


Figure 3.13. Forest plot for perioperative neurological deficit of indirect bypass and direct/combined bypass revascularizations in adult patients.

### 3.3.5 Short term angiographic revascularization

A narrative synthesis of angiographic revascularization was carried out due to heterogeneity in the mode of assessment and reporting of outcomes that make the average effect difficult to interpret and potentially misleading. No long-term (>5 years) angiographic result was available for comparative analysis of the efficiency between the different bypass types.

In aggregate, 8 studies reported short-term angiographic revascularization outcomes across adult and pediatric patients, but none reported angiographic revascularization data >5 years. 1 study reported revascularization outcomes in percentages and 6 studies reported newly developed collateral vessels according to Matsushima's grading classification of the proportion of the MCA territory revascularized.(Matsushima et al., 1992) Grade A when revascularisation of the MCA territory was > 2/3; grade B when extent of revascularization covered between 1/3 and 2/3 of the MCA distribution and grade C, when revascularization <1/3 of the MCA distribution.

5 studies reported short-term angiographic revascularization outcomes in adult patients.

Abla et al. performed computed tomography perfusing (CTP) imaging in 18 and 17 patients in the adult indirect and adult direct groups, respectively, after

surgery. Mean radiographic follow up was 22.0 ± 26.9 and 36.7 ± 32.4 months, respectively in the indirect and direct groups. In the 2 adult groups, CTP was the same in 4 patients in each group and worse in 2 patients in each group. All other adult patients had improvement. (Abla et al., 2013)

Bang et al. reported mean values for the extent of revascularization among 5 different bypass surgeries at 6 months. Extent of revascularization achieved were 32.4% for EDAS only, 57.4% for SMA only, 58.4% for SMA with EMS, 66.1% for SMA with EDAS, and 70.8% for SMA with EDAMS. (Bang et al., 2012)

Choi et al. reported angiographic revascularisation of the MCA distribution using a grading classification system described first by Matsuhima et al. Average follow-up period was 23 ± 20.0 months (range, 6-67 months). Grade A collateral formation occurred in 2 of 13 hemispheres (15.4%), 7 of 20 hemispheres (35%) and 12 of 25 hemispheres (48%) treated by EDAG, EDAMS and combined approaches, respectively. Grade B collateral formation occurred in 7 of 13 hemispheres (53.8%), 8 of 20 hemispheres (40%) and 11 of 25 hemispheres (44%) treated by EDAG, EDAMS and combined approaches, respectively. Grade C collateral formation occurred in 4 of 13 hemispheres (30.8%), 5 of 20 hemispheres (25%) and 2 of 25 hemispheres (8%) treated by EDAG, EDAMS and combined approaches, respectively. (Choi et al., 2012)

Kim et al. reported angiographic revascularisation of the MCA distribution using a grading classification system described first by Matsuhima et al. Mean follow-up period was 6.8 months (range, 2 – 16 months). Grade A collateral formation occurred in 46 of 61 hemispheres (75.4%), 57 of 71 hemispheres (35%) treated by indirect and combined approaches, respectively. Grade B collateral formation occurred in 9 of 61 hemispheres (14.8%) and 10 of 71 hemispheres (14.1%) treated by indirect and and combined approaches, respectively. Grade C collateral formation occurred in 6 of 61 hemispheres (9.8%), 2 of 71 hemispheres (2.8%) treated by indirect and combined approaches, respectively. (Kim et al., 2012)

Postoperative angiograms were obtained for 138 hemispheres in Lee et al. The follow-up duration ranged from 12 to 112 months (mean, 54.5 months). Grade A collateral formation was found in 7 of 30 (23.3%) hemispheres treated by direct approach, 8 of 77 (10.4%) hemispheres treated by indirect approach, and 9 of 31 (29%) hemispheres treated by combined approach. Grade B moderate collateral formation was found in 18 of 30 (60%) hemispheres treated by direct approach, 28 of 77 (36.4%) hemispheres, treated by indirect approach and 17 of 31 (54.9%) hemispheres treated by combined approach. Grade C poor collateral formation was found in 5 of 30 (16.7%) hemispheres treated by direct approach, 41 of 77 (53.2%) hemispheres, treated by indirect approach and 5 of 31 (16.1%) hemispheres treated by combined approach. (Lee et al., 2012a)

3 studies reported short-term angiographic revascularization outcomes in pediatric patients.

Matsushima et al performed selective angiography at 4 to 25 months postsurgery in all patients. Postoperative collateral formation results were attained using the lateral view on serial external carotid artery angiograms. Grade A collateral formation occurred in 8 of 18 hemispheres (44%) treated by indirect approach alone, 18 of 35 hemispheres (52%) treated by combined approach, and 14 of 19 hemispheres (74%) treated by direct anastomosis. Collateral formation of the whole MCA distribution was observed in 7of 35 hemispheres (20%) treated by combined approach and in 4 of 19 hemispheres (21%) treated by direct approach, none in indirect approach. Furthermore, the combined procedure resulted in well-formed collaterals in the ACA distribution in 33 of 35 hemispheres (94%). On the other hand, the indirect bypass alone showed no collateral formation in 3 of 35 hemispheres (17%). (Matsushima et al., 1992)

Ng et al. assessed 36 revascularized hemispheres (2 direct, 34 indirect hemispheres) by catheter cerebral angiography. Newly developed collateral vessels were graded according to Matsushima’s classification of the proportion of the MCA territory revascularized.(Matsushima et al., 1992) Grade A >2/3

revascularisation of the MCA territory was achieved in 7 hemispheres (19.4%); grade B when extent of revascularization covered between 1/3 and 2/3 of the MCA distribution, was achieved in 13 hemispheres (33.3%). Finally, 13 hemispheres (33.3%) were categorised as grade C, revascularization of <1/3 of the MCA distribution. No collateral development was identified in 3 out of 36 hemispheres (8.3%), which were all treated with indirect bypass. (Ng et al., 2012)

### 3.3.6 Long term stroke risk

The reported of long term stroke risks were variable for all the studies, and none of the comparative studies reported long term stroke risks beyond 5 years that could be used for analysis.

In 346 patients, Yu et al reported that during the 1285.7 patient-years of follow-up (beyond 30 days postoperatively), 14 patients experienced 15 subsequent strokes, yielding an annual subsequent stroke rate of 1.2%. Of the 15 subsequent strokes, 9 patients had ischemic stroke, 4 patients had hemorrhagic stroke, and 1 patient had both ischemic and hemorrhagic stroke. The annual subsequent stroke rate was 0.98% (8 events in 817.9 patient-years of follow-up) for adults and 1.5% (7 events in 467.8 patient-years of follow-up) for children. Subsequent stroke events tended to occur throughout the first 5 years after surgery in adults, whereas in children they mainly occurred within the first 2 years after surgery (Yu et al., 2019c). However, we were unable to determine the types of revascularization and the associated long term stroke risks.

## 3.4 Discussion

### 3.4.1 Summary of findings

To the best of our knowledge, this is the first meta-analysis to systematically assess the outcomes of direct/combined versus indirect revascularization for both pediatric and adult patients. This meta-analysis of 20 studies showed comparable perioperative complications efficacy in direct/combined revascularization compared with indirect revascularization for adult MMD, with better short term angiographic outcomes. In paediatric MMD, there is similar rates of perioperative risks for direct/combined revascularization compared to indirect revascularization. There was a lack of data from the literature for robust assessment of long term (>5 years) stroke risk, angiographic revascularization between direct/combined bypass and indirect bypass.

### 3.4.2 Perioperative complication rates

Our meta-analyses showed relatively low rates of perioperative complications (in adults, 8% risk of stroke, 0.3% risk of death, 20% risk of neurological event, likely linked to TNE; and in children 7.5% risk of stroke, 0.1% risk of death) in both the direct/combined and indirect groups. When compared with the indirect approach, combined bypass is usually thought to be more technically challenging and also have more risk for postoperative complications such as symptomatic hyperperfusion, cerebral infarction, and intracerebral hemorrhage.(Gross and Du, 2013b, Arias et al., 2014, Guzman et al., 2009a, Fujimura et al., 2009a) However, of 16 studies included in our analysis reporting perioperative complications, none has explicitly verified this hypothesis to show fewer perioperative complications in indirect bypass compared with direct/combined bypass. The lower rates of perioperative complication in our meta-analysis may reflect surgical selection bias, but it is more likely to be explained by the increasing experience with techniques. Particularly in the direct/combined bypass cohort, lower rates may be the result of greater experience with the technique in certain centers. Our meta-analysis suggests that, with adequate training and sufficient experience in performing the direct/combined bypasses, one can minimize the rates of perioperative complications despite it being more technically demanding. For example, enhanced proficiency may lead to a shorter period of temporary vessel

occlusion during anastomosis, reducing the risk of perioperative ischaemia. Notably, while cerebral hyperperfusion led to transient neurological deficit (TNE) more commonly after direct revascularization in adult patients, this phenomenon is less frequently observed in pediatric patients and should not dissuade one from choosing this approach.(Uchino et al., 2012, Yu et al., 2019b)

Several studies have reported higher mortalities associated with direct bypass, vis a vis with indirect bypass.(Mesiwala et al., 2008a, Okada et al., 1998, Khan et al., 2003a) However, despite evidence demonstrated by these series, our meta-analysis demonstrated no significance of perioperative mortality was found between direct/combined and indirect approaches, and did not show any significant difference in rates of either perioperative haemorrhage or perioperative ischemia among direct, indirect, or combined bypass procedures.

### 3.4.3 Published systematic review and meta-analysis on moyamoya disease

We identified 10 published meta-analyses on the treatment of moyamoya disease, addressing different aspects of the condition (Jeon et al., 2018, Kim et al., 2016, Qian et al., 2015, Sun et al., 2016, Lin et al., 2021, Ravindran et al., 2019, Wouters et al., 2019, Kronenburg et al., 2018, Ding et al., 2018, Li et al., 2019), and summarised in Table 3.3.

Table 3.3 Summary of Published meta-analysis on various aspects of MMD management and surgical treatment

| First Author (Year) | Journal | Country | Cohort | Included Studies | Comparison | | Limitation |
|---|---|---|---|---|---|---|---|
| **Jeon 2018** | JNS | Korea | Adult MMD | 11 studies | Surgery vs Cons, reduce future stroke OR 0.3, p<0.001 | | periop complication included all - wound problem to death |
| | | | | | DB vs IB, reduce future stroke, OR 0.494, p=0.0028<br>DB vs IB, no diff periop complication (bleed, ischemia, seizure, hyperperfusion, wound problem, permanent ND, death)<br>DB vs IB, better angio outcome OR 6.832, p<0.001 | | |
| | | | | | | | |
| **Kim 2016** | WNS | Korea | Adult MMD | 8 studies<br>1990-2015<br>536 patients, 732 hemisphere<br>FU 1-6yr | DB vs IB | better angio outcome, OR 2.85, p=0.002<br>no diff periop complication<br>no diff HDR<br>no diff stroke recurrence | LT stroke risk included periop stroke risk |
| | | | | | | | |
| **Qian 2015** | Medicine | China | Adult MMD | 16 studies | 1◦ outcome recurrent stroke >6mth<br>2◦ outcome periop complication | | |
| | | | | 8 studies<br>692 Sx, 269 cons | Sx vs cons | Sx reduce risk of stroke, OR 0.17, p<0.001 | periop comp included all - stroke, bleed, wound prob, seizure, hyperperfusion, death |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | 12 studies<br>536 DB/CB,<br>301 IB | DB vs IB | secondary stroke reduction<br>OR 1.79 p=0.01 | |
| | | | | | | | |
| **Sun 2016** | WNS | USA | Adult MMD | 47 studies<br>2013 patients<br>796DB, 709CB, 508IB | DB vs IB | DB: favourable LT outome, reduce LT ischemia, bleed<br>However, DB higher periop heamorrhage rate | Poor inclusion criteria, some duplicated dataset included.<br>3-ways comparison of DB, CB, IB, can be confusing |
| | | | | Single arm & comparative studies | Analysis included periop bleed, periop ischemia, LT bleed, LT ischemia, fav outcome | | |
| | | | | | | | |
| **Lin 2021** | Brain Behavio r | China | MMD | 18 studies | 3 ways comparison DB vs IB, CB vs IB, DB vs CB<br>Similar effect of DB & CB, superior to IB | | |
| | | | | | | | |
| **Ravindran 2019** | JNS Peds | Australia | Peds MMD | 29 studies<br>2258 patients<br>FU avrg 71.4mths<br>Single arm & comparative studies | 154 DB<br>680 CB<br>1424 IB | DB: 1/190 future stroke<br>CB: 1/108 future stroke<br>IB: 1/61 future stroke | |
| | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Wouters 2019** | Acta Neurol Belg | Belgium | Adult MMD | 10 studies<br>2484 patients | Sx vs cons | reduced stroke, death risk<br>4.6% vs 18.6%<br>0.6% vs 2.9% | |
| | | | | | | | |
| **Li 2019** | WNS | China | MMD | 27 studies | Sx vs cons | Sx: reduced future stroke risk | |
| | | | | | DB vs IB | DB: reduced LT stroke, better angio result | |
| | | | | | | | |
| **Kronenburg 2018** | J Stroke | Netherland | MMD cognition | 17 studies<br>11 studies 281 children<br>6 studies 153 adults | Children, 30% with impaired cognition (13%-67%)<br>Adult, 31% with impaired cognition (0-69%) | | Unable to determine the effect of revascularization on cognitive function |
| | | | | | | | |
| **Ding 2018** | WNS | China | Haem MMD | 9 studies<br>1050 patients | Network Analysis<br>DB > IB > cons Mx | | |
| | | | | | to reduce recurrent strokes, but not reducing mortality | | |

The fundamental question of whether to perform surgical revascularization for moyamoya patients was addressed in 5 meta-analyses, and all the studies showed that revascularization was superior to medical treatment alone. Li et al showed that surgery group was more advantageous in reducing the risk of future stroke events than conservative treatment in MMD patients (OR 0.26, 95% CI 0.20-0.33, P <0.001). In addition, surgical group also resulted in increased cerebral perfusion (OR 7.16, 95% CI 3.28-15.64, P <0.001) and lower risk of death due to rebleeding (OR 0.27, 95% CI 0.10-0.72, P <0.01). (Li et al., 2019)

With regards to comparing the various bypass techniques, a recent meta-analysis performed a 3-way comparison of direct bypass (DB), combined bypass (CB) and indirect bypass (IB). Lin et al included a total of 18 studies including the various surgical treatment, and the result revealed that indirect bypass was related to a higher incidence of recurrence stroke compared to the direct and combined bypass treatment (p=0.001). They also showed that the effect of DB and CB is equivocal. (Lin et al., 2021)

Although it is sensible to analyse the effect of direct bypass and combined bypass together (as we did in this study), such view was not universal. Macyszyn et al, in their comparative analysis in 2016, grouped CB and IB together, and wrongly concluded that direct bypass was inferior. In the meta-regression pooled analysis, despite the long-term risk of ischemic stroke in the indirect bypass group (10.5%) far exceeded that in the direct bypass group (1.4%), they concluded that such difference was not statistically significant. (Macyszyn et al., 2017)

5 studies included only adult MMD patients, stratified into ischaemic and haemorrhagic subgroups to analyse the effect of surgical revascularisation and bypass types. Jeon et al included 11 comparative articles for symptomatic adult MMD, and showed that direct bypass resulted in lower incidence of future stroke compared with indirect bypass (OR 0.494, p = 0.028), higher angiographic revascularization (good angiographic outcome 89.6% in DB,

52.8% in IB, OR 6.832, p<0.001), and similar perioperative complications (Jeon et al., 2018).

In a meta-analysis comparing perioperative complications among the different bypasses in adult MMD which included 47 studies (mostly single arm case series), the pooled analyses showed that perioperative hemorrhage rates were significantly (P<0.02) lower with indirect compared with direct (OR 0.03; 95% CI, 0.002-0.55) or combined (OR, 0.03; 95% CI, 0.002 - 0.53) bypasses. They showed that DB was better than IB in producing long term favourable outcomes. The interinstitutional differences of surgical procedure and perioperative management, in addition to relatively low rates of surgical complications, might explain this discrepancy. (Sun et al., 2016)

Ravindran et al studied only paediatric MMD, and they included single arm and comparative studies. The pooled perioperative complication rates with indirect revascularization and combined/direct bypass were comparable, at 15.4% with indirect revascularization and 9.0% in the combined/direct group. The frequencies of future stroke events in patients undergoing either direct bypass alone, combined bypass, or indirect bypass alone were 1 per 190.3 patient-years, 1 per 108.9 patient-years, and 1 per 61.1 patient-years, respectively. When pooling comparative and single arm studies, the overall RR of future stroke events after indirect versus combined/direct revascularization did not achieve statistical significance. (Ravindran et al., 2019)

With network meta-analysis gaining popularity as a research tool, Ding et al included 9 comparative studies to compare the management of patients with haemorrhagic MMD. They used Bayesian hierarchical models to perform pairwise comparisons among DB, IB and conservative treatment, and concluded that direct bypass is the optimal strategy for treating haemorrhagic MMD to reduce recurrent strokes (including ischaemic and haemorrhagic stroke), but not in reducing mortality (OR 0.53, 95% CI 0.24-1.17). (Ding et al., 2018)

### 3.4.4 Comparing and contrasting findings of adult and paediatric MMD revascularization

Although several bypass methods have been shown to improve cerebral hemodynamics whilst reducing the incidence of future stroke events in both pediatric and adult patients with MMD, the optimal revascularization strategy is still debated and may differ in children and adults(Arias et al., 2015b, Imai et al., 2015)

Direct anastomosis allows for immediate and long-lasting augmentation of cerebral blood flow and does not rely on the plasticity and angiogenic potential unlike indirect revascularization. It hence provides a more predictable hemodynamic outcome and is highly recommended in adult patients, especially when combined with indirect revascularization.(Acker et al., 2018) In contrast to the immediate flow augmentation by the anastomosis of direct bypass, indirect revascularization generally relies on the slow neovascularization and recruitment of leptomeningeal collaterals over time.(Kazumata et al., 2014a, Cho et al., 2014) Due to this, interpretation of angiographic outcomes from indirect revascularization may be limited if time to collateral angiogenesis is inadequate. It is easier to perform as compared to its direct counterpart and is mainly undertaken as the first-line surgical strategy in pediatric MMD cases.(Smith and Scott, 2012)

Included studies in our meta-analysis reflected current patterns of practice favouring indirect revascularization in the pediatric MMD population, in terms of long-term revascularisation.(Ravindran et al., 2019) While EDAS and EDAMS were among the originally described techniques for indirect revascularization, over the years, new techniques such as pial synangiosis and multiple burr holes have been used.(Blauwblomme et al., 2017, Choi et al., 2015, Sainte-Rose et al., 2006a) However, there is no general consensus of the optimal indirect revascularization strategy. Factors dissuading use of direct bypass in the pediatric MMD population include smaller-caliber recipient and donor vessels, longer operative times, potential for poor scalp wound healing.(Yu et al., 2019b) In pediatric patients in particular, direct bypass remains a technically

challenging procedure and is only performed by a handful of senior surgeons.(Abla et al., 2013)

Our narrative synthesis of angiographic outcomes indicated that direct bypass yielded a more preferable angiographic improvement than its indirect counterpart, which was in accordance with previous meta-anlayses.(Jeon et al., 2018, Kim et al., 2016) A 2018 meta-analysis conducted by Jeon et al.(Jeon et al., 2018) demonstrated a significantly lower risk of future stroke events for direct bypass compared with indirect bypass in symptomatic adult patients. In contrast, Kim et al.(Kim et al., 2016) analyzed the literature involving direct bypass and indirect bypass and concluded no significant differences between these two approaches in terms of overall stroke rate. These conflicting results can be explained by the considerable heterogeneity of the original articles, which can be attributed to diverse study population of varying ethnicity and the various different indirect revascularization procedures employed by different studies.

Bang et al.(Bang et al., 2012) studied the adult moyamoya population after bypass surgery and found that the extent of angiographic revascularization was greatest in the combined STA-MCA direct bypass with EDAMS group and lowest in the EDAS-only group. Lee et al.(Lee et al., 2012b) observed the patients' postoperative angiographic changes 6-12 months after surgery and also found more significant angiographic changes in patients who underwent either direct and combined bypass.

Although there was limited class 1 evidence in moyamoya literature, based on the various analyses performed, surgical revascularization is the optimal strategy for MMD. For the types of bypass in adults or paediatric age group, ischaemic or haemorrhagic presentation, variables such as surgeons' experience, vascular conditions, vessels calibre, and patients' clinical conditions could all affect the choice and outcomes.

### 3.4.5 Limitations

The current study has several limitations. First, only studies published in English were included; therefore, selection bias may exist because MMD has greater incidence rates among Asian populations. Second, the meta-analysis did not compare the effectiveness of bypass methods according to clinical presentation, although heterogeneous cohorts such as ischemic, hemorrhagic, and even clinically asymptomatic were included. Third, this study was weakly representative because single-arm studies were excluded from the analysis. Fourth, there were no standard surgical methods used in any of the bypass groups and heterogeneous hemodynamic assessment to detect changes after bypass surgeries. Fifth, there was no standard time frame with different lengths of clinical follow-up in each study. Our meta-analysis is also limited by the retrospective and observational nature of included studies and the significant heterogeneity among the studies. However, RCTs for surgical interventions have proven challenging to conduct due to ethical reasons.(Yu et al., 2019a) Furthermore, the results of our meta-analysis implicate the lack of clinical equipoise and further highlight the difficulty of patients with MMD for revascularization. The findings from our meta-analysis contribute to addressing this gap in the current literature, as long as they are interpreted judiciously with the aforementioned limitations in mind. Our study has also highlighted the limited number of studies currently available on this topic and the absence of studies directly comparing direct/combined and indirect revascularization for MMD. The small number of studies available in the literature limited our ability to perform certain analyses such as meta-regression to explore possible confounders in our dataset. Studies with small numbers may also introduce publication bias and exacerbate the file-drawer problem. To minimize the extent of these limitations, we performed sensitivity analyses to identify outlier studies which may have significantly influenced the pooled outcome estimates. Publication bias was evaluated in multiple ways, and quantitative analysis revealed no evidence of publication bias in our included studies. Nonetheless, we performed adjustment of the pooled estimates for any existing publication bias and presented both the adjusted and unadjusted figures. Quality

assessment via JBI of all included studies was also performed to ensure adequate methodological quality.

### 3.5 Conclusions

Our meta-analysis showed that both direct and indirect bypasses have similar rates of perioperative complications in pediatric and adult patients, however there was no comparative data to report long term (>5 years) stroke risk, angiographic revascularization between direct/combined bypass and indirect bypass.

# CHAPTER FOUR

# SHORT AND LONG TERM OUTCOME OF MOYAMOYA PATIENTS POST REVASCULARISATION

## 4.1 Introduction

Moyamoya disease (MMD), steno-occlusive disease affecting terminal ICAs, proximal MCAs, typically affects children and young adults, causing strokes. However due the rarity in the western world, very little is known about the long term treatment outcome, functional status in terms of employment, education, family life, and what prognostic factors are predictive of good or poor outcome for these patients. In the literature, only 10 studies have reported on mean follow-up of 5 years or longer, and none of the adult studies are from the west (Rashad et al., 2016, Liu et al., 2016a, Funaki et al., 2014, Mukawa et al., 2012, Ulrich and Januschek, 2011, Scott et al., 2004(Ozaki et al., 2016, Liu et al., 2016b, Cho et al., 2014, Bao et al., 2012). In view of the differences in MMD in the east and west, the long term result from the eastern population might not be directly applicable to patient cohort from the western hemisphere.

One of the previous study from Stanford based on 450 revascularisations did not identify statistically significant risk factors associated with postoperative surgical adverse outcome (Guzman et al., 2009b). With one of the largest patient cohort with treated moyamoya disease in the west, we assessed and identified the factors associated with postoperative stroke risks, and presented their long-term physical, functional, social outcomes after 1250 revascularisations.

## 4.2 Methods

### 4.2.1 Patient Population

From Jan 1991 to Dec 2014, all consecutive MMD patients who underwent surgical revascularisation at Stanford University Medical Center were included, with prospectively collected demographic data entered in the MMD database. The diagnosis of MMD is based on published guidelines (Fukui, 1997), incorporating the clinical symptomatology, neuroimaging studies (MRI, CVRS with acetazolamide challenge, 6-vessel DSA), and discussed at a

neurovascular multidisciplinary meeting prior to decision made for surgery. Patients with unilateral MMD and moyamoya syndrome (such as Down syndrome, neurofibromatosis, primordial dwarfism patients with angiographic findings of MMD) were included in the study.

### 4.2.2 Radiological Imagings

Preoperative radiological imaging scores were assigned based on the 6-vessels DSA, MRI brain and haemodynamic studies, with modifications made to the Berlin moyamoya grading score (Czabanka et al., 2011c). Suzuki stage was assigned as proposed ((Suzuki and Takaku, 1969), while a simplified DSA score was also applied (stenosis/occlusion = 1point; stenosis/occlusion + intracranial-intracranial (ICIC) collateralisation = 2 points; stenosis/occlusion + ICIC + extra-intracranial (ECIC) collateralisation = 3 points, Figure 4.1).

mMRI brain score was assigned as follow: no sign of ischemia/hemorrhage/atrophy = 0 point; signs of ischemia/hemorrhage/atrophy = 1 point; DWI +ve infarct within 1 month of surgery = 2 points.

Haemodynamic reserve (HDR) studies to assess CVRC include MRI perfusion, SPECT, Xe-CT with acetazolamide challenge, due to technological and practise changes over the 24-year study period. HDR score: Good augmentation = 0 point, impaired augmentation with acetazolamide = 1 point, steal phenomenon = 2 points.

### 4.2.3 Surgical Techniques

Details and types of various surgical techniques were covered previously. In principle, for patients with bilateral MMD, the more symptomatic side would be revascularised first, otherwise the nondominant side if no lateralising signs or symptoms are present. The second surgery is usually performed 1 week after the first, unless clinically contraindicated. Direct revascularisation (STA-MCA bypass) is usually the treatment of choice, except when the donor or recipient vessels are too small (<1mm), too fragile, or in very young patients. Indirect

bypass, such as EDAS, EMS, omental-cranial transposition would be selected according to the clinical requirement. All procedures are performed under mild hypothermia (33°C), with burst suppression using thiopental and increasing MAP during M4 branch temporary occlusion for primary microanastomosis. Typical hospitalisation of 3 to 4 days with the first night in the intensive care unit, strict MAP management, and MRI brain prior to discharge.

### 4.2.4 Clinical Follow-Up

Patients are evaluated clinically 1-week post discharge, and at 6 months, 3 years, 10 years, 20 years with MRI, haemodynamic studies (MRI perfusion, SPECT or Xe-CT) and 6-vessels cerebral angiography (to assess bypass patency and extent of revascularisation).

Surgical morbidity is defined as new neurological deficit lasting 24 hours or longer after revascularisation surgery, and associated with a new infarct or haemorrhage on MRI or CT within 30 days postoperatively. Transient neurological episode (TNE) is recorded when patients developed intermittent temporary neurological symptoms without the associated radiological changes.

For longer term outcome analysis, patients with at least a minimum of 6-months follow-up was included. Combination of clinical review, questionnaires (as detailed previously), telephone calls, electronic correspondence were used. The occurrence of stroke, haemorrhage, TIA, ongoing neurological symptoms, were recorded. mRS was recorded at the latest clinical follow-up available, and compared with preoperative mRS.

We analysed potential risk factors associated with long term stroke risk, including age of patient at first surgery, patients who suffered with 30-day perioperative stroke, and types of bypasses.

### 4.2.5 Statistical Analysis

Pearson chi-square or Fisher exact test were used for comparing categorical variables, while Mann-Whitney U-test or t-test were used for continuous variables. Univariate and multivariate logistic regression analyses were performed to determine risk factors for postoperative morbidity. Risk of subsequent stroke and death was determined using Kaplan-Meier, with log-rank statistic for comparisons. Differences were considered statistically significant at $p<0.05$.

## 4.3 Results

769 patients with 1250 bypasses (1991-2014) were identified from the moyamoya database. Follow up of at least 6 months was available on 95% (730/769) of patients, with a mean follow up of 7 years (0.5 – 25 years).

### 4.3.1 Demographics and Clinical Presentation

548 females, 357 males, age range 0-69 years underwent 1250 bypasses (1118 direct, 132 indirect revascularisations) for MMD. The bimodal peak age distribution of 6-10 years in paediatric cohort, and 31-40 years in adult cohort is shown in Figure 3.1. The gender and ethnicity distribution for the whole MMD cohort is shown in Figure 3.2.

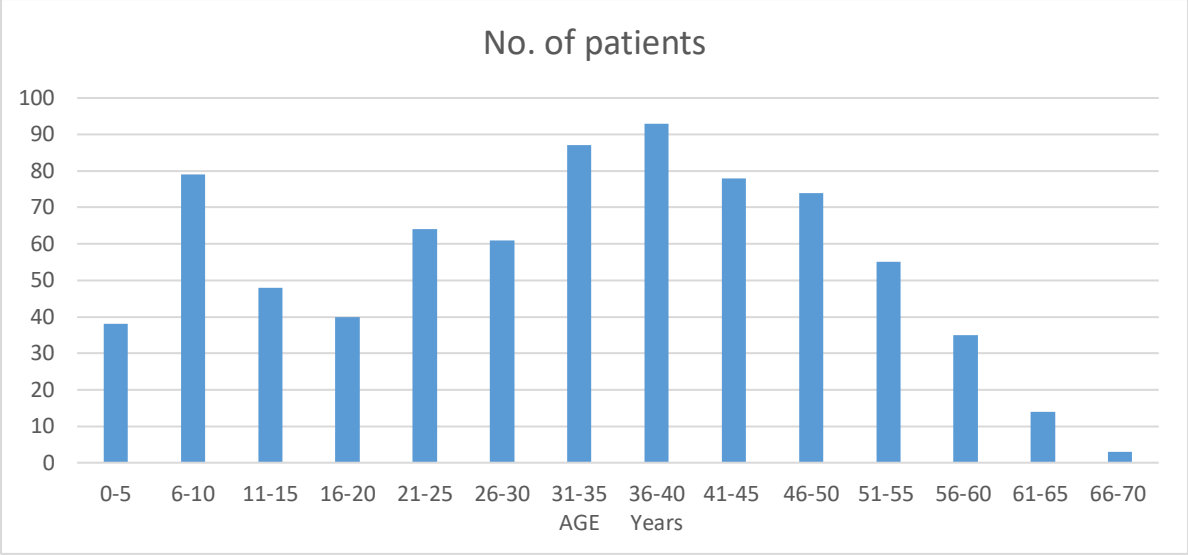


**Figure 4.1.** Age distribution of MMD patients at first bypass surgery. Note the bimodal peak age distribution of 6-10 years in paediatric cohort, and 31-40 years in adult cohort.

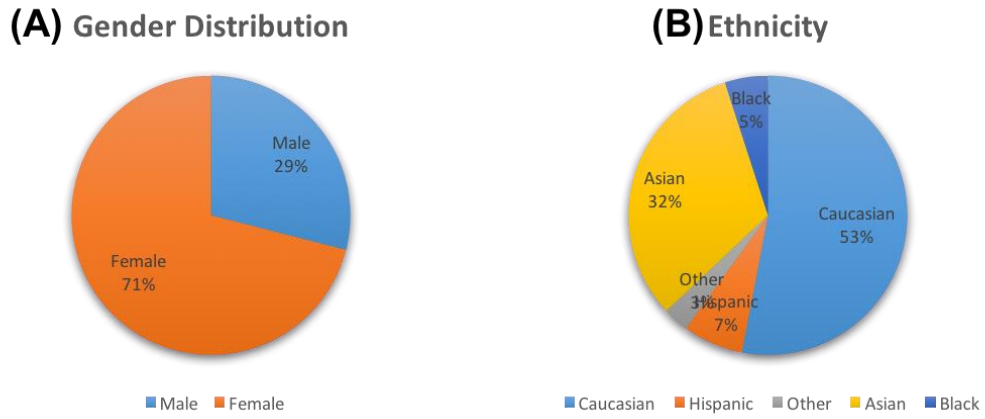


**Figure 4.2**. (A) Gender distribution for MMD patients, with female predominance. (B) Ethinicity distribution with Caucasian predominance in western MMD.

Over the last 25 years, the number of MMD bypass cases per year from Stanford University Medical Center is shown in Figure 3.3, with approximately 100 procedures per year in the 10 years between 2006-2015.

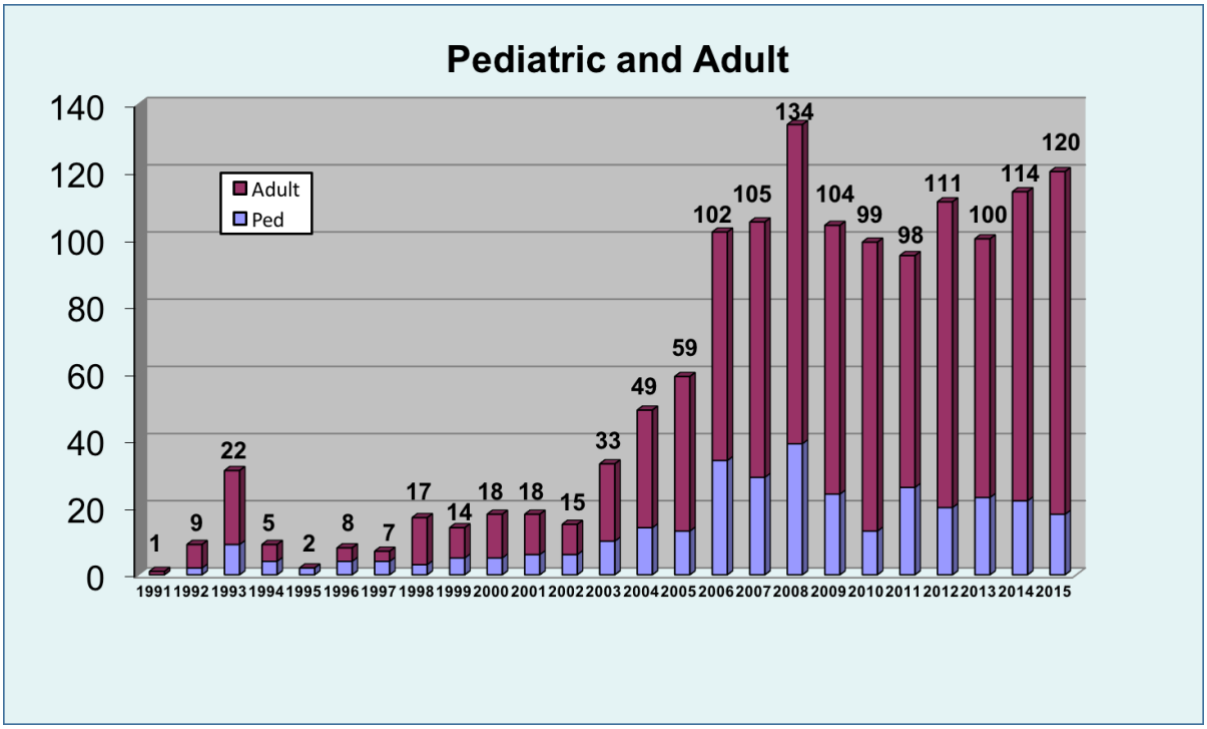


**Figure 4.3**. The number of MMD bypass cases per year from Stanford University Medical Center from 1991-2015.

The patients are referred from various parts of USA, with most patients from California, followed by Hawaii (Figure 3.4). Most patients are Caucasian (53%), with a small group of Hispanic (7%), and African-American (5%). Diabetes and hyperlipidaemia was reported in 13.5% and 22.4% of patients respectively. Unsurprisingly, most patients presented with ischemic symptoms (TIA or stroke, 82.2%), while haemorrhagic presentation was recorded in 13.1%, headache in 46%, seizure in 11.7% of patients.

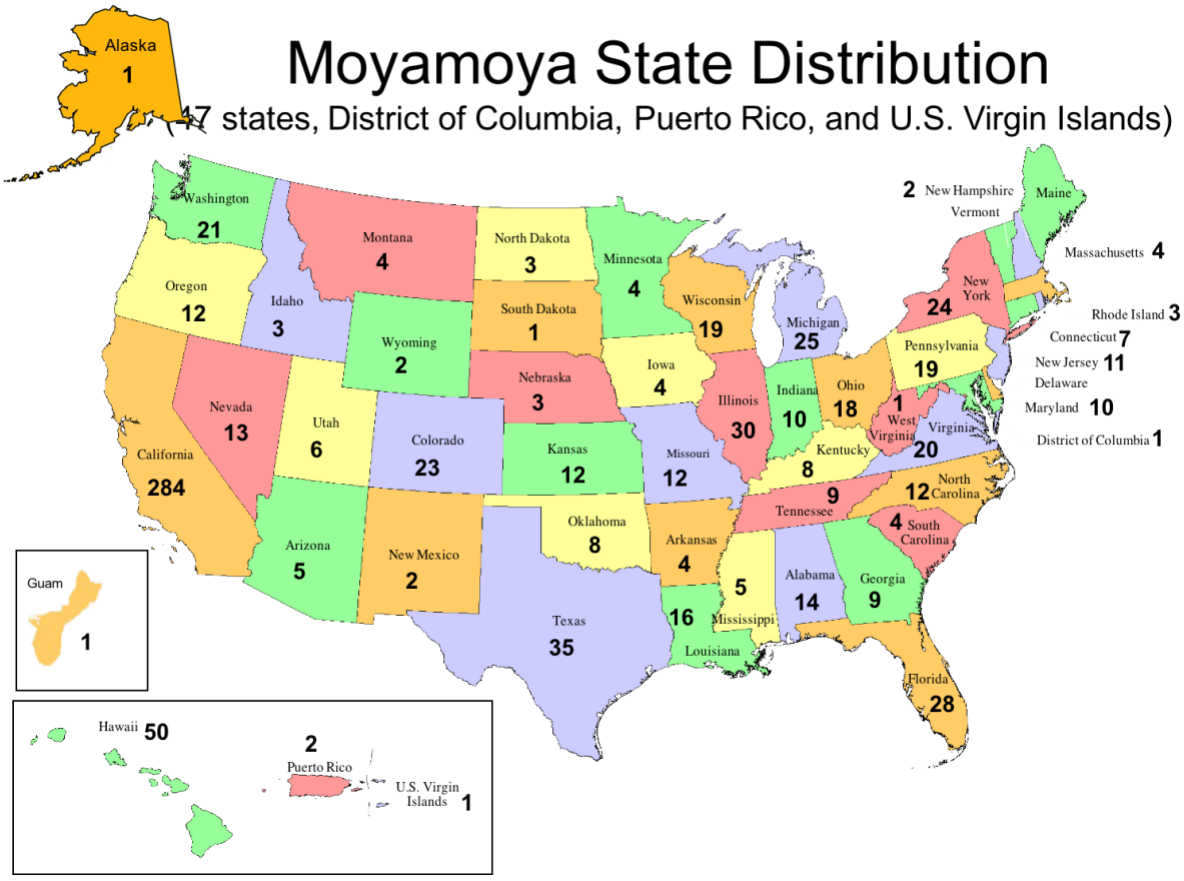


**Figure 4.4.** Distribution of moyamoya patients referred to Stanford University Medical Center for cerebral revascularisations (1991-2015).

### 4.3.2 Paediatric and Adult MMD

205 paediatric patients (mean age 11 years, 58.5% females) were compared to 564 adults (mean age 41, range 19-69, 75.9% females) (Table 3.1). There is a higher proportion of non-caucasian, non-asian MMD patients in the paediatric group (21.5%) compared to 11.3% in adults. Moyamoya syndrome is more commonly associated with paediatric patients (26.8%) compared to 6.6% in adults, while diabetes, hyperlipidaemia is more common in the adults ($p<0.0001$). The mode of presentation is similar between the 2 groups, except a higher proportion of haemorrhagic presentation in adults (15.2% vs 7.3% in children, $p=0.004$). The baseline radiological findings are comparable between the 2 groups. Amongst the 1250 bypasses, direct bypass was done in 96% and 73% of adult and paediatric patients respectively (Figure 3.5).

Table 4.1. Comparison of the baseline demographics, associated conditions, clinical presentations, radiological findings and types of bypass between paediatric and adult MMD patients.

| | | Paediatric | | Adult | | |
|---|---|---|---|---|---|---|
| | | No. of Patients | Column % | No. of Patients | Column % | p-value |
| **Gender** | **Female** | 120 | 58.5% | 428 | 75.9% | <0.0001* |
| | **Male** | 85 | 41.5% | 136 | 24.1% | |
| **Ethnicity** | **Caucasian** | 99 | 48.3% | 313 | 55.5% | 0.002* |
| | **Asian** | 62 | 30.2% | 187 | 33.2% | |
| | **Others** | 44 | 21.5% | 64 | 11.3% | |
| **FHx MMD** | **No** | 31 | 86.1% | 84 | 79.2% | 0.364 |
| | **Yes** | 5 | 13.9% | 22 | 20.8% | |
| **Moyamoya Syndrome** | **No** | 150 | 73.2% | 527 | 93.4% | <0.0001* |
| | **Yes** | 55 | 26.8% | 37 | 6.6% | |
| **Downs Syndrome** | **No** | 189 | 92.2% | 557 | 98.8% | <0.0001* |
| | **Yes** | 16 | 7.8% | 7 | 1.2% | |
| **Neurofibromatosis 1** | **No** | 193 | 94.1% | 561 | 99.5% | <0.0001* |
| | **Yes** | 12 | 5.9% | 3 | 0.5% | |
| **Sickle cell disease** | **No** | 203 | 99.0% | 560 | 99.3% | 0.71 |
| | **Yes** | 2 | 1.0% | 4 | 0.7% | |
| **Dwarfism** | **No** | 197 | 96.1% | 563 | 99.8% | <0.0001* |
| | **Yes** | 8 | 3.9% | 1 | 0.2% | |
| **Diabetes** | **No** | 146 | 95.4% | 372 | 83.4% | <0.0001* |
| | **Yes** | 7 | 4.6% | 74 | 16.6% | |
| **Hyperlipidemia** | **No** | 145 | 96.7% | 312 | 71.1% | <0.0001* |
| | **Yes** | 5 | 3.3% | 127 | 28.9% | |
| **Presentations** | | | | | | |
| **Haemorrhagic** | **No** | 190 | 92.7% | 478 | 84.8% | 0.004* |
| | **Yes** | 15 | 7.3% | 86 | 15.2% | |
| **Ischaemic** | **No** | 42 | 20.5% | 95 | 16.8% | 0.243 |
| | **Yes** | 163 | 79.5% | 469 | 83.2% | |
| **Headache** | **No** | 116 | 56.6% | 299 | 53.0% | 0.38 |
| | **Yes** | 89 | 43.4% | 265 | 47.0% | |
| **Seizure** | **No** | 179 | 87.3% | 500 | 88.7% | 0.61 |
| | **Yes** | 26 | 12.7% | 64 | 11.3% | |
| **Radiological Findings** | | | | | | |
| **suzuki_stage** | **2** | 8 | 4.0% | 20 | 3.6% | 0.098 |
| | **3** | 62 | 31.3% | 232 | 42.0% | |
| | **4** | 112 | 56.6% | 267 | 48.4% | |
| | **5** | 16 | 8.1% | 32 | 5.8% | |
| | **6** | 0 | 0.0% | 1 | 0.2% | |
| **DSA score** | **1** | 4 | 2.0% | 12 | 2.2% | 0.56 |
| | **2** | 144 | 73.5% | 426 | 77.0% | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | **3** | 48 | 24.5% | 115 | 20.8% | |
| **mMRI score** | **0** | 51 | 25.8% | 102 | 18.5% | 0.03 |
| | **1** | 142 | 71.7% | 418 | 75.9% | |
| | **2** | 5 | 2.5% | 31 | 5.6% | |
| **HDR score** | **0** | 42 | 27.6% | 126 | 26.1% | 0.17 |
| | **1** | 93 | 61.2% | 272 | 56.3% | |
| | **2** | 17 | 11.2% | 85 | 17.6% | |
| **Types of Surgery** | **Direct** | 157 | 76.6% | 549 | 97.3% | <0.0001* |
| **First Bypass** | **Indirect** | 48 | 23.4% | 15 | 2.7% | |

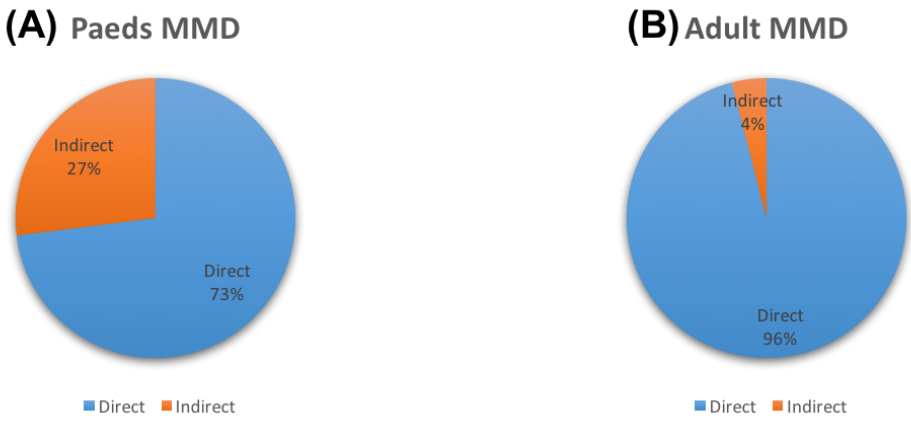


**Figure 4.5**. Distribution of bypass types between paediatric (A) and adult (B) MMD.

### *4.3.3 Stroke (ischaemic and haemorrhagic) and postop haematoma risks (within 30 days)*

80 patients (10.4%) developed ischaemic strokes within 30-days postop. Including intraparenchymal haemorrhage (IPH) and ischemic stroke risks, the combined postop stroke risk is 84/769 (10.9%). 10 patients had postop extraaxial haematoma (subdural or extradural haematoma) requiring evacuation surgery. 5 patients (0.6%) died of stroke within 30 days postop.

The 30-days ischaemic stroke risk is 7.8% (60/769) and 6.2% (29/467) after the first and second bypasses respectively. With a total of 1250 bypasses, 92

strokes (ischaemic and haemorrhagic) were recorded, leading to a 7.3% per procedure stroke risk.

Univariate analysis of potential risk factors associated with 30-days postoperative ischaemic and haemorrhagic stroke was shown in Table 3.2.

Table 4.2. Univariate analysis of risk factors associated with 30-days postoperative ischaemic and haemorrhagic stroke

| | | 30Day Postop Ischaemic / Heamorrhagic CVA | | | | |
|---|---|---|---|---|---|---|
| | | No | | Yes | | p-value |
| | | No. of Patients | Row % | No. of Patients | Row % | |
| **Age Category** | **<18 yr** | 194 | 94.6% | 11 | 5.4% | 0.001* |
| | **19-39 yr** | 262 | 90.7% | 27 | 9.3% | |
| | **40- 59 yr** | 213 | 83.5% | 42 | 16.5% | |
| | **>60 yr** | 16 | 80.0% | 4 | 20.0% | |
| **Gender** | **Female** | 483 | 88.1% | 65 | 11.9% | 0.189 |
| | **Male** | 202 | 91.4% | 19 | 8.6% | |
| **Ethnicity** | **Caucasian** | 373 | 90.5% | 39 | 9.5% | 0.257 |
| | **Asian** | 220 | 88.4% | 29 | 11.6% | |
| | **Others** | 92 | 85.2% | 16 | 14.8% | |
| **Family Hx of MMD** | **No** | 104 | 90.4% | 11 | 9.6% | 0.324 |
| | **Yes** | 26 | 96.3% | 1 | 3.7% | |
| **Presentations** | | | | | | |
| **Haemorrhagic** | **No** | 589 | 88.2% | 79 | 11.8% | 0.039* |
| | **Yes** | 96 | 95.0% | 5 | 5.0% | |
| **Ischaemic** | **No** | 132 | 96.4% | 5 | 3.6% | 0.003* |
| | **Yes** | 553 | 87.5% | 79 | 12.5% | |
| **Headache** | **No** | 360 | 86.7% | 55 | 13.3% | 0.025* |
| | **Yes** | 325 | 91.8% | 29 | 8.2% | |
| **Seizure** | **No** | 604 | 89.0% | 75 | 11.0% | 0.765 |
| | **Yes** | 81 | 90.0% | 9 | 10.0% | |
| **PMHx** | | | | | | |
| **Diabetes** | **No** | 469 | 90.5% | 49 | 9.5% | <0.0001* |
| | **Yes** | 61 | 75.3% | 20 | 24.7% | |
| | **Unknown** | 155 | 91.9% | 15 | 9.1% | |
| **Hyperlipidemia** | **No** | 415 | 90.8% | 42 | 9.2% | 0.004* |
| | **Yes** | 108 | 81.8% | 24 | 18.2% | |
| | **Unknown** | 162 | 90.0% | 18 | 10.0% | |
| **Moyamoya Syndrome** | **No** | 603 | 89.1% | 74 | 10.9% | 0.986 |
| | **Yes** | 82 | 89.1% | 10 | 10.9% | |
| **Downs Syndrome** | **No** | 667 | 89.4% | 79 | 10.6% | 0.091 |
| | **Yes** | 18 | 78.3% | 5 | 21.7% | |
| **Neurofibromatosis** | **No** | 670 | 88.9% | 84 | 11.1% | 0.171 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | **Yes** | 15 | 100.0% | 0 | 0.0% | |
| **Dwarfism** | **No** | 676 | 88.9% | 84 | 11.1% | 0.291 |
| | **Yes** | 9 | 100.0% | 0 | 0.0% | |
| **Radiological Findings** | | | | | | |
| **Suzuki stage** | **2** | 28 | 100.0% | 0 | 0.0% | <0.0001* |
| | **3** | 276 | 93.9% | 18 | 6.1% | |
| | **4** | 327 | 86.3% | 52 | 13.7% | |
| | **5** | 34 | 70.8% | 14 | 29.2% | |
| | **6** | 1 | 100.0% | 0 | 0.0% | |
| **DSA score** | **1** | 16 | 100.0% | 0 | 0.0% | <0.0001* |
| | **2** | 526 | 92.3% | 44 | 7.7% | |
| | **3** | 123 | 75.5% | 40 | 24.5% | |
| **mMRI score** | **0** | 148 | 96.7% | 5 | 3.3% | <0.0001* |
| | **1** | 506 | 90.4% | 54 | 9.6% | |
| | **2** | 12 | 33.3% | 24 | 66.7% | |
| **HDR score** | **0** | 166 | 98.8% | 2 | 1.2% | <0.0001* |
| | **1** | 328 | 89.9% | 37 | 10.1% | |
| | **2** | 69 | 67.6% | 33 | 32.4% | |
| **Types of Surgery First Bypass** | **Direct** | 644 | 91.2% | 62 | 8.8% | 0.046* |
| | **Indirect** | 62 | 98.4% | 1 | 1.6% | |

#### 4.3.3.1 Basic Demographics

Younger age groups are associated with lower postop stroke risk, 5.4% (11/205) in paediatric cohort, compared with 12.9% (73/564) in adults. Furthermore, the older the age category, the higher the postop stroke risk, 9.3% in 19-39 years, 16.5% in 40-59 years, and 20% in the above 60 years (p=0.001).

Although there is a trend for female to slightly higher postop stroke risk (11.9% female vs 8.6% male), this difference is not statistically significant. Similar trend is also noted for non-Asian, non-Caucasian ethnicity, and for patients with family history of MMD.

#### 4.3.3.2 Clinical Presentations and Past Medical History

Patients with ischaemic presentations (TIA or stroke) are associated with a higher postop stroke risk (12.5%) compared to patients with non-ischaemic

presentation (3.6%). Similarly, patients who are diabetic and hyperlipidaemic also have higher postop stroke risk.

Interestingly, patients with haemorrhagic or headache presentation are associated with a lower postop stroke risk. Only 5% of patients with haemorrhagic presentation developed postop stroke compared to 11.8% of those with non-haemorrhagic presentation (p=0.039).

Despite the common belief that patients with Moyamoya syndrome have higher postop stroke risk, no such difference was detected in this cohort (10.9% in each group). Downs syndrome patients however, trended towards higher postop stroke risk (21.7%, p=0.091).

#### 4.3.3.3 Radiological Findings

All the radiological scores (Suzuki stage, Angio score, mMRI score, HDR score) are highly correlated with postoperative stroke risks, all with statistically significant p-value <0.0001. Patients with recent strokes prior to bypass (DWI +ve infarct within 1 month of surgery, mMRI score 2) have a 66.7% postop stroke risk, compared to 3.3% of patients with normal MRI findings, and 9.6% of patients with old strokes.

Patients with steal phenomenon (HDR score 2) on CVRC studies have a 32.4% postop stroke risk, compared to patients with good augmentation on heamodynamic studies (1.2%). Furthermore, patients with impaired cerebrovascular reserve (HDR score 1) during acetazolamide challenge are also associated with higher postop stroke risk (10.1%).

Severe stenosis of ICA or MCA on DSA findings is currently not accountable based on the DSA scoring. Apart from ICIC (DSA score 2) and ECIC (DSA score 3) collateralisation, it is likely that there is a statistical significant difference for ICA or MCA with severe stenosis and increased postop stroke risk after direct bypass.

#### 4.3.3.4 Types of surgery (Direct vs Indirect)

With 1250 bypasses performed in 769 patients, some patients have different operations for different hemispheres. When we assess the risk of surgery types – direct or indirect bypass during the first operation, and correlate with the postop per procedure stroke risk, 8.8% of direct bypass is associated with postop stroke compared to 1.6% of indirect bypass (p=0.046). Despite the univariate analysis showing a difference in postop stroke risk after direct or indirect bypass, when accounted for confounding factors using logistic regression analysis, such difference is no longer significant (p=0.273, Table 4.3).

#### *4.3.3.5 Logistic Regression Analysis for 30 Days Stroke Risk*

To address the issue of confounding factors, logistic regression analysis was performed (Table 3.3), and only older age, DSA score, mMRI score, HDR score, are clearly associated with higher postop stroke risks. Haemorrhagic presentation is still showing a trend towards lower stroke risk (OR 0.279, 95% CI 0.069-1.124, p=0.072). Ischaemic presentation is associated with a higher postop stroke risks, a finding not unexpected considering the close relationship with mMRI findings.

Table 4.3. Logistic Regression Analysis for risk factors associated with 30-days postoperative stroke (ischaemic and haemorrhagic) risk

| Variable | Coefficient | Standard Error | P-value | Odds Ratio | 95% Confidence Interval |
|---|---|---|---|---|---|
| **Age** | 1.295 | 0.579 | 0.025* | 3.650 | 1.173-11.359 |
| **Haemorrhagic presentation** | -1.277 | 0.711 | 0.072 | 0.279 | 0.069-1.124 |
| **Ischaemic presentation** | 2.172 | 1.072 | 0.043 | 8.774 | 1.074-71.711 |
| **Diabetes** | 0.527 | 0.479 | 0.271 | 1.693 | 0.663-4.327 |
| **Hyperlipidaemia** | 0.025 | 0.435 | 0.955 | 1.025 | 0.437-2.403 |
| **Suzuki Stage** | 0.335 | 0.685 | 0.625 | 1.398 | 0.365-5.349 |
| **DSA score** | 1.294 | 0.415 | 0.002* | 3.648 | 1.618-8.222 |
| **mMRI score** | 2.740 | 0.765 | <0.0001* | 15.494 | 3.462-69.335 |
| **HDR score** | 2.866 | 0.805 | <0.0001* | 17.559 | 3.626-85.037 |
| **Surgery Types** | -1.227 | 1.119 | 0.273 | 0.293 | 0.033-2.631 |

### *4.3.4 TNE risks (within 30 days)*

TNE was recorded in 20% (154/769) of patients post revascularisation, and the rate is consistent regardless of gender, ethnicity, mode of presentations, diabetic, hyperlipidaemic (Table 3.4). It is interesting to note that paediatric cohort has a lower postop TNE risk (11.2%) compared to adults (23.2%, 131/564). Similar lower postop TNE risk is also seen in patients with moyamoya syndrome. For the various radiological scores, although there is a trend towards higher TNE risk with increasing scores, such findings are not statistically significant. Direct surgery is also associated with a non-statistically significant higher postop TNE risk (20.8% for direct surgery vs 11.1% for indirect surgery, p=0.065).

Table 4.4. Univariate analysis of risk factors associated with 30-days postoperative Transient Neurological Episodes (TNE)

| | | 30Day Postop TNE | | | | |
|---|---|---|---|---|---|---|
| | | No | | Yes | | |
| | | No. of Patients | Row % | No. of Patients | Row % | P-value |
| **Age Category** | **<18 yr** | 182 | 88.8% | 23 | 11.2% | 0.002* |
| | **19-39 yr** | 216 | 74.7% | 73 | 25.3% | |
| | **40-59 yr** | 201 | 78.8% | 54 | 21.2% | |
| | **>60 yr** | 16 | 80.0% | 4 | 20.0% | |
| **Gender** | **Female** | 440 | 80.3% | 108 | 19.7% | 0.729 |
| | **Male** | 175 | 79.2% | 46 | 20.8% | |
| **Ethnicity** | **Caucasian** | 327 | 79.4% | 85 | 20.6% | 0.857 |
| | **Asian** | 202 | 81.1% | 47 | 18.9% | |
| | **Others** | 86 | 79.6% | 22 | 20.4% | |
| **Family Hx of MMD** | **No** | 75 | 65.2% | 40 | 34.8% | 0.61 |
| | **Yes** | 19 | 70.4% | 8 | 29.6% | |
| **Presentations** | | | | | | |
| **Haemorrhagic** | **No** | 533 | 79.8% | 135 | 20.2% | 0.744 |
| | **Yes** | 82 | 81.2% | 19 | 18.8% | |
| **Ischaemic** | **No** | 118 | 86.1% | 19 | 13.9% | 0.047* |
| | **Yes** | 497 | 78.6% | 135 | 21.4% | |
| **Headache** | **No** | 336 | 81.0% | 79 | 19.0% | 0.458 |
| | **Yes** | 279 | 78.8% | 75 | 21.2% | |
| **Seizure** | **No** | 543 | 80.0% | 136 | 20.0% | 0.995 |
| | **Yes** | 72 | 80.0% | 18 | 20.0% | |
| **PMHx** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Diabetes** | **No** | 418 | 80.7% | 100 | 19.3% | 0.168 |
| | **Yes** | 60 | 74.1% | 21 | 25.9% | |
| | **Unknown** | 137 | 80.6% | 33 | 19.4% | |
| **Hyperlipidemia** | **No** | 365 | 79.9% | 92 | 20.1% | 0.762 |
| | **Yes** | 107 | 81.1% | 25 | 18.9% | |
| | **Unknown** | 143 | 79.4% | 37 | 20.6% | |
| **Moyamoya Syndrome** | **No** | 534 | 78.9% | 143 | 21.1% | 0.039* |
| | **Yes** | 81 | 88.0% | 11 | 12.0% | |
| **Downs Syndrome** | **No** | 595 | 79.8% | 151 | 20.2% | 0.396 |
| | **Yes** | 20 | 87.0% | 3 | 13.0% | |
| **Neurofibromatosis** | **No** | 601 | 79.7% | 153 | 20.3% | 0.192 |
| | **Yes** | 14 | 93.3% | 1 | 6.7% | |
| **Dwarfism** | **No** | 607 | 79.9% | 153 | 20.1% | 0.501 |
| | **Yes** | 8 | 88.9% | 1 | 11.1% | |
| | | | | | | |
| **Radiological Findings** | | | | | | |
| **Suzuki stage** | **2** | 24 | 85.7% | 4 | 14.3% | 0.496 |
| | **3** | 237 | 80.6% | 57 | 19.4% | |
| | **4** | 300 | 79.2% | 79 | 20.8% | |
| | **5** | 34 | 70.8% | 14 | 29.2% | |
| | **6** | 1 | 100.0% | 0 | 0.0% | |
| **DSA score** | **1** | 14 | 87.5% | 2 | 12.5% | 0.632 |
| | **2** | 455 | 79.8% | 115 | 20.2% | |
| | **3** | 127 | 77.9% | 36 | 22.1% | |
| **mMRI score** | **0** | 131 | 85.6% | 22 | 14.4% | 0.051 |
| | **1** | 441 | 78.8% | 119 | 21.3% | |
| | **2** | 25 | 69.4% | 11 | 30.6% | |
| **HDR score** | **0** | 135 | 80.4% | 33 | 19.6% | 0.18 |
| | **1** | 290 | 79.5% | 75 | 20.5% | |
| | **2** | 73 | 71.6% | 29 | 28.4% | |
| | | | | | | |
| **Types of Surgery** | **Direct** | 559 | 79.2% | 147 | 20.8% | 0.065 |
| **First Bypass** | **Indirect** | 56 | 88.9% | 7 | 11.1% | |

### *4.3.5 Long Term Outcome*

#### *4.3.5.1 Questionnaire study*

Completed questionnaires were received and available for analysis on 391 patients, with a mean follow up of 6.3 years (6 months to 25 years). Of the returned questionnaires, 277 patients reported preoperative headache, 234 (84%) experienced improvement in their headache post revascularisation. 108 patients were noted to have hypertension preoperatively, and in selective

patients antihypertensives were either discontinued (18 patients) or dosage reduced (47 patients) postoperatively (Figure 4.6).

83% (325/391) of patients remained in employment or education in the long term follow up. Excluding children and adults with learning difficulty, 87% (303/348) of patients are self-caring and 75% (260/348) are living independently or has family (Figure 3.6).

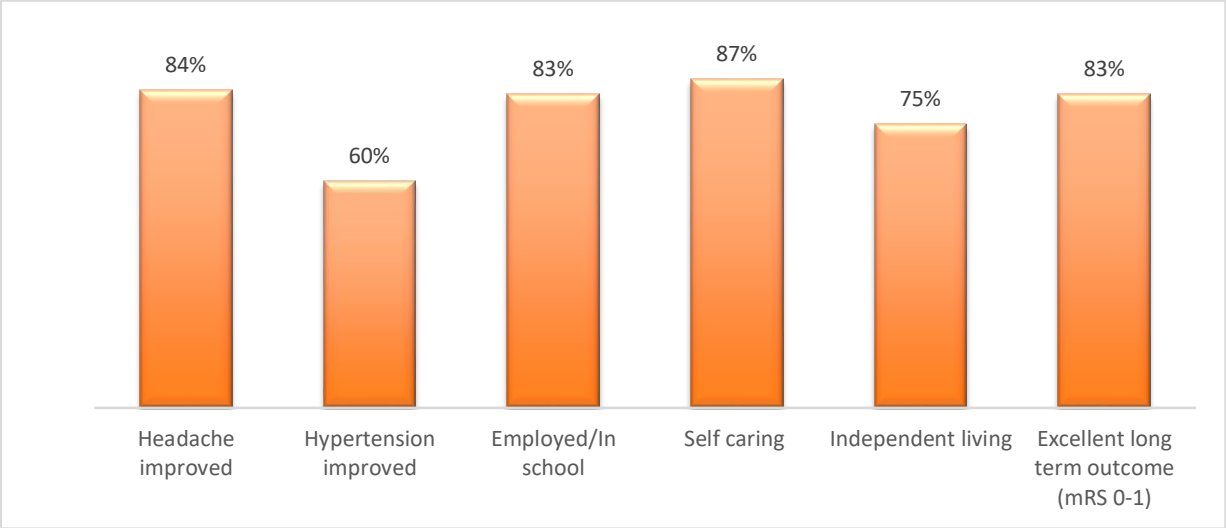


**Figure 4.6.** Analysis of the long term physical, social, functional outcome of MMD patients with returned questionnaires.

### *4.3.5.2 Long Term Stroke Risk*

In 741 patients, with a mean follow up of 7.3 years (0.5-26 years), 32 patients developed strokes (20 ischaemic strokes, 12 haemorrhagic strokes). Therefore, the long term estimated stroke risk is 0.59%/patient year.

According to the Kaplan meier analysis, the estimated mean stroke free interval for the entire cohort was 23.8 years (95% CI 21.3-24.7 years) (Figure 4.7).

When stratifying the long term stroke risk with different age groups, 1% of paediatric cohort (≤18 years) compared to 5% of the adult patients developed strokes (p=0.003). Furthermore, amongst the adult patients, 4% of 19-39 year-old compared to 8% of >40 year-old developed long term strokes. The estimated mean stroke free interval was 24.8 years, 19.9 years, 21.9 years and 10.3 years for ≤18, 19-39, 40-59, ≥60 age categories respectively (log rank p=0.001, Figure 4.8).

30-day stroke is not a risk factor for long term stroke. Based on our analysis, 8.5% (4/47) of patients with 30-day stroke developed long term stroke, compared to 3.8% (27/706) of patients without 30-day stroke, but this difference was not statistically significant (p=0.121).

The types of bypasses were not associated with long term stroke risk in the paediatric group (age ≤18 years). For the adult population, 5%(27/541) of patients with direct bypass had long term stroke, compared with 13.3% (2/15) of patients with indirect bypass, but this difference was not statistically significant (p=0.181).

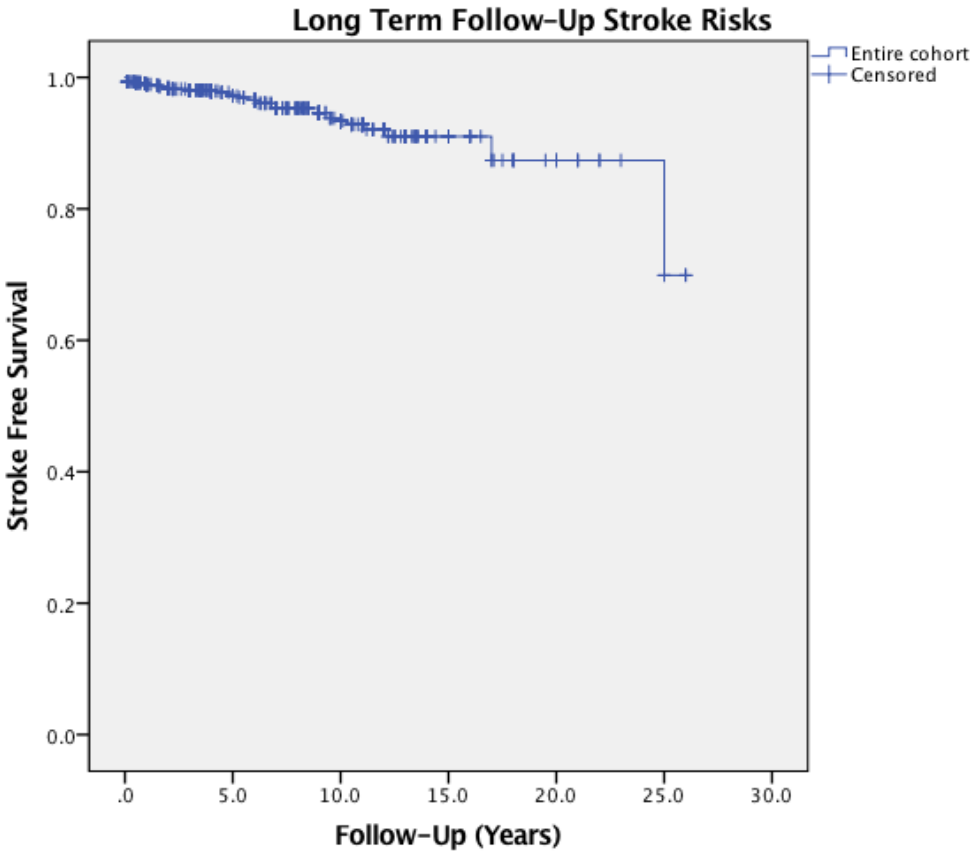


**Figure 4.7**. Kaplan Meier analysis for long term stroke risk in MMD patients post revascularisation, with 4% stroke risk at the end of follow up.

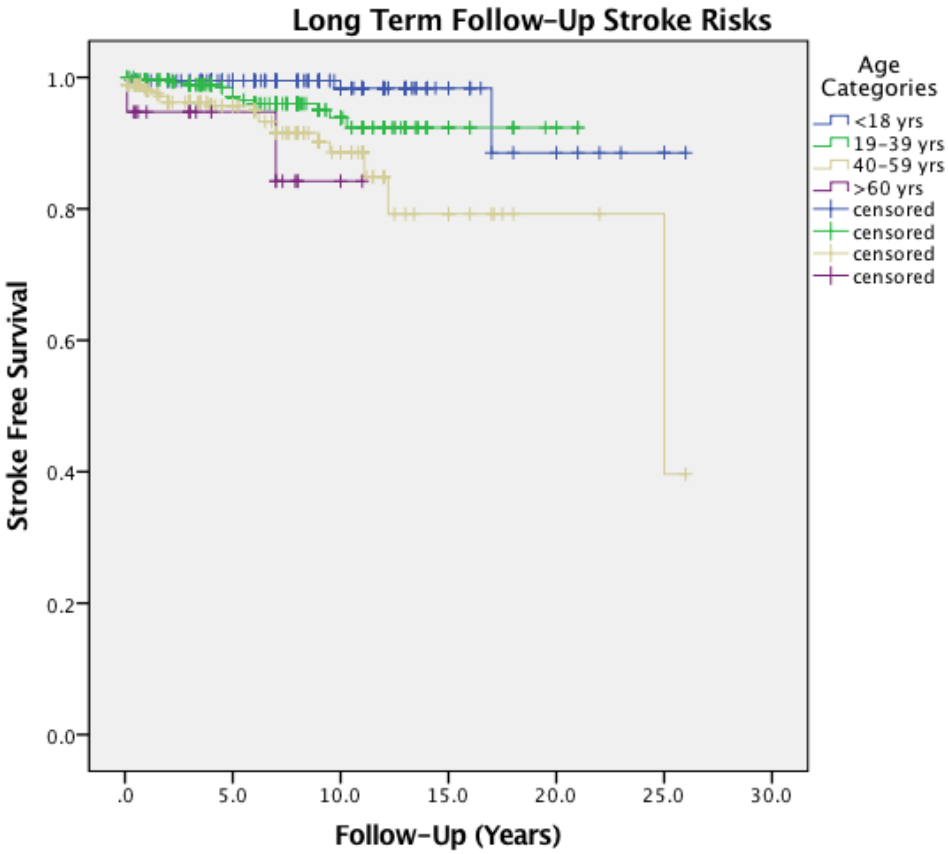


**Figure 4.8.** Kaplan Meier curves comparing the long term stroke risks in different age categories. The estimated mean stroke free interval is 24.8 years, 19.9 years, 21.9 years and 10 years for <18, 19-39, 40-59, >60 age categories respectively (log rank p=0.001). Furthermore, 1% of paediatric cohort (<18 years) 4% of 19-39 year-old compared to 8% of >40 year-old developed long term strokes.

#### *4.3.5.3 Long Term* mRS outcome

Preoperatively, majority of MMD patients (53.7%) had mRS 2, and 25.6% mRS 0-1. Postoperatively, at the latest follow-up (mean 7 years, 0.5-25 years), 75% of patients are mRS 0-1, i.e. normal or with very mild symptoms but able to carry out all duties and activities (Figure 3.9). At the last follow up, 40 deaths were recorded, and 13 (1.8%) were stroke related.

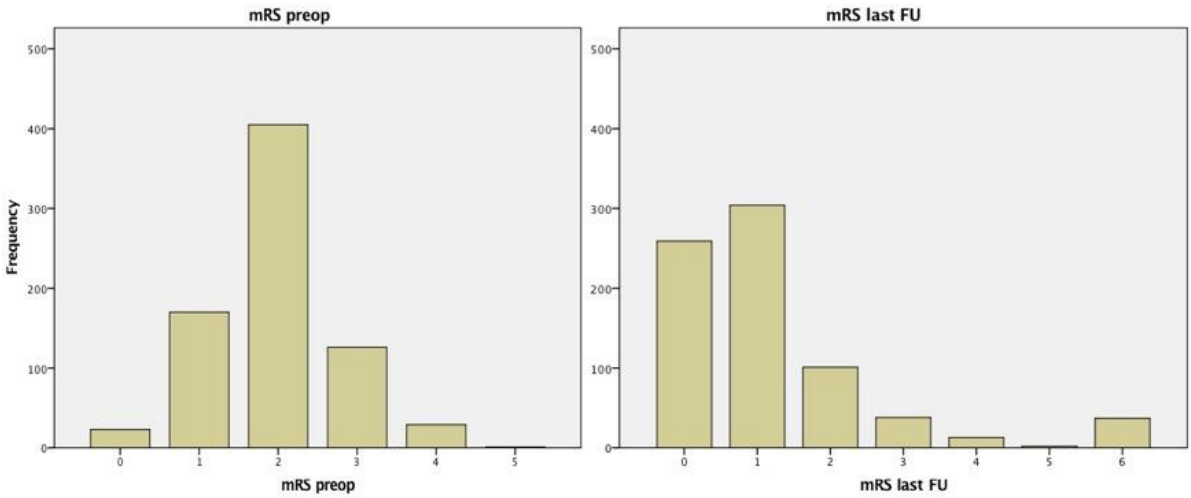


Figure 4.9 Comparison of pre and postoperative mRS at last follow up for 741 MMD patients post revascularisations.

#### 4.3.5.4 Angiographic Outcome

With a mean angiographic follow up of 3 years (range 0.5-20 years), 99% of the bypasses were patent. In the very few occluded direct STA grafts, indirect collateralisation developed to supply the territory at risk.

#### 4.3.5.5 Repeat Revascularisation

Of the MMD patients who underwent initial revascularisation within our own institution, 17 needed repeat revascularisation. The repeat revascularisation rate was 4% for indirect and 1% for direct bypasses (p=0.03). Together with patients who underwent initial revascularisation from other institutions, but have persistent or new symptoms due to inadequate collateralisation, in total 57 patients underwent repeat revascularisation of the same hemisphere. This formed be the subject of another study and presented in Chapter 6.

### 4.4 Discussion

This is the largest study of MMD patients post revascularisation from the western population, which reported the short and long term outcome of 769 patients undergoing 1250 revascularisations, with a mean follow-up of 7.3

years. 53% are Caucasian, 32% Asian, 7% Hispanic, and 5% African-American. The mean age of presentation was 31.9 years (range 1-68), with bimodal age distribution that peaked between 6-10 years and between 31-40 years, and 2.4:1 for female/male ratio.

Comparing the paediatric and adult MMD groups, there is a higher proportion of non-caucasian, non-asian MMD patients (21.5% in paeds vs 11.3% in adults), and moyamoya syndrome is more commonly associated with paediatric patients (26.8%) compared to 6.6% in adults. Most the patients (82%) have ischaemic presentations (TIAs or ischaemic strokes), while haemorrhagic presentation is more commonly seen in adults (15%) compared to 7% in children. Headache was recorded in 46% of patients. In the questionnaire study, 84% reported resolution or improvement in their headache postop.

Based on previous natural history study on patients with MMD, the 5-year risk of recurrent ipsilateral stroke after symptoms onset and angiographic diagnosis, was 65% and 27% respectively (Hallemeier et al., 2006b). The only RCT in MMD – Japan Adult Moyamoya (JAM) Trial, comparing surgical revascularisation and medical management, showed 8% rehaemorrhage and stroke risks per year for patients with conservative management (Miyamoto et al., 2014a). Therefore, we advocate surgical treatment for MMD patients when appropriate.

In this study, 96% and 73% of the adults and paediatric cohort respectively underwent direct revascularisation. There is still ongoing debate on the safety and efficacy of the various revascularisation procedure, with mixed results from the literature. Many studies are suggesting that direct bypass is superior (Kazumata et al., 2014b, Nakashima et al., 1997, Houkin et al., 1996), whereby the main advantages include the establishment of augmented flow immediately following surgery, a more consistent and higher extent of angiographic collateralization (Arias et al., 2015a, Matsushima et al., 1998), superiority in restoring cerebrovascular reserve capacity post-bypass (Czabanka et al., 2011a), more patients with symptomatic improvement, less recurrent ischemic risk and more patients with stroke-free survival (Kazumata et al., 2014b, Bang

et al., 2012, Houkin et al., 2000). However, it is technically more challenging, especially for patients with very small donor and recipient vessels. In our study, with a total of 1250 bypasses, 92 strokes (ischaemic and haemorrhagic) were recorded, leading to a 7.3% per procedure stroke risk. The postoperative stroke risks is not statistically significant between direct and indirect revascularisation after taking into account of confounding factors.

With the uni- and multivariate logistic regression analyses, multiple risk factors were associated with higher postoperative stroke risks, including older age group, higher DSA score, mMRI score, HDR score. We showed very convincingly that younger patients have lower postop stroke risks (5% in paediatric compared to 20% of over 60 years-old). Furthermore, patients with recent DWI +ve infarct within a month of surgery has the highest postop stroke risk (67% in our study), therefore we recommend delaying surgery for these patients to avoid such risks. Based on the 30-days logistic regression analysis, we plan to continue the work on predictive modelling on postop stroke risk using the various risk factors identified, and assigned the appropriate scores. This new scoring system would then be validated prospectively in another cohort of MMD post bypass patients. This information will help to stratify patients' surgical morbidity, and is invaluable in the consent, decision making process.

The TNE rate is consistent at approximately 20% regardless of gender, ethnicity, mode of presentations, comorbidities, or preoperative radiological findings. Left sided bypass had a higher TNE risk than right sided surgery (17% and 10% respectively). TNE rate was approximately 10% for children, patients with MMS, and those with indirect bypasses. The etiology is still uncertain, possibly due to global cerebral hyperperfusion (Fujimura et al., 2007a, Fujimura et al., 2009b, Kim et al., 2008) or local hypoperfusion, (Mukerji et al., 2015) after changes in cerebral blood flow to ischemic brain post revascularization. Regardless of pathophysiology, there were no DWI changes on postoperative MRI, and patients' symptoms generally resolved within 6 weeks postoperatively.

Very few studies reported long term outcome (over 5 years) of MMD patients post revascularization. In this long term study, combining the outcome from questionnaires survey, clinical reviews, radiological findings, 80% of MMD patients post revascularisation remained in excellent long term physical, social, functional wellbeing, with up to 26 years of follow-up.

In 741 patients with at least 6 months follow up (mean 7.3 years, range 0.5-26 years), 32 patients developed strokes (20 ischaemic strokes, 12 haemorrhagic strokes). Therefore, the long term estimated stroke risk is 0.59%/patient year. However, this risk is not generally applicable across all ages. According to the Kaplan meier logrank analysis, 1% of paediatric cohort (<18 years) compared to 5% of the adult patients developed strokes. The estimated stroke free interval is 20 years or more for patients younger than 60, while it is 10 years for those 60 or older (as this cohort of older patients are also prone to atherosclerotic strokes).

30-days perioperative stroke was not indicative of long term stroke risk. In paediatric group, the bypass types were not associated with long term stroke risk; whereas in the adult population, indirect bypass was associated with nearly 3 times higher long term stroke risk and also higher chance of needing repeat revascularization.

### 4.5 Conclusion

MMD typically affects children and young adults, with devastating natural history if untreated. In this surgical series, 96% and 73% of the adults and paediatric cohort respectively had direct revascularisation, with 7.3% per procedure 30-days stroke risk, and 0.6% per patient year long term stroke risk. We also identified various risk factors that are highly correlated with postoperative morbidity (age, DSA score, mMRI score, HDR score), and plan to develop the predictive modelling for future patient care.

Combining the outcome from questionnaires, clinical reviews, and radiological findings, we found 80% of MMD patients post revascularization have excellent

long-term physical, social, functional wellbeing, with up to 26 years of follow-up (mean 7.3 years). The long-term estimated stroke risk is 0.6% per patient year, with 1% of the pediatric cohort compared to 5% of the adult patients developed strokes in the long-term follow-up. The estimated stroke free interval is 20 years or more for patients younger than 60, while it is 10 years for those 60 or older (as this cohort of older patients are also prone to atherosclerotic strokes).

# CHAPTER FIVE

# VALIDATION AND APPLICATION OF A NEW GRADING SYSTEM OF MOYAMOYA DISEASE IN ADULT

## 5.1 Introduction

Based on the classification of Suzuki et al (Suzuki et al 1969), the appearance and extent of steno-occlusion, and revascularisation is divided into 6 distinct stages:
Stage 1, stenosis of the ICA;
Stage 2, initial appearance of moyamoya vessels;
Stage 3, increasing ICA stenosis and further definition of collateral vessels;
Stage 4, occlusion of circle of Willis, minimization of collateral vessels;
Stage 5, further reduction of collateral vessels; and
Stage 6, disappearance of collateral vessels.

However, purely morphological criteria as assessed by cerebral angiography do not reflect the hemodynamic status and might not correlate with clinical symptoms or with surgical treatment outcome. The new moyamoya preoperative symptomatology grading system proposed by Berlin group (Czabanka et al., 2011c) incorporated angiographic findings (DSA) and features of chronic cerebrovascular insufficiency (MRI, Xenon CT), showed good hemispheric symptoms stratification in their pilot study of 40 MMD patients. Fourteen hemispheres were graded as mild (grade I), 35 as moderate (grade II) and 31 as severe (grade III); 21% of grade I, 63% of grade II and 93% of grade III hemispheres were clinically symptomatic according to their study. It is therefore important to validate this new grading system in a larger patient cohort, in a different country, different ethnicities prior to advocating its widespread application.

To assess for surgical risk stratification, we also examined the wider application of the grading system in predicting radiological and clinical outcome after surgical revascularization. Furthermore, the present grading system graded each hemisphere separately even though they cannot be regarded as independent in a strict sense when assessing our patients holistically. Therefore, we also examined its application and correlate with our patients' clinical outcome using mRS.

## 5.2 Methods

96 MMD patients (192 hemispheres) with all 3 investigations (6 vessels-DSA, MRI brain, Xenon CT) performed preoperatively at Stanford (2007-2013) were included. Some preoperative symptoms were attributed to the corresponding hemisphere: TIA, stroke, ICH, focal seizure; while some were accounted for both hemispheres: cognitive impairment, personality change, generalized seizures, headache.

In this study, CVRC studies were performed using stable xenon-CT technology (XeCT; DDP Inc., Houston, Tex., USA), with a second scan performed 15min after administration of acetazolamide (15mg/kg body weight; Goldshield Pharmaceuticals Ltd., Croydon, UK) in order to quantify the stimulated CBF. To ensure consistency with the methods employed by the Berlin group (Czabanka et al 2013), the percentage change in CBF between baseline and the acetazolamide stimulated scans were determined using a specialized, dedicated software (XeCT System; DDP Inc.). CVRC with more than 5% decrease (that is CVRC < -5%) after acetazolamide challenge (steal phenomenon) is considered severely impaired CVRC, and this cutoff was shown to be a significant risk factor for stroke predictor in patients with symptomatic occlusive cerebrovascular disease (Webster et al 1995, Yonas et al 1993). Representative regions of interest (ROI) for MCA, ACA and PCA were studied before and after acetazolamide challenge, and for the analysis of CVRC, the area with the worst change was used.

The imaging findings were independently graded by 2 clinicians (MT, OK) according to the criteria proposed (Czabanka et al., 2011c):

- DSA (stenosis/occlusion = 1point; stenosis/occlusion + intracranial-intracranial (ICIC) collateralisation = 2 points; stenosis/occlusion + ICIC + extra-intracranial (ECIC) collateralisation = 3 points, Figure 5.1);
- MRI (no sign of ischemia/hemorrhage/atrophy = 0 point; signs of ischemia/hemorrhage/atrophy = 1 point, Figure 5.2);

- Cerebrovascular reserve capacity (CVRC > -5%, no steal = 0 point; CVRC < -5%, steal phenomenon = 2 points, Figure 5.3).

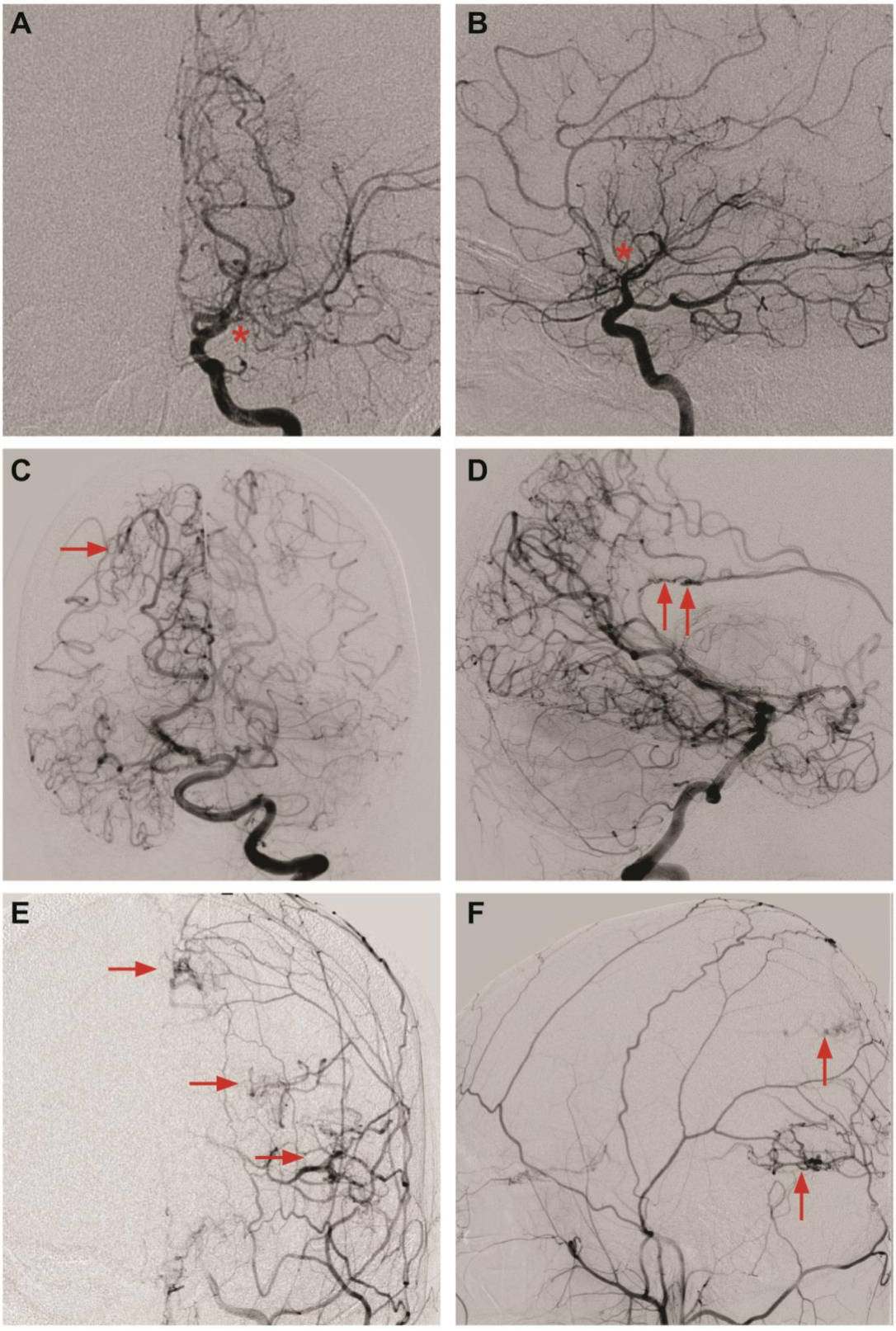

Figure 5.1 DSA Score on Berlin moyamoya symptomatology grade

A. Cerebal angiogram (internal carotid artery (ICA) injection, AP view); B. Cerebral angiogram (ICA injection, lateral view) showing early steno-occlusion of distal ICA, proximal MCA with moyamoya vessels formation (asterisks). DSA score = 1point.
C. Cerebral angiogram (vertebral artery injection, AP view) showing PCA to MCA collateralization (black arrow); D. Cerebral angiogram (verterbral artery injection, lateral view) showing PCA to pericallosal collateralization (black arrows). These are types of intracranial-intracranial (ICIC) collateralizations. DSA = 2 points.
E. Cerebral angiogram (common carotid artery (CCA) injection, AP view); F. Cerebral angiogram (CCA injection, lateral view) showing extracranial-intracranial (ECIC) collateralization via superficial temporal arteries and occipital arteries (block arrows). DSA = 3 points.

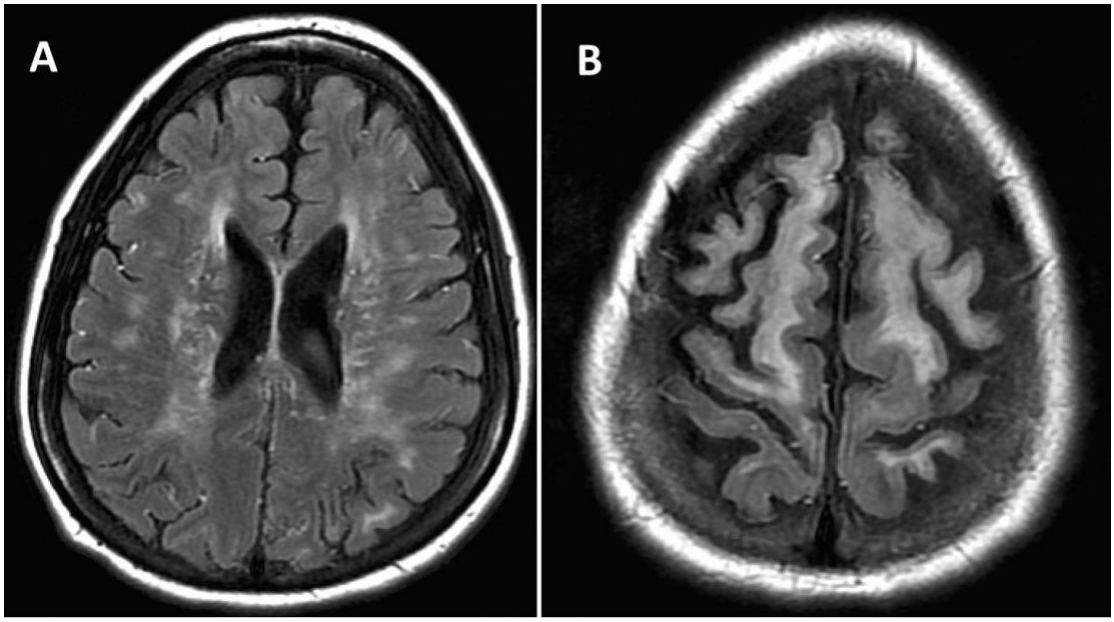


Figure 5.2. MRI score on Berlin moyamoya symptomatology grade

A. MRI brain, axial slices, fluid-attenuated inversion recovery (FLAIR) sequence showing periventricular ischemic changes. MRI = 1 point.
B. MRI brain (axial, FLAIR) showing bilateral anterior cerebral artery territories ischemia. MRI = 1 point.

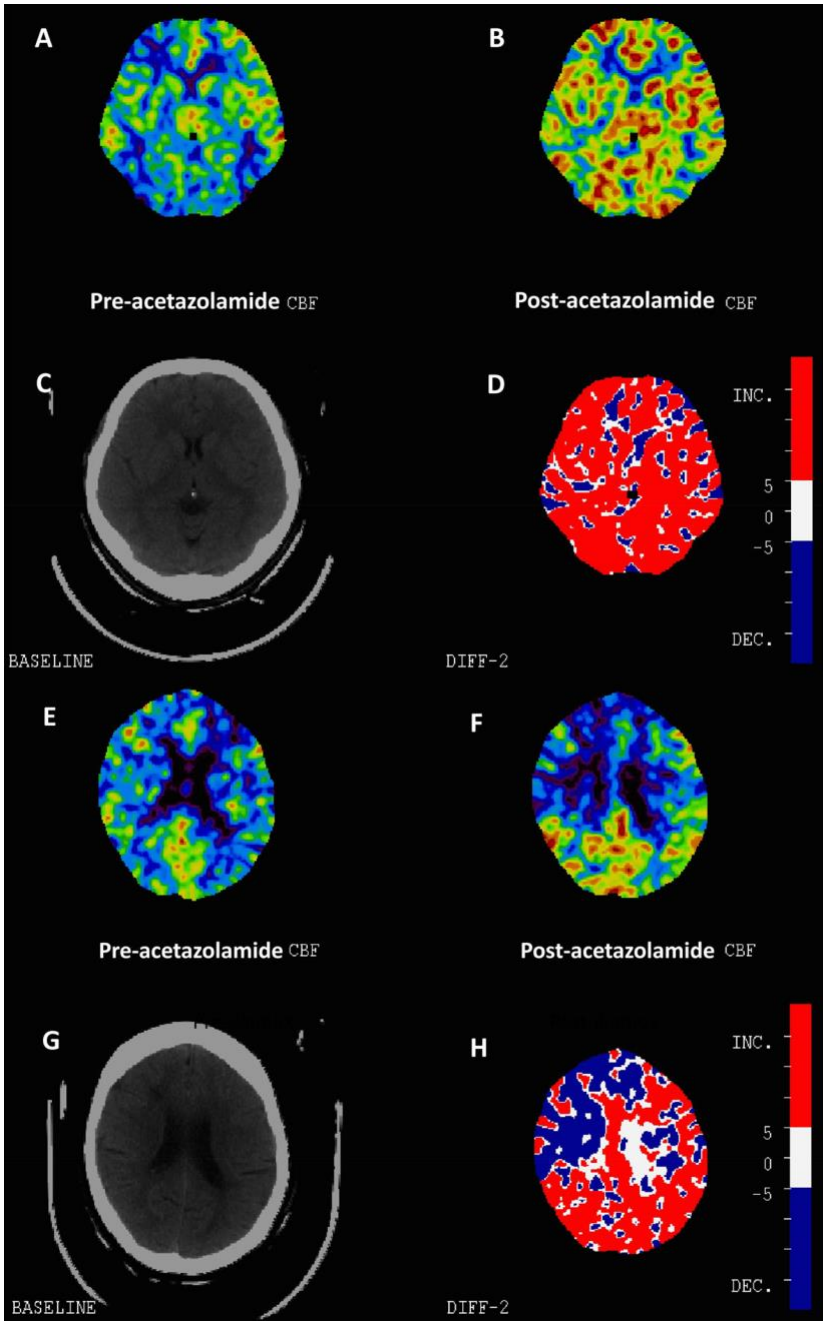


Figure 5.3. Xenon CT to assess cerebrovascular reserve capacity

A. Pre-acetazolamide CBF measurement using stable xenon-CT technology, B. Post-acetazolamide CBF on the corresponding axial slice after administration of 15mg/kg body weight of acetazolamide to calculate stimulated CBF. C. Baseline acquisitions of CT brain slices to ensure no underlying infarction. D. A specialized, dedicated software (XeCT System; DDP Inc) is used to determine the percentage difference of CBF pre- and post- acetazolamide challenge. Red color corresponds with over 5% CBF increase, white color corresponds with no CBF

changes (+/- 5%), blue corresponds with over 5% CBF decrease (steal phenomenon). Overall red in the axial slice, CVRC = 0 point.

E. A 65 year-old MMD patient with worsening cognitive impairment. Pre-acetazolamide CBF measurement using stable xenon-CT technology, F. Post-acetazolamide CBF on the corresponding axial slice, where increased CBF was mainly noted in the posterior circulation. G. Baseline acquisitions of CT brain slices to ensure no underlying infarction. H. A specialized, dedicated software (XeCT System; DDP Inc) is used to determine the percentage difference of CBF pre- and post-acetazolamide challenge, where steal phenomenon was noted in bilateral MCA territories, worse on the right. CVRC = 2 points.

MMD grade I referred to 1-2 points, grade II to 3-4 points, grade III to 5-6 points. Patients' mRS score (preop, postop, at last follow up), postop infarct (radiological, clinical) were collected and statistical correlation performed using SPSS software.

To correlate the grading system with patients as individuals (instead of per hemisphere) the highest score was assigned (if both hemispheres were differently affected), and mRS 0-1 was considered excellent outcome.

### 5.3 Results

157 direct STA-MCA bypass procedures were performed on 96 adult patients (66 females, 30 males, mean age 40.6 years (range 18-65), with a mean follow up of 52 months (range 1 – 90 months). Preoperative symptomatic hemispheres included 129 with ischemia (TIAs, TIAs with choreiform movement or strokes), 14 with intracranial hemorrhages, 24 with cognitive impairment, 8 with seizures, and 34 with headache.

On the angiographic (DSA) findings, of the 192 hemispheres studied, 25 (13%) showed early ICA steno-occlusive (Figure 5.1A, 4.1B) without ICIC or ECIC collateralisation, 120 (62.5%) showed ICIC collateralization (Figure 5.1C,

5.1D), and 47 (24.5%) showed ECIC collateralization (Figure 5.1E, 5.1F). With increasing angiographic scores, increasing proportion of symptomatic hemispheres were correlated. 2/25 (8%) of hemispheres without ICIC or ECIC collateralization were symptomatic, compared with 107/120 (89%) of hemispheres with ICIC collateralization. When ECIC collateralization occurred, all the hemispheres were symptomatic (Table 5.1).

55 hemispheres showed no ischemic or hemorrhagic changes on the MRI, but despite that 49% (27/55) of the hemispheres were symptomatic. When ischemic or hemorrhagic changes were detected on the MRI, 94% (129/137) of the hemispheres were symptomatic (Table 5.1, Figure 5.2).

When assessing CVRC using Xenon CT with and without acetazolamide, 40% (77/192) of the hemispheres showed steal phenomena, and all of them were symptomatic hemispheres (Table 5.1, Figure 5.3).

DSA, MRI and CVRC were independent factors associated with the occurrence of clinical symptoms (when analysed individually or in the combined grading system, $p<0.0001$). Based on the Berlin grading system, 45 hemispheres were graded as mild (grade I), 71 as moderate (grade II), 76 as severe (grade III); 33% of grade I, 92% of grade II, 100% of grade III hemispheres were clinically symptomatic ($p<0.0001$) (Table 5.1).

When correlating with postoperative outcome, 2% (1/45) of grade I, 11% (8/71) of grade II, 20% (15/76) of grade III hemispheres showed postoperative radiological DWI positive ischemic changes or hemorrhage on MRI ($p=0.018$). Although not statistically significant, a strong trend was also found when correlating with clinical postoperative stroke (0% of grade I, 1.4% of grade II, 6.6% of grade III hemisphere patients had clinical postop deficits associated with a new DWI positive acute infarct or hemorrhage, $p=0.077$) (Table 5.2).

Table 5.1. Correlation of new moyamoya grading system and hemispheric symptomatology.

| Method | Grade | Symptoms | | Total | p-value |
|---|---|---|---|---|---|
| | | No | Yes (%) | | |
| **DSA** | 1 | 23 | 2 (8) | 25 | <0.0001 |
| | 2 | 13 | 107 (89) | 120 | |
| | 3 | 0 | 47 (100) | 47 | |
| **MRI** | 0 | 28 | 27 (49) | 55 | <0.0001 |
| | 1 | 8 | 129 (94) | 137 | |
| **CVRC** | 0 | 36 | 79 (69) | 115 | <0.0001 |
| | 2 | 0 | 77 (100) | 77 | |
| **Grading** | I | 30 | 15 (33) | 45 | <0.0001 |
| | II | 6 | 65 (91) | 71 | |
| | III | 0 | 76 (100) | 76 | |
| **Total** | | 36 | 156 (81) | 192 | |

Table 5.2. Correlation of new moyamoya grading system with postop acute DWI+ MR ischemia and clinical stroke .

| | | Postop DWI+ ischemia on MRI | | Total | p-value |
|---|---|---|---|---|---|
| | | **No** | **Yes (%)** | | |
| Grade | **I** | 44 | 1 (2) | 45 | 0.018 |
| | **II** | 63 | 8 (11) | 71 | |
| | **III** | 61 | 15 (20) | 76 | |
| | | | | | |
| Total | | 168 | 24 (12) | 192 | |

| | | Postop clinical stroke (DWI+) | | Total | p-value |
|---|---|---|---|---|---|
| | | **No** | **Yes (%)** | | |
| Grade | **I** | 45 | 0 | 45 | 0.077 |
| | **II** | 70 | 1 (1) | 71 | |
| | **III** | 71 | 5 (7) | 76 | |
| | | | | | |
| Total | | 186 | 6 (3) | 192 | |

### *5.3.1 Correlation with mRS (preop, postop and last follow up)*

No patients were asymptomatic preoperatively, and 31 patients (32%) had mRS 2-5. 66 patients (69%) reported mRS 0-1 (excellent outcome) at 4-6

weeks postop, and this proportion increased to 75% (72 patients) at the last follow-up.

Despite good correlation of the Berlin grade with symptomatic hemispheres, when assessing the patient as a whole, the new grading system did not correlate with patients' preoperative mRS status (either individual component of DSA, MRI, CVRC or combined grade). However, the preoperative grade for individual patients correlated well to dichotomized mRS outcome at 4-6 weeks post op (excellent outcome in 92% of grade I, 78% of grade II, 55% of grade III, p=0.016) and at last follow up (100% of grade I, 78% of grade II, 66% of grade III, p=0.025) (Table 5.3, Figure 5.4).

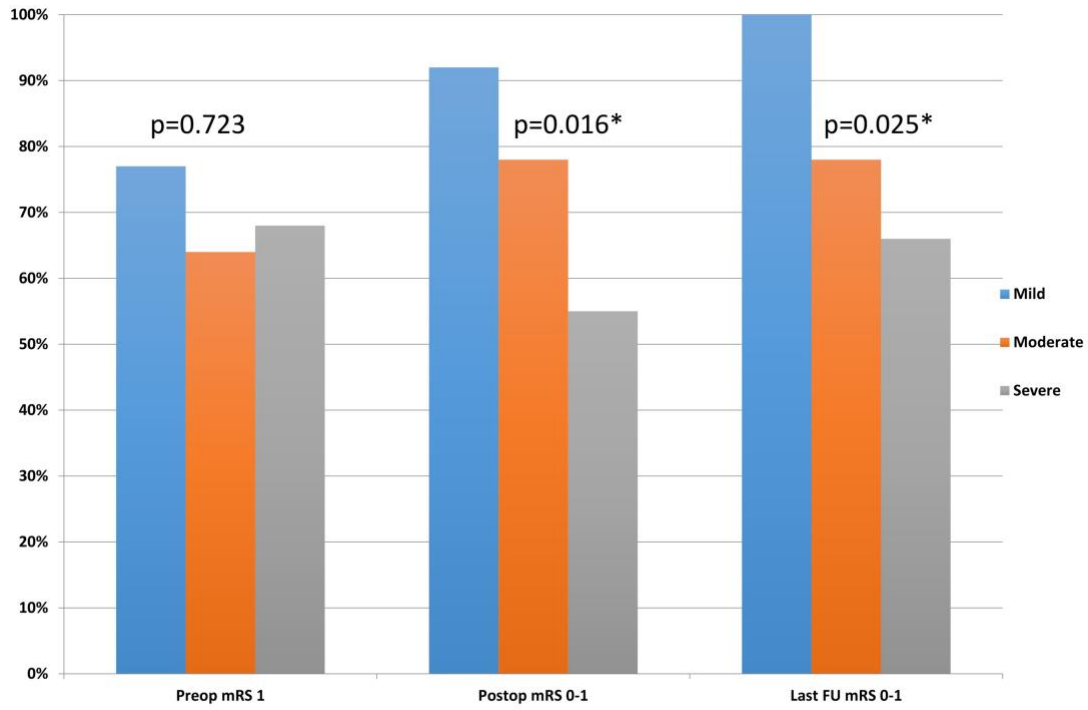


Figure 5.4 The Berlin moyamoya grading system did not correlate with patients' preoperative mRS status (either individual component of DSA, MRI, CVRC or combined grade). However, the preoperative grade for individual patients correlated well to dichotomized mRS outcome at 4-6 weeks post op (excellent outcome in 92% of grade I, 78% of grade II, 55% of grade III, p=0.016) and at last follow up (100% of grade I, 78% of grade II, 66% of grade III, p=0.025).

Table 5.3. Correlation of the new moyamoya grading system to patients' mRS (preop, postop and at last follow up).
* mean 4.3 years, range <1 – 7.5 yrs

| Method | Grade | No. of patients | Preop mRS | | p-value | Postop mRS | | p-value | Last FU mRS* | | p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | **mRS 1 (%)** | **mRS 2-5** | | **mRS 0-1 (%)** | **mRS 2-6** | | **mRS 0-1 (%)** | **mRS 2-6** | |
| DSA | **1** | 3 | 2 (67) | 1 | 0.402 | 3 (100) | 0 | 0.013* | 3 (100) | 0 | 0.165 |
| | **2** | 67 | 48 (72) | 19 | | 51 (76) | 16 | | 53 (79) | 14 | |
| | **3** | 26 | 15 (58) | 11 | | 12 (46) | 14 | | 16 (62) | 10 | |
| MRI | **0** | 20 | 15 (75) | 5 | 0.593 | 17 (85) | 3 | 0.105 | 18 (90) | 2 | 0.144 |
| | **1** | 76 | 50 (66) | 26 | | 49 (64) | 27 | | 54 (71) | 22 | |
| CVRC | **0** | 47 | 29 (62) | 18 | 0.276 | 36 (77) | 11 | 0.126 | 39 (83) | 8 | 0.101 |
| | **2** | 49 | 36 (73) | 13 | | 30 (61) | 19 | | 33 (67) | 16 | |
| Grading | **I** | 13 | 10 (77) | 3 | 0.723 | 12 (92) | 1 | 0.016* | 13 (100) | 0 | 0.025* |
| | **II** | 36 | 23 (64) | 13 | | 28 (78) | 8 | | 28 (78) | 8 | |
| | **III** | 47 | 32 (68) | 15 | | 26 (55) | 21 | | 31 (66) | 16 | |
| Total | | 96 | 65 (68) | 31 | | 66 (69) | 30 | | 72 (75) | 24 | |

## 5.4 Discussion

The existing MMD classification system proposed by Suzuki et al (Suzuki and Takaku, 1969), which later adopted by the Japanese Ministry of Health and Welfare (Fukui, 1997) was based on angiographic findings. However, DSA would not provide information about important functional features of MMD, including hemodynamic cerebrovascular insufficiency and recurrent ischemic events. Many groups including our own clinical experiences found that in many cases the angiographic picture differs from the clinical severity of the disease (Lee et al., 2009). Therefore, the existing Suzuki grading system did not allow for the estimation of the severity of disease, or the associated risk for clinical symptoms, and is of limited clinical use.

The Berlin group (Czabanka et al., 2011c) developed a new MMD grading system incorporating DSA, MRI and CVRC using Xenon-CT. They used a simplified angiographic classification, and regarded ICIC compensation mechanisms (for example, leptomeningeal anastomosis and PCA-pericallosal anastomosis) as a result of hemodynamic compromise and therefore as a marker of advanced disease (assigned 2 points). The development of ECIC collaterals was regarded as indicator for the most severe angiographic form of MMD, as the recruitment of extracranial compensation is supposed to be the result of long-standing and severe hemodynamic compromise (Grubb et al., 1998) (assigned 3 points). Our study showed that hemispheric symptomatology correlated well with the advancement of ICA stenoocclusive disease, and the development of ICIC or ECIC collateralization. Nearly 90% of the hemispheres were symptomatic when ICIC collateralization occurred, and all were symptomatic when ECIC compensatory vessels developed.

MRI was identified as the second important variable for grading MMD. The presence of acute or chronic ischemic lesions provided important information about structural damage and historical disease severity (Horn et al., 2005). In 20% of MMD patients clinically silent infarctions have been reported, emphasizing the importance of MRI for estimating the clinical severity of the disease (Kuroda et al., 2007). In our study, despite the absence of radiological ischemia or haemorrhage, 50% of the hemispheres were symptomatic. Previous study also showed that normal-appearing white matter on MRI might still be associated with impaired CVRC (Cronklin et al

2010). Furthermore, previous radiological ischemia detected on MRI are associated with postoperative stroke risk and outcome as shown by Kim et al (Kim et al., 2010). In their series of 410 pediatric moyamoya disease Korean patients, preoperative clinical infarct (odds ratio [OR] 4.33, 95% confidence interval [CI] 2.55-7.36, p<0.001) and radiological infarct (OR 4.14, 95% CI 2.45-7.01, p<0.001) were associated with unfavorable clinical outcome postoperatively (Kim et al., 2010).

CVRC is another key variable identified by the Berlin group. Currently, there are different techniques available to quantify the hemodynamic compromise in MMD, which include PET, SPECT, Xenon-enhanced CT, dynamic perfusion CT, MR imaging with dynamic susceptibility contrast and with arterial spin labeling, and Doppler ultrasonography (Lee et al., 2009). Xenon-CT was the workhorse for measuring and quantifying rCBF in MMD patients, and reduced CVRC was shown as a stroke risk predictor in patients with occlusive cerebrovascular disease (Webster et al., 1995, Horowitz et al., 1995, McAuley et al., 2004, Nambu et al., 1995, Suzuki et al., 1996). In our cohort, steal phenomena were observed in 40% of the hemisphere using Xenon CT (with and without acetazolamide challenge).

Combining the 3 imaging modalities with the points assigned, and stratifying the hemispheres of MMD patients into mild (grade I, score 1-2), moderate (grade II, score 3-4) and severe (grade III, score 5-6), we were able to correlate the increasing grades with increasing proportion of symptomatic hemispheres. Our findings reconfirmed that of the Berlin group (Czabanka et al., 2011c), and validated the new scoring system using a larger patient cohort in a different population. Furthermore, we were also able to stratify the surgical risk for our patient groups more accurately, where 2% of grade I, 11% of grade II, 20% of grade III hemispheres showed radiological evidence of postoperative ischemia or hemorrhage. More importantly, clinical stroke post revascularization was encountered in none of grade I, 1.4% of grade II and 6.6% of grade III hemispheres. This would be very helpful in preoperative counseling of patients with no preoperative radiological ischemic changes or hemodynamic compromise, in contrast to patients with recent strokes or hemodynamic steal phenomenon. Recently, the Berlin group also applied their scoring system in a very small group of 37 patients, and showed that it can be used to stratify for ischaemic

complications in MMD patients post revascularization. No postop stroke was found in grade I patients, compared to 16% of grade III patients (Czabanka et al., 2016).

Additionally, we also showed that when assessing patients as a whole instead of per hemisphere, this grading scale did not correlate with patients' preoperative mRS, but correlated with postop and long term excellent outcome. In our study, all of grade I, nearly 80% of grade II, and two-third of grade III patients have no or very mild symptoms, and lead a normal lifestyle in the long term.

There is still room for development of the proposed grading system. As only adult patients with idiopathic MMD were included in this validation study, pediatric MMD patients and patients with moyamoya syndrome who would present with identical clinical and angiographic features as those with moyamoya disease, but have an underlying associated condition, such as Down's syndrome, sickle cell disease, primordial dwarfism, or previous cranial irradiation were excluded. Furthermore, we adopted the same criteria developed by the Berlin group using Xenon-CT to assess CVRC. However due to regulatory issues and some of the disadvantages of Xenon-CT (which include relatively long acquisition time, prone to motion artifacts, some patients cannot tolerate inhalation of Xenon through a face mask during the procedure), currently, we routinely perform hemodynamic MR perfusion studies to assess CVRC. It is therefore important in future studies to repeat similar work to assess if hemodynamic MR perfusion studies are good substitute for Xenon-CT, and also to validate the grading system in wider cohort of patients.

Another similar preoperative symptomatology scoring system was recently proposed that take into account of Prior Infarcts, Reactivity and Angiography in Moyamoya Disease (PIRAMD) based on 11 healthy control and 25 patients, where the CVRC was assessed using MRI techniques. For each hemisphere, 1 point was assigned for prior infarct, 3 points for reduced CVR, 3 points for a modied Suzuki Score ≥ Grade II, and 3 points for flow impairment in ≥ 2 of 7 predetermined vascular territories. The hemispheres were divided into 3 severity grades based on total PIRAMD score, as follows: Grade 1, 0–5 points; Grade 2, 6–9 points; and Grade 3, 10 points. They showed increasing proportion of symptomatic hemispheres with increasing PIRAMD

grade (0% (0/8), 55.6% (10/18), 90% (18/20) of Grade 1, 2 and 3 hemispheres respectively) (Ladner et al., 2016).

Several limitations still occur with the current proposed scoring systems, as they concentrate on determining preoperative symptomatology, and other risk factors, e.g. female sex (Khan et al., 2012), presence of an acute infarct on preop MRI, impaired CVRC (Antonucci et al., 2016), unstable MMD (Funaki et al., 2015), associated conditions (Koss et al., 2013) identified from recent studies that could be predictive of postoperative ischemic events, was not accountable in the current proposed scoring systems (Czabanka et al., 2011c, Czabanka et al., 2016, Ladner et al., 2016).

## 5.5 Conclusion

The moyamoya grading system proposed by the Berlin group is now validated with a larger patient cohort in a different country with similar findings, as an important tool to stratify preoperative hemispheric symptomatology. Furthermore, it also correlated with postop new ischemic changes on MRI, and showed a strong trend in predicting clinical postop stroke.

When assessing the patients holistically (instead of per hemisphere) using mRS, the grading system did not correlate with patients' clinical state preop, but was highly predictive of 4-6 week postop and long term outcome.

# CHAPTER SIX

# COMPARATIVE STUDY OF REPEAT REVASCULARISATION FOR MOYAMOYA DISEASE

## 6.1 Introduction

Revascularizations for MMD are effective, however, small subsets of patients have persistent or new symptoms due to inadequate collateralization, hence needing repeat revascularization. These repeat surgeries are technically more challenging due to scar tissue from previous surgery, the meticulous attention required not to violate the previous bypass donor and its collateralization, and less suitable ECA branches for donor choices. There are a variety of strategies for repeat revascularizations after previous indirect bypass reported in the literature (Pandey and Steinberg, 2011, Miyamoto et al., 1988, Matsushima et al., 1990, Touho et al., 1996), but these were mostly small series, and the majority of them were from Japanese cohorts. Furthermore, repeat revascularization after previous direct bypass is not well documented. With an institutional experience of over 1200 extracranial to intracranial bypasses, we are increasingly faced with patients who require repeat revascularization. We therefore reviewed our strategies and outcomes of repeat revascularization surgery for moyamoya disease, and compared patients with previous direct or indirect bypasses.

## 6.2 Methods

All patients with repeat revascularization of the same hemisphere was identified from a prospectively maintained database of patients with treated MMD from 1991 to 2014. 57 patients had repeat revascularization (38 patients had previous indirect procedures, 19 patients had previous direct bypass) of the same hemisphere. These patients were included in the study and the medical records, operative notes, radiology imaging, follow-up data were analyzed retrospectively.

For patients who underwent previous revascularizations from outside institution, their clinical and radiological information were obtained from the initial institutions. After referral to our institution, all patients were evaluated with a clinical history and examination, MR imaging of the brain with perfusion, a 6-vessel angiogram and CBF studies with either SPECT or Xe-CT or MR perfusion before and after the administration of acetazolamide. The clinical findings and the radiological data were discussed in a multidisciplinary meeting attended by neurosurgeons,

neuroradiologists, advanced nurse practitioners, and stroke neurologists. Results from all investigations and clinical information were used to assess the adequacy of the previous revascularization. Repeat revascularization would be recommended if:

1. Patients were symptomatic, and the angiographic and/or CBF data suggested incomplete revascularization.
2. Patients had new infarcts on MR imaging of the brain, with imaging studies suggesting incomplete revascularization.

### 6.2.1 Choice of Procedures

In most of the patients, direct revascularization with STA-MCA bypass was our procedure of choice, with the technique as previously described (Teo et al., 2017b). In most cases, the branch used for EDAS was left intact and another branch of the STA or the OA was used for direct revascularization. This was done to avoid disrupting the donor and collateral vessels from previous surgeries, and the potential for ischemic complications. For patients without suitable donor or recipient vessels, we used indirect procedures, such as EMS, omental transposition, or EDAS for further revascularization, the techniques of which were described previously (Havlik et al., 1992, Karasawa et al., 1993, Kim et al., 2002, Matsushima et al., 1989).

### 6.2.2 Follow-Up Data

Follow-up was obtained from the clinic visit notes or through telephone communication when there was no clinic visit after the surgery. Imaging studies, including MR images of the brain, SPECT scans with and without acetazolamide, and 6-vessel angiogram were obtained at 6 months, 3 years, and 10 years following surgery.

## 6.3 Results

57 patients had repeat revascularization at our institution, of whom the majority (70%, 40/57) had the first revascularization performed at an outside institution, and a majority had previous indirect bypass (67%, 38/57). Only 17 patients had previous surgeries at our institution. With our experience of 765 patients in 1244 procedures (1107 direct bypass, 137 indirect bypass), the rate of repeat surgery was 1.4%. Of the 17 patients,

5 had previous indirect bypass of the same hemisphere, and 12 had previous direct bypass. Hence, the estimated rate of repeat revascularization after in-house indirect or direct bypass was 4% (5/137) and 1% (12/1107), respectively (p = 0.0312).

### 6.3.1 Cohort with Previous Indirect Bypass

In the group with previous indirect bypass, 38 patients (23 female, 15 male, mean age 23 years, age range 5-49 years) needed 56 repeat revascularizations. 42% (16/38) were pediatric patients. Ischemic symptoms were the initial presentations for 95% (36/38) of these patients; 17 with TIAs, 19 with ischemic infarct, 10 with major hemispheric stroke with residual deficits, and 9 with cortical/subcortical infarct with deficit that mostly improved prior to surgery. Two patients (5%) had hemorrhagic presentation. Brain MR imaging showed watershed infarcts in 20, large cortical infarcts in 10, and hemorrhagic infarct in 2. Angiographic studies were done in all the patients; 26 had bilateral moyamoya disease and 12 had unilateral disease. For their initial surgeries, 65 bypasses were performed, which included 56 EDAS, 3 EMS, 2 burr holes, and 4 STA-MCA bypasses. Of note, repeat revascularization was not required for any of the hemispheres with previous STA-MCA bypasses in this cohort.

#### 6.3.1.1 Indications for Repeat Surgery

The mean duration between initial and repeat surgery was 49 months (range 3-264 months), with the indications for repeat surgery that included: TIAs (25 patients, 66%), TIA with choreiform movement (1 patient), new ischemic stroke (7 patients), new hemorrhagic stroke (2 patients), and worsening developmental delay with seizure (3 patients). New infarcts on the side ipsilateral to indirect surgery were noted on MR imaging in 9 patients. Details of CBF studies were available on 34 patients (12 had Xe-CT, 15 had SPECT, 7 had MR perfusion), and all of them had perfusion deficit on baseline studies. Hemodynamic studies were performed on 29 patients with and without administration of acetazolamide, with 5 patients showing acetazolamide reactivity, 16 patients showing no augmentation, and 8 patients showing steal phenomena after acetazolamide administration. DSA was performed in all patients and showed poor revascularization in all of the symptomatic hemispheres (characterized by filling of fewer than 2 cortical branches of the MCA).

#### 6.3.1.2 Types of Repeat Revascularization

Of these patients, 59% (33/56) had direct bypasses (28 STA-MCA bypasses, 4 OA-MCA bypasses, 1 saphenous vein-MCA bypass) and 23 hemispheres had indirect bypasses (4 EMS, 6 EDAS, 4 EDAMS, 8 omental-cerebral transpositions, 1 BH). Postoperative complications included reperfusion hemorrhage in the patient with ECA (saphenous vein)-MCA bypass, who developed a large intracerebral hematoma and died. 2 patients had DWI +ve postoperative infarct, 3 patients had postoperative transient neurological events with no new ischemic changes seen on MR imaging, and 1 patient developed a postoperative subdural hematoma requiring surgical evacuation. None of the other patients had neurological worsening following surgery.

#### 6.3.1.3 Follow-Up

With a mean follow-up of 4.8 years (range 0-16 years), 81% (29/36) of the surviving patients are well with no TIAs/stroke. Apart from the patient with postoperative reperfusion hemorrhage who died, another patient with an underlying hematological disorder died of marrow failure 6 years after surgery. Six patients had occasional TIAs, but were at least back to their baseline. One patient did well for 1 year, then developed frequent TIAs. He was evaluated at another institution, and his MR imaging studies showed no new ischemic lesions. However, an angiogram revealed nonvisualization of the anastomosis. Hence, he underwent repeat EMS and multiple burr holes, after which he did well, with no further ischemic episodes.

Studies of dynamic CBF at 6 months were available on 29 patients and showed normalization of flow with good augmentation following acetazolamide in 26 patients, except in areas of prior infarct. In 3 patients, an interval decrease in the size of acetazolamide-induced perfusion defect was observed. Six-month follow-up DSAs were available for 30 patients, showing improved flow in the hemispheres in all except 1 patient described above. MR imaging studies obtained at 6 months revealed no new infarcts in any patients. Figure 6.1A-H are representative radiological studies of patients with inadequate revascularization after a first indirect procedure and robust collateralization after repeat surgery.

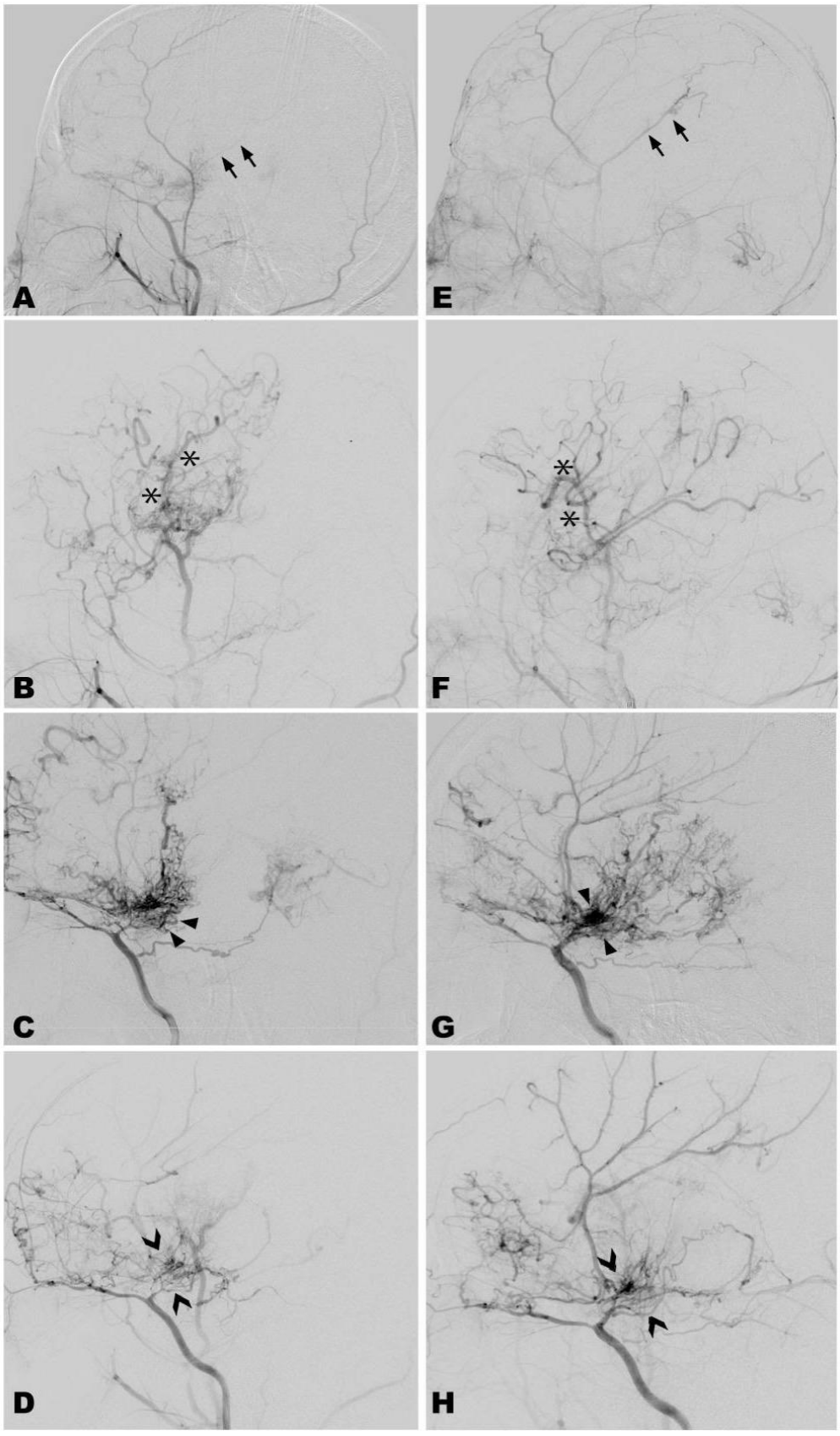
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FIGURE. 6.1**.** Radiological studies of a patient with inadequate revascularization after initial bilateral indirect procedures, followed by bilateral repeat revascularizations using frontal STA branches to achieve robust collateralization after repeat surgery. (A) lateral view right ECA showing inadequate vascularization of right hemisphere from previous EDAS using right parietal STA branch (arrows). (B) lateral view right ECA injection 6 months after repeat revascularization. Due to persistent symptoms, frontal STA branch was used for repeat revascularization of the right hemisphere, with good direct and indirect collateralization seen (asterisks). (C) lateral view right ICA injection showing extensive moyamoya vessels (arrowheads) with underlying ICA steno-occlusion prior to repeat revascularization. (D) lateral view right ICA injection 6 months after repeat revascularization which showed regression of the moyamoya vessels (chevron arrows). (E) lateral view left ECA showing inadequate vascularisation of the left hemisphere from previous EDAS using left parietal STA branch (arrows). (F) lateral view left ECA injection 6 months after repeat revascularization of the left hemisphere using frontal STA branch showing good direct and indirect collateralization (asterisks). (G) lateral view left ICA injection showing underlying ICA stenoocclusive disease and extensive moyamoya vessels. (H) lateral view left ICA injection 6 months post repeat revascularization of the left hemisphere showing regression of the moyamoya vessels (chevron arrows). (Adopted from Teo M**,** Johnson JN, Steinberg GK. Strategies for and outcome of repeat revascularization surgery for moyamoya disease: an American institutional series. *Neurosurgery* 2017 Nov 1; 81: 852-859.)

### 6.3.2 Cohort with Previous Direct Bypass

In the group with previous direct bypasses, 19 patients (16 female, 3 male, mean age 30 years, age range 5-60 years) needed 20 repeat revascularizations. Twenty-six percent (5/19) were pediatric patients. Ischemic symptoms were the initial presentation for 89% (17/19) of these patients; 10 patients with TIAs and 7 patients with cortical infarcts. Two patients presented with hemorrhagic infarct. Brain MR imaging showed watershed infarcts in 4, cortical infarcts in 7, and hemorrhagic infarcts in 2. Angiographic studies were done in all patients; 10 patients had bilateral moyamoya disease and 9 had unilateral disease. Their initial surgeries included 28 direct STA-MCA bypasses, and 1 ECA (saphenous vein) -MCA bypass.

#### 6.3.2.1Indications for Repeat Surgery

The mean duration between initial and repeat surgery was 47 months (range 0.2-200 months), including 1 patient who had acute graft occlusion and had repeat surgery within postoperative week 1. The rest of the indications for repeat surgery include TIAs (12 patients, 63%), TIA with choreiform movement (1 patient), new ischemic stroke (2 patients), new hemorrhagic stroke (2 patients), and radiologically persistent poor cerebrovascular reserve and steal despite surgery (1 patient).

New infarcts on MR imaging on the side ipsilateral to the previous direct surgery were noted in 4 patients. Details of CBF studies with and without administration of acetazolamide were available for 17 patients (5 had Xe-CT, 8 had SPECT, 4 had MR perfusion), with 7 patients showing acetazolamide reactivity, 6 patients showing no augmentation, and 4 patients showing steal phenomena after acetazolamide administration. DSA was performed in all patients who generally showed good graft patency with a wide area of revascularization from the first surgery, except 1 patient with graft occlusion and 2 with poor flow in bypass grafts. However, regional poor filling was detected in the ACA territory in 5, anterior MCA territory in 8, and posterior MCA area in 4.

#### 6.3.2.2 Types of Repeat Revascularization

The majority of repeat revascularizations for this group were to augment blood supply in another vascular territory (55% (11/20), achieved using another direct bypass technique (ie, frontal STA branch or OA). Other procedures included 3 EMS, 1 EDAS, and 5 omental-cerebral transpositions. Postoperatively, 1 patient developed DWI +ve infarct, 1 had a transient neurological deficit with no radiological changes, and 2 patients had postoperative superficial wound infection.

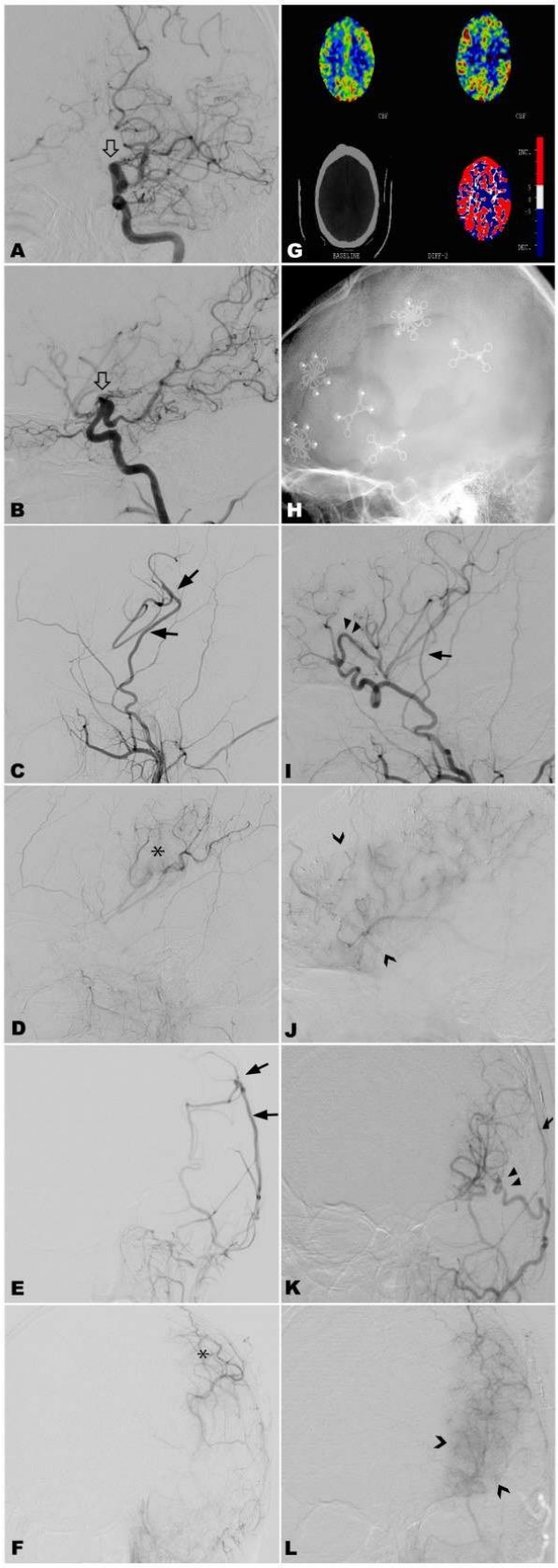



**FIGURE 6.2.** Radiological studies for a patient with initial left direct STA-MCA bypass and repeat revascularization using frontal STA branch required to augment another

vascular territory. (A) AP view left ICA, (B) lateral view left ICA showing left terminal ICA, M1, A1 occlusion (block arrow) with moyamoya vessels, and lack of left hemispheric perfusion. (C), (D) lateral view left ECA injection showing patent left STA-MCA bypass graft (arrows) with revascularisation of the mid-MCA territory (asterisk). (E), (F) AP view left ECA injections showing the same findings as C, D. (G) Due to new neurological symptoms, Xenon-CT with and without diamox study performed 6 months later showed an area of reduced perfusion in the anterior MCA, with evidence of steal in keeping with compromised cerebrovascular reserve. (H) Repeat revascularization is therefore performed with a bone flap anterior to preexisting craniotomy. (I), (J) lateral view of left ECA injections showing left frontal branch STA-MCA bypass graft (arrow heads), previous left parietal branch STA-MCA bypass graft (arrow), and extensive anterior MCA revascularization from the frontal STA-MCA bypass graft. (K), (L) AP view left ECA injections showing the same findings as I, J. (Adopted from Teo M**,** Johnson JN, Steinberg GK. Strategies for and outcome of repeat revascularization surgery for moyamoya disease: an American institutional series. *Neurosurgery* 2017 Nov 1; 81: 852-859.)

#### 6.3.2.3 Follow-Up

With a mean follow-up of 4.7 years (range 0.5-21 years), 82% (14/17) of the known surviving patients are well with no TIAs/stroke. One patient was lost to follow-up, and 1 died at age 72, 12 years after repeat bypass surgery. Three patients had some residual TIA symptoms, but were at least 70% better than prior to repeat surgeries.

At 6 months, CBF studies were available on 14 patients; all showed blood flow improvement compared with preoperative studies. DSA was available for 14 patients, with improved revascularization in all and patent direct bypass grafts. None of the patients with 6-month brain MR imaging showed evidence of new infarcts. Figure 6.2 A-L is representative of radiological studies for patients with initial direct bypass and repeat surgery required to augment another vascular territory.

### 6.3.3 Comparison Between the 2 Cohorts

In the previous direct bypass cohort, the patients were slightly older (mean age 30 years, range 5-60 years versus 23 years, range 5-49 years), and there were more females (84%, 16/19) compared with the cohort with previous indirect bypass (61%, 23/38) ($p = 0.08$) who underwent repeat revascularization (Table 6.1).

There was a larger proportion of pediatric patients who underwent repeat revascularization after previous indirect bypass compared with those with previous direct bypass (42%, 16/38 versus 26%, 5/19, respectively), but this difference was not statistically significant ($p = 0.244$) (Table 1). In the patients with previous indirect bypasses and needed repeat revascularizations, majority of the first operations were performed at outside institution (91%, 51/56).

In both cohorts, the mean duration between initial bypass procedures and repeat revascularization was similar (48.8 months in the previous indirect group, 47.4 months in the previous direct group). The indication for repeat revascularization due to TIAs was similar in both groups (66% in the previous indirect group, 63% in the previous direct group), however the types of new infarcts that led to repeat revascularization were different in both groups (ischemic stroke 18% versus 11%, hemorrhagic stroke 5% versus 10% for the group with previous indirect and direct bypasses, respectively).

Over 50% of repeat revascularizations performed in both groups was achieved by direct bypass methods, but the major difference was that the repeat bypass for the previous direct group was to augment another vascular territory. Furthermore, parietal STA branch could be used in repeat revascularization of the hemisphere in 46% (26/56) for those with previous indirect surgeries, compared to none with previous direct surgeries as the parietal STAs were already used in the prior surgeries ($p<0.001$).

With similar mean follow-up of nearly 5 years in both groups, over 80% of patients in both groups are well and free from stroke/TIA symptoms.

Table 6.1. Comparison of repeat revascularization cases between cohort with initial indirect or direct bypasses

| | Previous Indirect | Previous Direct | p-value |
|---|---|---|---|
| **Number of patients** | 38 | 19 | |
| **Female: Male** | 23F: 15M | 16F: 3M | 0.08 |
| **Age (mean)** | 23 yrs | 30 yrs | |
| **Age (range)** | 5–49 yrs | 5–60 yrs | |
| **Pediatric cases (< 18 yrs)** | 16 | 5 | 0.24 |
| **Adult cases (> 18 yrs)** | 22 | 14 | |
| **No. of repeat revascularizations** | 56 | 20 | |
| **Location of previous revascularization** | | | < 0.001 |
| **Stanford** | 5 | 12 | |
| **Outside institution** | 51 | 8 | |
| **Duration between 2 surgeries (Mean)** | 48.8 mos | 47.4 mos | |
| **Duration between 2 surgeries (Median)** | 36 mos | 30 mos | |
| **Duration between 2 surgeries (Range)** | 3–264 mos | 0.2–200 mos | |
| **Indications for repeat revascularization** | | | 0.60 |
| **TIAs** | 25 | 12 | |
| **TIA and choreiform movement** | 1 | 1 | |
| **Developmental delay, seizure** | 3 | | |
| **Ischemic stroke** | 7 | 2 | |
| **Hemorrhagic stroke** | 2 | 2 | |
| **Graft occlusion** | | 1 | |
| **Radiological-persistent poor reserve and steal** | | 1 | |
| **Types of repeat revascularization** | | | < 0.001 |
| **Parietal branch STA-MCA bypass** | 26 | 0 | |
| **Frontal branch STA-MCA bypass** | 2 | 9 | |
| **OA-MCA bypass** | 4 | 2 | |
| **Saphenous vein-mca bypass** | 1 | 0 | |
| **EMS** | 4 | 3 | |
| **EDAS** | 6 | 1 | |
| **EDAMS** | 4 | 0 | |
| **Omental graft** | 8 | 5 | |
| **Burr holes** | 1 | 0 | |
| **Duration of follow up** | | | |
| **Mean (years)** | 4.8 | 4.7 | |
| **Range (years)** | 0–16 | 0.5–21 | |
| **Follow up outcomes** | | | 0.81 |
| **Well, no TIAs/strokes** | 29 | 14 | |
| **Occasional TIAs** | 7 | 3 | |
| **Died** | 2 | 1 | |

## 6.4 Discussion

The main aims of revascularization in moyamoya disease are for CBF augmentation, symptomatic control, and prevention of future ischemic events. However, small subsets of patients have persistent or new symptoms due to inadequate collateralization. Because of the large moyamoya referral base for our center, including patients with previous surgeries who remained symptomatic, in this study over two-thirds of repeat surgeries were performed on patients who had previous surgeries at another institution, and a similar proportion had previous indirect bypasses. Considering patients with previous extracranial-intracranial bypass performed at our institution, the rate of repeat revascularization was 1.4%. Furthermore, the rate of repeat revascularization was higher for patients who had previous indirect bypass compared with those with previous direct bypass (4% versus 1%, respectively).

Indirect procedures are very popular, especially in the pediatric population, since they are technically less demanding, are highly effective due to children's robust potential for angiogenesis, and have lower short-term complication rates. It is therefore not surprising that a larger proportion of patients with previous indirect bypass who needed repeat revascularization are children (42%) compared with those with previous direct bypass, since indirect bypass is the treatment of choice for revascularization in many pediatric neurosurgical centers. Although the efficacy of various indirect procedures has been well established in children (Fung et al., 2005a, Houkin et al., 2000, Irikura et al., 2000, Isono et al., 2002, Karasawa et al., 1993, Kim et al., 2007, Kim et al., 2002, Komotar et al., 2009, Matsushima et al., 1989, Ross et al., 1994, Sainte-Rose et al., 2006b, Scott et al., 2004, Veeravagu et al., 2008), the efficacy in adults is still controversial. Despite a recent publication (Starke et al., 2009) suggesting that indirect revascularization is also effective in reducing the risk of future ischemic events for adults with moyamoya disease, many authors have published studies showing superior results after performing direct procedures (Abla et al., 2013, Kazumata et al., 2014b, Kawaguchi et al., 2000b, Arias et al., 2015a, Bang et al., 2012, Houkin et al., 2000, Czabanka et al., 2011a).

One of the disadvantages of indirect procedures is the inconsistent and sometimes incomplete collateralization post-revascularization. A recent study from an American center that analyzed radiographical outcomes for 15 symptomatic patients who underwent 20 surgical revascularization procedures, with a mean interval of 15.2 months for postoperative angiograms, showed that 90% and 30% with direct and indirect bypasses, respectively, had “good” angiographic outcomes, a statistically significant finding with $p = 0.0198$ (Arias et al., 2015a). This result echoed findings from other studies from the Asian continents where there is more literature on moyamoya disease. Matsushima et al. (Matsushima et al., 1998) found that collateral formation in more than two-thirds of the hemisphere occurred in only 44% of the hemispheres after a single indirect procedure, compared with 52% after multiple combined indirect procedures and 74% after STA-MCA anastomosis. Other authors have also reported on failed indirect procedures, in which collateral formation is inadequate and some patients continue to be clinically symptomatic (Hayashi et al., 2010, Matsushima, 1985, Miyamoto et al., 1988).

Miyamoto et al. (Miyamoto et al., 1988) observed newly formed collateral vessels on repeat angiography studies after additional STA-MCA bypass or omental transposition and reported good results in a series of 11 patients with failed indirect anastomosis. Matsushima et al. (Matsushima et al., 1990) described the addition of an EMS or EncephaloMyoArterioSynangiosis (EMAS) procedure in 3 patients with failed EDAS, and obtained better angiographic collateralization. Touho et al (Touho et al., 1993) performed STA-MCA anastomosis in all patients (and an additional omental transposition in 1 individual), for the treatment of 28 hemispheres in patients who had previously been treated with indirect revascularization using EDAS, but who remained symptomatic, leading to excellent recovery in all of them. Their subsequent report on omental transplantation using a branch of the STA previously used in the EDAS, and that did not provide adequate collateral vessels, with good clinical and angiographic results in all 5 patients (Touho et al., 1996).

In our series, for patients with previous indirect revascularization, we performed direct anastomosis for nearly 60% of the 56 hemispheres revascularized using STA-MCA bypass, OA-MCA bypass, and 1 case of saphenous vein graft-MCA bypass. In the rest of the hemispheres, we could not find an adequate recipient vessel, or there was

extensive adhesion as a result of the first operation, and we performed indirect procedures. We usually left intact the branch used for EDAS to avoid disrupting the collaterals and the dense adhesions formed around it. Therefore, for these hemispheres where direct bypass was not feasible for repeat revascularization, we added another indirect bypass, which consisted of 4 EMS, 6 EDAS, 4 EDAMS, 8 omental-cerebral transpositions, and 1 burr hole revascularization. With a mean follow-up of nearly 5 years in these patients with previous indirect bypass who underwent repeat revascularization using various modalities, over 80% of the surviving patients are well with no TIAs/stroke.

Direct revascularization for moyamoya disease is another very well-established technique and a number of authors, including our group, have described good results in both adult and pediatric populations (Burke et al., 2009, Golby et al., 1999, Guzman and Steinberg, 2010, Khan et al., 2003b). The main advantages of direct anastomosis are the establishment of augmented flow immediately following surgery, a more consistent and higher extent of angiographic collateralization (Arias et al., 2015a, Kazumata et al., 2014b, Bang et al., 2012, Houkin et al., 2000, Czabanka et al., 2011a), and superiority in restoring cerebrovascular reserve capacity post-bypass (Czabanka et al., 2011a).

Direct anastomoses also have very good clinical outcomes, including more patients with symptomatic improvement, less recurrent ischemic risk, more patients with stroke-free survival (Abla et al., 2013, Kazumata et al., 2014b, Kawaguchi et al., 2000b), and as shown in a recent randomized controlled trial, reduced risk for hemorrhagic stroke ((Miyamoto et al., 2014a). This study showed another benefit of direct bypass with a lower rate of repeat revascularization (1% in the direct bypass group and 4% in the indirect bypass group)

Repeat revascularization post-direct bypass in the English literature is rare (Hori et al., 2016), most likely due to the effectiveness of direct bypass in providing adequate collateralization after the first procedure. In our setting with 1107 direct bypasses over the last 25 years, 12 patients have had their first direct surgery performed at our institution, with a repeat revascularization rate of 1%. Combined with patients who had previous direct bypasses from other institutions, we performed 20 repeat

revascularizations in 19 patients. Apart from 1 patient who had the repeat direct revascularization due to acute graft occlusion within a week of the initial surgery, the duration between the initial and repeat surgery was about 4 years. The majority of repeat revascularizations for this group were to augment blood supply in another vascular territory, over half of which were achieved using another direct bypass technique (ie, frontal STA branch or OA). Those patients for whom no bypass graft was deemed suitable for another direct bypass, other techniques used included 3 EMS, 1 EDAS, and 5 omental-cerebral transpositions.

A recent study on surgical treatment of failed revascularisation from Germany included 308 MMD patients with 405 surgically treated hemispheres. Of the 405 hemispheres treated, 15 patients (3.7%) underwent repeat revascularization. Contrary to our finding, in that series, time to repeat revascularization in 60% of patients was within 1 year of first surgery, and the most common cause of repeat revascularisation was symptomatic bypass occlusion. Intermediate-flow bypass using a radial artery graft was most commonly used for repeat revascularization in 9/15 (60%) (Lucia et al., 2021).

The disadvantages of the direct procedures included: more challenging technical expertise required; the nonavailability of appropriate donor or recipient vessels, particularly in the pediatric population; and a slightly higher incidence of early postoperative complications compared with indirect procedures (Kazumata et al., 2014b)Kazumata et al 2014). There is also a 10% to 20% risk of transient neurological deficits postoperatively (negative DWI changes on MR imaging) due to sudden change in the blood flow to an ischaemic brain, but the aetiologies of global cerebral hyperperfusion (Fujimura et al., 2007b, Fujimura et al., 2009b, Kim et al., 2008) or local hypoperfusion (Mukerji et al., 2015) remain uncertain.

### 6.4.1 Choice of Procedures

In our opinion, the clinical symptoms, radiological and angiographic findings, and the results of CBF studies should be analyzed and correlated before subjecting the patient to a repeat procedure. Various authors have described the use of both direct and indirect procedures for reconstruction of an inadequate indirect procedure

(Matsushima et al., 1990, Miyamoto et al., 1988, Touho et al., 1993, Touho et al., 1996, Touho and Iseda, 2003), but very few have reported on a post-direct bypass. In our experience, judicious use of either procedure gives good results, and direct revascularization strategies could be achieved in over half of repeat cases in both groups. As is our policy for initial revascularization in most patients with moyamoya disease, we prefer direct anastomosis with STA-MCA bypass (including repeat revascularization) to provide immediate and reliable augmentation of blood supply to the ischemic hemisphere. However, in cases in which the recipient vessels are small or there are multiple adhesions, we use indirect procedures. For example, to revascularize a large area of brain parenchyma, omental-cranial transposition would be used. For a focal area of revascularization, in the presence of a small STA branch, EDAS is preferred, otherwise EMS.

### 6.5 Conclusion

Repeat revascularization procedures are clinically effective in preventing future ischemic events and can be safely performed when clinically indicative, including in patients with previous direct bypass. Patients with previous indirect bypass have a higher rate of repeat revascularization. Over 50% of our repeat revascularizations were achieved with direct procedures for patients with previous direct or indirect bypass. However, the choice of procedure depends on the operative findings and the status of donor and recipient vessels.

# CHAPTER SEVEN

# MOYAMOYA SYNDROME AND CLINICAL OUTCOME

i

## 7.1 Introduction

It is generally accepted that patients with moyamoya syndrome have worse outcome compared to classical MMD. However, no large studies have been conducted to compare and contrast these patients. Some of the various conditions associated with MMD include prior radiotherapy to the head and neck or brain, Down's syndrome, neurofibromatosis type 1, tuberous sclerosis, MOPD II, Fanconi's anemia, sickle cell disease (Scott and Smith, 2009, Smith et al., 2009, Bober et al., 2010, Jea et al., 2005).

We present such comparison as a whole, and also show some examples of the difficulty we encounter for patients with MM syndrome. In this mini-thesis we concentrate on patients with MOPD II. They are among the smallest human beings at maturity. Their pleasant outgoing personality, high-pitched nasal voice, and distinctive facial features make them quite recognizable. Their life expectancy is decreased to 20s or 30s. In a natural-history study from Hall et al.(Hall et al., 2004) of 58 patients with MOPD II or other forms of primordial dwarfism, 4 of 11 deaths were a result of rupture of intracranial vessels. MOPD II is a rare, autosomal recessive genetic disorder caused by mutations in the *pericentrin* (*PCNT*) gene, which organizes the mitotic spindle. The loss of *PCNT* impedes cell division, decreases cellularity of the embryo, and leads to severe growth restriction (Rauch et al., 2008). Features include proportionate intrauterine growth retardation, poor postnatal growth, extremely small stature (adult height < 100 cm), severe microcephaly, skeletal dysplasia, characteristic facial features, and normal or near-normal intelligence (Majewski and Goecke, 1998).

Previous studies (Bober et al., 2010, Hall et al., 2004) have shown that 25%–50% of patients with MOPD II have intracranial vascular anomalies, which include moyamoya disease (MMD) and multiple intracranial aneurysms, both of which can be a major cause of stroke or early death (Hall et al., 2004). Early diagnosis is critical to reduce morbidity and postpone death in these patients, and a screening program using MR angiography has been implemented (Bober et al., 2010). However, because of the patients' extremely small size, diminutive arteries, and narrow anatomical corridors, surgical management of these intracranial anomalies is quite challenging, and few

successful surgical cases have been reported in the literature. Here, we present our institutional results for this patient group.

## 7.2 Methods

All MMD patients from a prospectively collected database was compared with patients identified as MMS.

A prospectively collected institutional surgical database of children with MOPD II and intracranial vascular anomalies who underwent surgery at Stanford University Medical Center between 2005 and 2012 was analyzed retrospectively. Patients' clinical notes, imaging findings, and operative video recordings were reviewed. Long-term outcome data were obtained from the Potentials Foundation Primordial Registry, an approved prospective registry of patients with MOPD II located at A. I. duPont Hospital for Children.

## 7.3 Results

### 7.3.1 MMS cohort

Of the 92 patients with MMS, Downs' syndrome is the most common association, followed by neurofibromastosis type 1 and primordial dwarfism. The other associated conditions are shown in Table 6.1, stratified by paediatric and adult cohort.

Table 7.1. Association of underlying conditions for patients with moyamoya syndrome in paediatric and adults.

| | Paediatric No. of Patients (55) | Adult No. of Patients (37) |
|---|---|---|
| **Downs Syndrome** | 16 | 7 |
| **Neurofibromatosis 1** | 12 | 3 |
| **Dwarfism** | 8 | 1 |
| **Craniospinal radiation** | 4 | 1 |
| **Sickle Cell Disease** | 2 | 4 |
| **Glycogen Storage Disorder Type 1a** | 1 | 1 |
| **Hurler Syndrome** | 1 | 0 |

| | | |
|---|---|---|
| **Alagile Syndrome** | 1 | 0 |
| **Thalassaemia** | 1 | 0 |
| **Fibromuscular Dysplasia** | 1 | 0 |
| **Vasculitis** | 0 | 2 |
| **Antiphospholipid Syndrome** | 0 | 2 |
| **SLE** | 0 | 1 |
| **Protein C&S deficiency** | 0 | 1 |
| **Polycystic Kidney Disease** | 0 | 1 |
| **Homocystinuria** | 0 | 1 |
| **Other** | 8 | 12 |

Patients with MMS more commonly presented during the paediatric ages (60%) compared to classical MMD where 78% presented during the adult years. There is also a lower proportion of Asian patients with MMS (13%) compared to the group with classical MMD. Ischaemic presentations (TIAs or strokes) are still the commonest presentation (about 80%) for both groups, but there is a higher proportion of seizure and lower proportion of haemorrhagic presentations for patients with MMS (Table 6.2). The underlying preoperative radiological characteristics, and postoperative stroke risks (10%) are very similar between the 2 groups, except a lower TNE risks noted amongst the MMS group (12%) compared to patients with classical MMD (21% TNE risk).

Table 7.2. Comparison of demographics, mode of presentation, radiological findings and postoperative risk between patients with classical MMD and MMS.

| | | **Classical MMD** | | **MMS** | | |
|---|---|---|---|---|---|---|
| | | **No. of patients** | **Column %** | **No. of patients** | **Column %** | **p-value** |
| **Age Group** | **Paediatric** | 150 | 22.2% | 55 | 59.8% | <0.0001* |
| | **Adult** | 527 | 77.8% | 37 | 40.2% | |
| **Gender** | **Female** | 490 | 72.4% | 58 | 63.0% | 0.063 |
| | **Male** | 187 | 27.6% | 34 | 37.0% | |
| **Ethnicity** | **Caucasian** | 356 | 52.6% | 56 | 60.9% | <0.0001* |
| | **Asian** | 237 | 35.0% | 12 | 13.0% | |
| | **Others** | 84 | 12.4% | 24 | 26.1% | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Presentations** | | | | | | |
| **Haemorrhagic** | **No** | 581 | 85.8% | 87 | 94.6% | 0.02* |
| | **Yes** | 96 | 14.2% | 5 | 5.4% | |
| **Ischaemic** | **No** | 118 | 17.4% | 19 | 20.7% | 0.449 |
| | **Yes** | 559 | 82.6% | 73 | 79.3% | |
| **Headache** | **No** | 355 | 52.4% | 60 | 65.2% | 0.021* |
| | **Yes** | 322 | 47.6% | 32 | 34.8% | |
| **Seizure** | **No** | 604 | 89.2% | 75 | 81.5% | 0.031* |
| | **Yes** | 73 | 10.8% | 17 | 18.5% | |
| | | | | | | |
| **Radiological Findings** | | | | | | |
| **Suzuki stage** | **2** | 24 | 3.6% | 4 | 4.3% | 0.263 |
| | **3** | 265 | 40.3% | 29 | 31.5% | |
| | **4** | 330 | 50.2% | 49 | 53.3% | |
| | **5** | 38 | 5.8% | 10 | 10.9% | |
| | **6** | 1 | 0.2% | 0 | 0.0% | |
| **DSA score** | **1** | 14 | 2.1% | 2 | 2.2% | 0.865 |
| | **2** | 502 | 76.4% | 68 | 73.9% | |
| | **3** | 141 | 21.5% | 22 | 23.9% | |
| **mMRI score** | **0** | 134 | 20.4% | 19 | 20.7% | 0.976 |
| | **1** | 491 | 74.7% | 69 | 75.0% | |
| | **2** | 32 | 4.9% | 4 | 4.3% | |
| **HDR score** | **0** | 150 | 26.4% | 18 | 26.9% | 0.822 |
| | **1** | 325 | 57.2% | 40 | 59.7% | |
| | **2** | 93 | 16.4% | 9 | 13.4% | |
| | | | | | | |
| **Postop CVA** | **No** | 603 | 89.1% | 82 | 89.1% | 0.986 |
| | **Yes** | 74 | 10.9% | 10 | 10.9% | |
| **Postop Haematoma** | **No** | 650 | 96.0% | 90 | 97.8% | 0.931 |
| | **Yes** | 27 | 4.0% | 2 | 2.2% | |
| **TNE** | **No** | 534 | 78.9% | 81 | 88.0% | 0.039* |
| | **Yes** | 143 | 21.1% | 11 | 12.0% | |

The long term stroke risk is not statistically significant between patients with MMS and classical MMD (5.5% for MMS vs 3.9% for MMD). Furthermore, taking into account of the Kaplan Meier estimate limitation as previously highlighted, the estimated stroke

free interval for patients with MMS is 23.2 years, and 21.8 years for patients with classical MMD (log rank p=0.881).

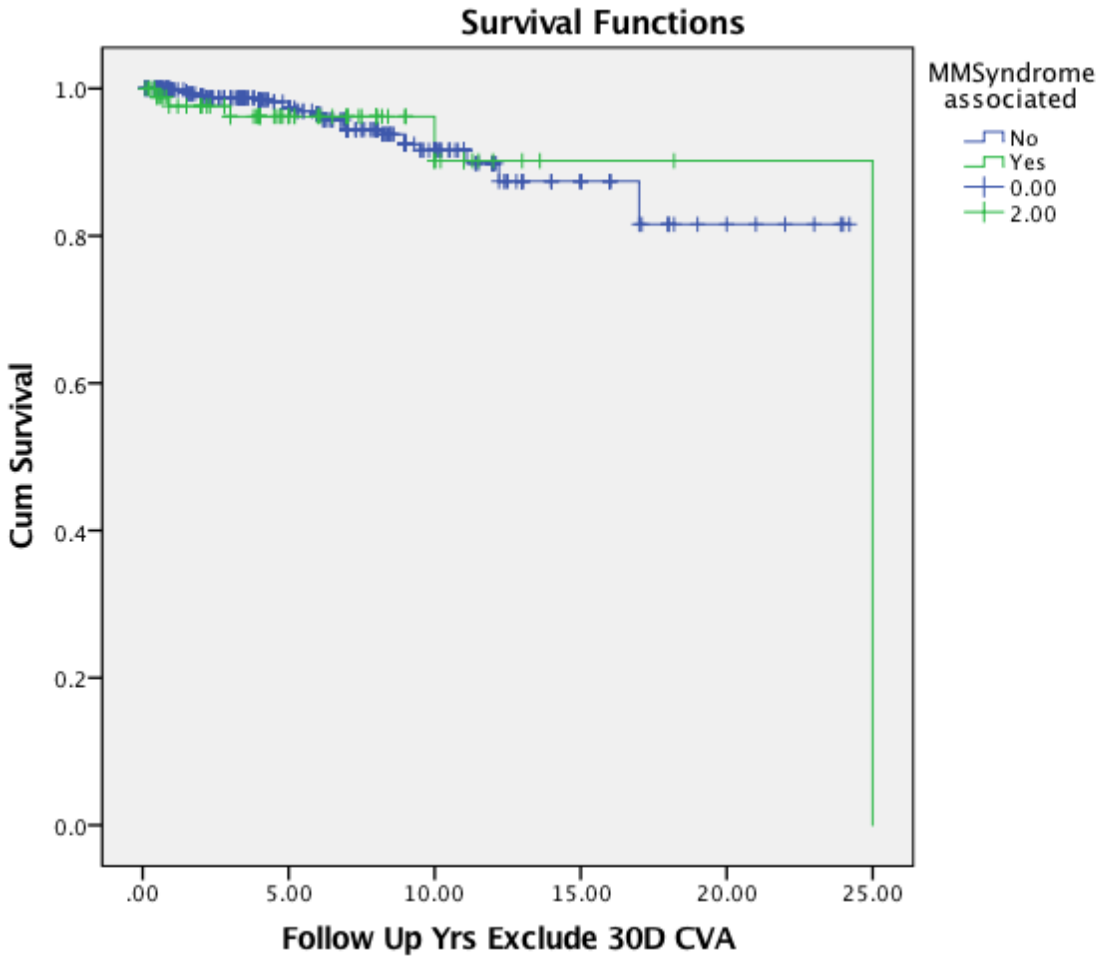



**Figure 7.1** Kaplan meier curves comparing the long term outcome of patients with MM syndrome and MMD, with no significant differences detected on the long term stroke risk (5.5% for MMS vs 3.9% for MMD), and estimated stroke free interval of 23.2years for MMS, 21.8 years for MMD (log rank p=0.881).

### 7.3.2 MOPD patients

Ten patients with MOPD II underwent surgery between 2005 and 2012; 5 patients had MMD, 2 had intracranial aneurysms, and 3 had both MMD and aneurysms. The patients presented with transient ischemic attack (TIA) (2), ischemic stroke (2), intraparenchymal hemorrhage from MMD (1), and aneurysmal subarachnoid hemorrhage (SAH) (1), and 4 were diagnosed on screening (Table 7.3).

The mean age of the 8 patients with MMD, all of whom underwent extracranial-intracranial revascularization (14 indirect, 1 direct), was 9 years (range 1–17 years). The diameter of the distal superficial temporal artery (STA) was 0.3–1.0 mm (mean 0.6 mm). There were no postoperative complications after bypass surgery.

The mean age of the 5 patients with aneurysms was 15.5 years (range 9–18 years). Two patients experienced postoperative complications, 1 with transient left-sided weakness after aneurysm clipping (no infarct seen on postoperative diffusion-weighted MRI of the brain) and 1 with femoral thrombosis (after a diagnostic angiogram), which required subsequent surgical repair. Two patients also underwent endovascular coiling of intracranial aneurysms.

During a mean follow-up of 6.6 years (range 4–11 years), 3 patients died (1 as a result of SAH caused by a new untreated aneurysm, 1 as a result of myocardial infarction 6 years after surgery, and 1 as a result of respiratory failure 4 years after surgery), and 1 patient had occasional mild TIAs. All surviving patients recovered to their neurological baseline.

Table 7.3. Summary of the MOPD-II patients with intracranial vascular anomalies, neurosurgical management and follow up outcome

| | Presentation | Age at surgery (years) | Intracranial anomalies | Year of surgery | Type of surgery | Latest follow up | Years of follow up | Clinical/Radiographic Outcomes |
|---|---|---|---|---|---|---|---|---|
| **Case 1** | Ischemic stroke | <1 | MMD | 2009 | bilateral indirect bypass | 2016 | 7 | Asymptomatic, bypasses patent |
| **Case 2** | Screening | 3 | MMD | 2008 | bilateral indirect bypass | 2016 | 8 | Occasional mild TIAs, bypasses patent |
| **Case 3** | Ischemic stroke | 4 | MMD | 2012 | bilateral indirect bypass | 2016 | 4 | Asymptomatic, bypasses patent |
| **Case 4** | Screening | 9 | MMD | 2009 | right indirect bypass | 2016 | 7 | Asymptomatic, bypass patent |
| **Case 5** | TIAs | 14 | MMD | 2008 | bilateral indirect bypass | 2014 | 6 | Asymptomatic, bypasses patent<br>Died of MI at 6 years |
| **Case 6** | Hemorrhage (ICH) | 10 | MMD | 2008 | bilateral indirect bypass | 2012 | 4 | Asymptomatic, bypasses patent at 3 years;<br>Died of respiratory failure at 4 years |
| | | | p1/p2 aneurysm | | surveillance | | | |
| **Case 7** | TIAs | 14 | MMD | 2005 | bilateral indirect bypass | 2016 | 11 | Asymptomatic, bypasses patent |
| | SAH | 18 | PCA aneurysm | 2009 | coiling | | | Stable aneurysm neck remnant |
| **Case 8** | SAH | 17 | MMD | 2008 | right direct bypass, left indirect bypass | 2016 | 8 | Asymptomatic, bypasses patent |
| | | | PICA aneurysm, PCA aneurysm | 2008 | clipping | | | Stable small PCA aneurysm |
| **Case 9** | Screening | 9 | ACOM aneurysm (new aneurysms on follow-up angiogram) | 2010 | clipping | 2015 | 5 | SAH 2012, died of SAH from new aneurysm 2015 |
| **Case 10** | Screening | 18 | 4 aneurysms (pericallosal, m1, ACOM, VB) | 2010, 2012 | clipping, coiling | 2016 | 6 | Asymptomatic |

#### 7.3.2.1 Case Examples

**Case 1** A 10-month-old girl (initial birth weight 1.0 kg, birth length 35 cm) with MOPD II and craniosynostosis presented with a new-onset seizure. Brain MRI showed a left posterior parietal infarct. An angiogram revealed bilateral high-grade stenoses of the middle cerebral arteries (MCAs) and anterior cerebral arteries, with a network of collateral blood vessels consistent with bilateral MMD (Fig. 7.2A-D). A SPECT scan revealed decreased perfusion in the bilateral parietal occipital regions with no augmentation after acetazolamide, indicating impaired hemodynamic reserve. She underwent uneventful bilateral indirect EDAS bypass procedures staged 1 week apart and was discharged after each surgery on Postoperative Day 3. Postoperative angiography at 18 months revealed patent bilateral bypass grafts supplying the bilateral MCA territories with progressive stenosis of the bilateral internal carotid arteries (ICAs) (Fig. 7.2E-H). At 2.5 years of age, she also underwent bilateral fronto-orbital advancement for craniosynostosis correction. Seven years after surgery, she remains neurologically normal.

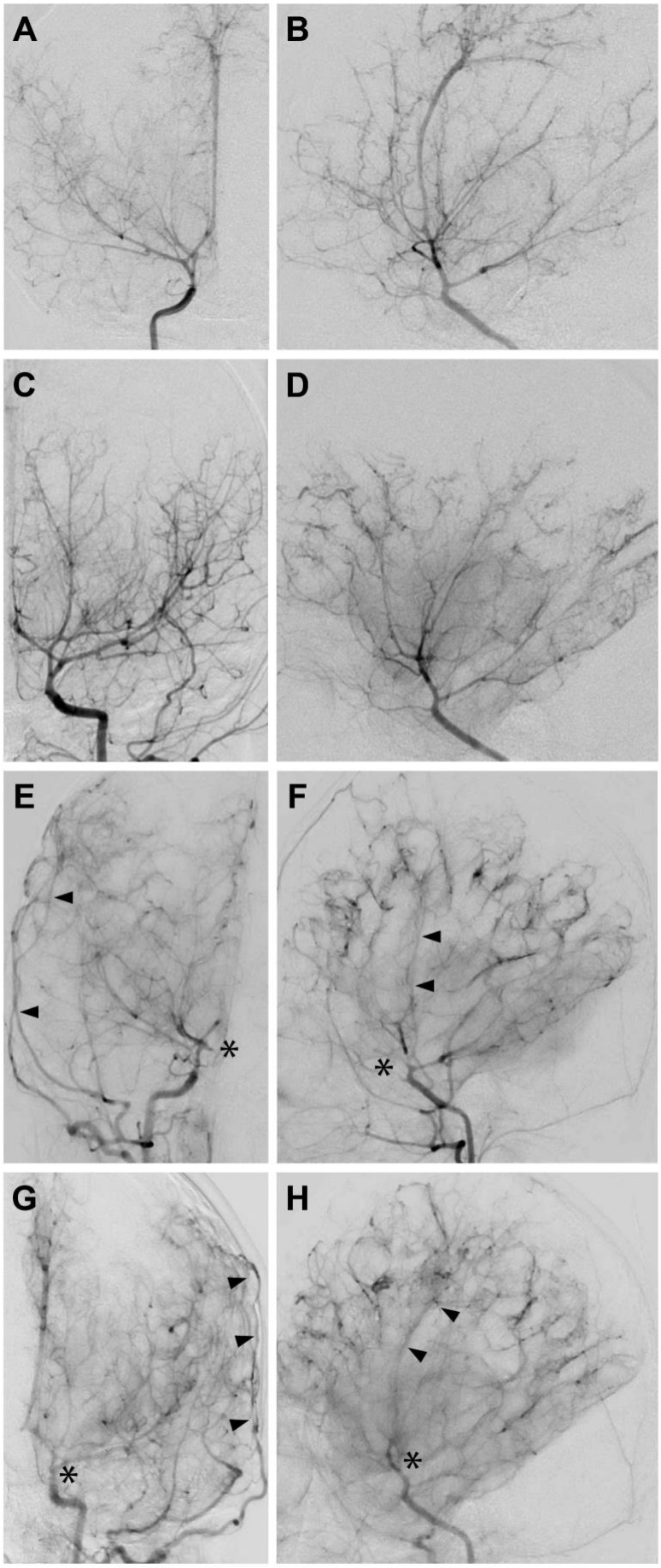
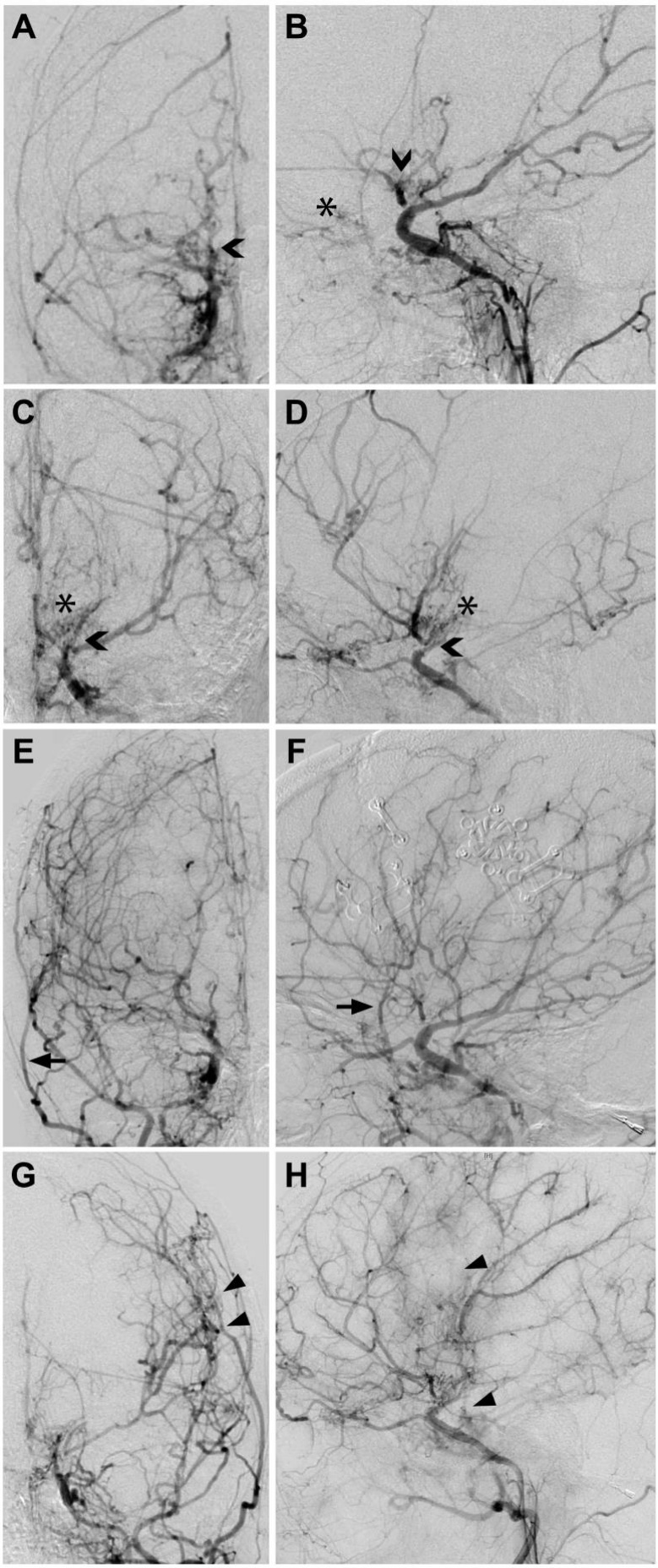

A
B
C
D
E
F
G
H

**Fig. 7.2.** Case 1. Cerebral angiograms of a 10-month-old girl with MOPD II, craniosynostosis, and MMD, before and after bilateral EDAS. Anteroposterior (**A**) and lateral (**B**) views of right ICA injection and anteroposterior (**C**) and lateral (**D**) views of left ICA injection show bilateral high-grade stenosis of MCAs and anterior cerebral arteries with a network of collateral blood vessels consistent with bilateral MMD (*arrows*). Anteroposterior (**E**) and lateral (**F**) views of right common carotid artery (CCA) injection and anteroposterior (**G**) and lateral (**H**) views of left CCA injection 18 months after encephaloduroarteriosynangiosis bypass showing patent bilateral indirect bypass grafts supplying the MCA territory (*arrowheads*), with progressive stenosis of the bilateral ICAs and moyamoya vessels (*chevron arrows*).

**Case 8.** A 17-year-old boy with MOPD II (weight 13.2 kg, height 100 cm) presented with sudden-onset severe headache, nausea, and vomiting consistent with SAH. He then was diagnosed with a ruptured left posterior inferior cerebellar artery (PICA) aneurysm, bilateral MMD with supraclinoid ICA stenosis, and extensive collateral vessels (Fig. 7.3A-D). Brain MRI showed no evidence of infarct, and SPECT revealed a perfusion defect in the right parietal cortex. Over a 3-week period he underwent clipping of the left PICA aneurysm, a right direct extracranial-to-intracranial bypass (using a 0.9-mm STA branch to a 0.9-mm $M_4$ branch of the MCA [Fig. 7.3]; indocyanine green videoangiography confirmed graft patency), and an indirect left extracranial-to-intracranial bypass. He had an excellent postoperative recovery; angiography 6 months after surgery confirmed complete obliteration of the PICA aneurysm and patent bilateral bypass grafts supplying the majority of the cortical hemispheres (Fig. 7.3E-F). After 8 years of follow-up, he remained neurologically normal; angiography revealed an asymptomatic 3-mm left $P_1$ aneurysm that had not changed over the 7 years.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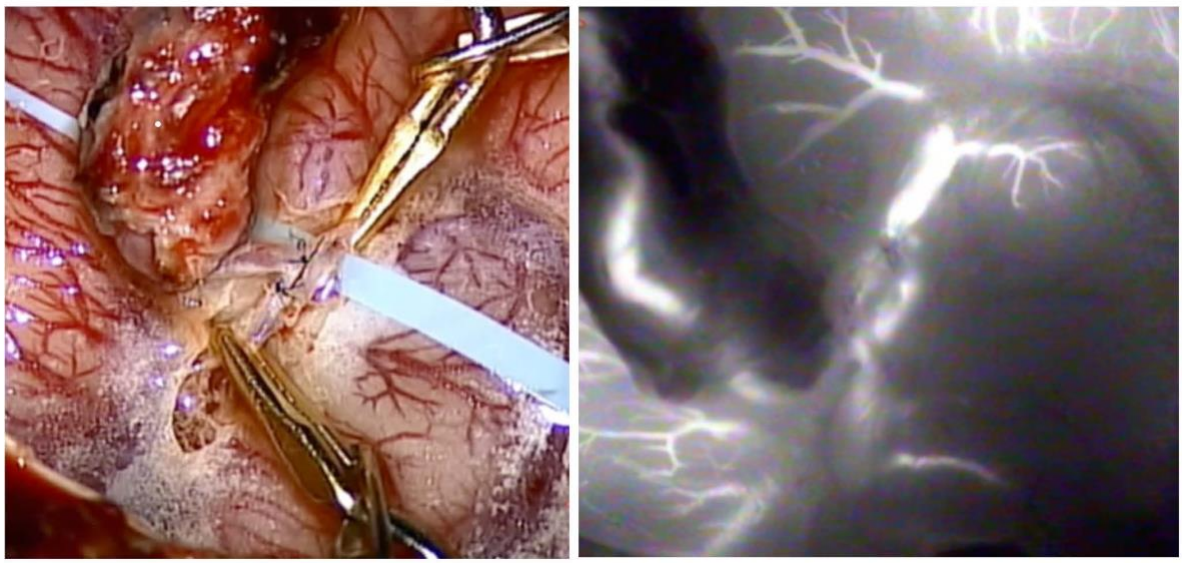


**Fig. 7.3.** Case 8. Cerebral angiograms of a 17-year-old boy with MOPD II, PICA aneurysm, and MMD. Preoperative (**A**–**D**) and 6-month postoperative (**E**–**F**) angiograms showing right direct STA–MCA and left indirect EDAS extracranial-to-intracranial bypasses. **A and B:** Anteroposterior and lateral views, respectively, of right CCA injection. **C and D:** Anteroposterior and lateral views, respectively, of left CCA injection. *Chevron arrows* indicate bilateral MMD with supraclinoid ICA stenosis, and *asterisks* indicate extensive collateral vessels. **E and F:** Anteroposterior and lateral views, respectively, of right CCA injection showing patent direct STA–MCA bypass graft (*arrows*). **G and H:** Anteroposterior and lateral views, respectively, of left CCA injection showing a patent indirect EDAS bypass graft. Both bypass grafts supply the majority of the cortical hemispheres. **I and J:** Intraoperative view of right direct extracranial-to-intracranial bypass (using a 0.9-mm STA branch to 0.9-mm M4 branch of the MCA).

## 7.4 Discussion

As shown in this study, there is a difference between patients with classical MMD and MMS, whereby MMS is more common in the paediatric age group, fewer Asian, with more seizure presentations compared to patients with classical MMD. However, their underlying radiological characteristics, 30-days postoperative risk, and long term

stroke risk did not appear to significantly differ compared to patients with classical MMD. We would therefore advocate aggressive management of MMS patients, and offer them revascularisations when required.

Similar to our findings, a recent study which included 185 patients with MMD or MMS presenting to the Johns Hopkins Medical Institutions between 1994 and 2015 found largely comparable clinical outcome after surgical treatment. Both groups had similar length of hospital stay after surgery, similar stroke free survival after diagnosis and surgical treatment (Feghali et al., 2019).

Majewski osteodysplastic primordial dwarfism Type II (Online Mendelian Inheritance in Man #210720) is a distinctive diagnostic entity within the microcephalic primordial dwarfism group and one of the most common conditions encountered (Rauch, 2011, Young et al., 2004). Aside from the classic features of severe prenatal and postnatal growth failure, individuals with MOPD II have a characteristic skeletal dysplasia,(Kantaputra et al., 2011, Hall et al., 2004, Willems et al., 2010) abnormal dentition (Kantaputra et al., 2011), insulin resistance (Huang-Doran et al., 2011), and an increased risk for cerebrovascular disease (Bober et al., 2010, Brancati et al., 2005, Waldron et al., 2009). The disorder is caused by mutations in the *PCNT* gene and is inherited in an autosomal recessive manner. Moyamoya disease and multiple intracranial aneurysms represent independent sources of morbidity and death in up to 50% of patients with MOPD II. Some of our patients also exhibited coexistence of the 2 intracranial vascular pathologies.

In our small series, MMD affected the younger patients, whereas older patients developed intracranial aneurysms (which ruptured in 2 patients). Because of the progressive nature of new intracranial vascular anomalies in patients with MOPD II, we recommend long-term vascular imaging surveillance for the development of new vascular anomalies or progression of existing ones. We advocate MR angiography (preferred to reduce the long-term radiation risk) or CT angiography at diagnosis and then annually for life; cerebral angiograms should be obtained when clinically indicated to study the cerebral vasculature in greater detail.

As found in our case series, 1 patient developed a new aneurysm 2 years after initial imaging. We believed that it was important to treat this aneurysm early even though it was small (less than 7 mm in diameter). According to International Study of Unruptured Intracranial Aneurysms (ISUIA) data, (Wiebers et al., 2003) aneurysms in the posterior circulation less than 7 mm in diameter have only a 2.5% 5-year cumulative rupture rate; however, these data would not necessarily apply to our cohort of patients with MOPD II, because such patients were not included in the ISUIA study. Therefore, we elected to treat the aneurysm aggressively and achieved successful complete occlusion. We developed this proactive aneurysm-treatment strategy after we followed a patient with MOPD II (Case 7) with a posterior cerebral artery aneurysm that ruptured 4 years later and another patient with MOPD II (Case 9) who suffered an SAH from a newly developed basilar artery aneurysm 2 years after clipping of an ACoA aneurysm, with no other aneurysms identified at the time of initial diagnosis. Additional aneurysms were also identified over the 5 years of subsequent follow up, and she underwent coiling of the ruptured basilar tip aneurysm, and pipeline-assisted coiling of a VB junction aneurysm and left ICA aneurysm. Five other tiny aneurysms were monitored (2 right MCA aneurysms, 1 left MCA aneurysm, 1 right terminal ICA aneurysm, and 1 right posterior communicating artery aneurysm), but unfortunately, she died as a result of a ruptured untreated right-sided aneurysm 5 years after her initial diagnosis.

Because the STA and $M_4$ arteries in patients with MOPD II are extremely small and fragile, it is not usually possible to perform a direct bypass, although we did so successfully in 1 patient. The indirect EDAS procedures provided robust angiographic revascularization, according to follow-up angiograms, and excellent short- and long-term neurological outcomes. Few successful neurovascular surgical cases of patients with MOPD II have been reported in the literature (Kannu et al., 2004, Waldron et al., 2009, Young et al., 2004). Young et al. and Kannu et al. separately described 1 case each of a child with MOPD II and MMD. Developmental delay was noted in the child studied by Young et al. at 2.5 years, and despite surgical attempts to restore the carotid circulation, the child experienced progressive disability and loss of skills caused by ongoing multiple cerebral infarctions. In the case described by Kannu et al.

the child developed sudden right-sided weakness at the age of 2 years, 11 months. Cranial imaging confirmed cerebral infarction secondary to MMD and progressive arterial stenosis; she underwent bilateral EDAS and had no additional strokes after surgery. However, her fine and gross motor skills were mildly delayed after the previous cerebral ischemic episodes. Waldron et al. reported 3 cases of patients with MOPD II, multiple intracranial aneurysms, and MMD. Two of the patients (a 15-year-old boy and a 17-year-old girl) presented with aneurysmal SAH, and aneurysm obliterations were performed by either clipping or coiling. One patient had recovered to baseline by discharge, and 1 died 5 months later secondary to basal ganglia hemorrhage. The third patient was a 22-month-old boy with bilateral MMD who experienced additional strokes despite EDAS procedures 6 months earlier. Magnetic resonance imaging revealed new infarcts, and DSA showed bilateral ICA occlusion and patent STA grafts but no revascularization from the onlay grafts. An attempted direct STA–M2 bypass failed to establish adequate cerebral blood flow, and temporalis muscle synangiosis and multiple burr hole placements were eventually performed to encourage hemispheric collateralization. No long-term outcome was reported in these cases.

As shown in our case series, these patients often have multiple other comorbidities. With a mean follow-up of 6.6 years (range 4–11 years), 2 of our 10 patients died of other medical problems. Of those remaining, 1 patient with MMD experienced non-disabling symptoms consistent with TIAs, and another patient who had undergone previous aneurysm clipping experienced an aneurysmal SAH from a newly developed aneurysm. Otherwise, at the time of this writing, the rest of the cohort had an active lifestyle and no new neurological symptoms.

Apart from the technical challenges of surgically managing the intracranial vascular anomalies in this group of patients, anesthesia risks are also an important consideration. Many of these children have severe respiratory problems, such as recurrent upper respiratory tract infection and pneumonia, during the newborn period, and scoliosis can compromise their respiratory capacity (Hall et al., 2004). Furthermore, there is increasing evidence that the vascular changes noted intracranially might be part of a more systemic problem, with patients developing

coronary artery stenosis, pulmonary artery stenosis, and renal artery aneurysms (Bober et al., 2010). Therefore, the involvement of an expert multidisciplinary team is paramount for managing these patients successfully.

## 7.5 Conclusions

Contrary to popular beliefs, the post revascularisation outcome (30 days and long term stroke risks) of MMS patients are very similar to patients with classical MMD. However, we need to be mindful of the other associated medical conditions when managing patients with MMS due to their underlying diagnosis. When we study patients with MOPD in details, to our knowledge, this is the largest reported surgical series of patients with MOPD II and intracranial vascular anomalies. Moyamoya disease presented at a younger age, whereas aneurysms were more prevalent in the older age group. Microneurosurgery with either intracranial revascularization or aneurysm clipping is extremely challenging but feasible at expert centers, and good long-term outcomes are possible. Long-term surveillance with vascular imaging is also extremely important in view of the progressive nature of these intracranial vascular anomalies.

# CHAPTER EIGHT

# DEVELOPMENT AND VALIDATION OF STANFORD-BERLIN MOYAMOYA GRADING SYSTEM AND DEVELOPMENT OF PREDICTIVE MODELLING FOR PERIOPERATIVE STROKE RISK

## 8.1 Introduction

Despite the popularity of the widely known Suzuki grading system for MMD, it did not allow for the estimation of the severity of disease, or the associated risk for clinical symptoms, and is of limited clinical use (Teo et al., 2020). We hypothesized of a robust and means tested scoring system that could be used to identify MMD subgroups with good and poor outcome, and thereby help with decision making process.

Therefore, together with the perioperative stroke risk factors identified from Chapter 4, and the validated Berlin symptomatic grading system (Czabanka et al., 2011c, Czabanka et al., 2016), we proposed the Stanford Berlin Moyamoya grading system, and a new moyamoya predictive modelling for assessing postoperative stroke risk.

## 8.2 Methods

### 8.2.1 Study Population

As shown in chapter 4, from 1991-2014, 769 patients with MMD underwent 1250 bypasses, 84 patients had a perioperative stroke (including ischaemic and haemorrhagic stroke) within 30-days. Potential risk factors for postop strokes were collected including patient demographics (age, gender, ethnicity), family history, comorbidities (hyperlipidaemia, diabetes, moyamoya syndrome), clinical presentations (ischaemic, haemorrhagic, seizure), radiological findings (Suzuki stage, DSA score, mMRI score, HDR) and types of bypasses. Univariate analysis of potential risk factors was performed.

### 8.2.2 Outcome measure

Strokes can have different severity, and chapter 4 studied the roles of the various risk factors on any postop strokes. We defined 30-day major strokes as postoperative stroke that resulted in changes to mRS as compared to their preoperative baseline score, with a corresponding new diffusion weighted imaging (DWI) lesion or hemorrhagic stroke.

In this chapter, we would determine if the newly proposed SBM grading system is applicable for postop strokes, and postop major strokes respectively.

### 8.2.3 Model Selection – Stanford Berlin Moyamoya Grade

Based on multivariate logistic regression analysis in Chapter 4, only the 4 factors are significantly associated with postoperative stroke risks.

Table 8.1. Logistic Regression Analysis for risk factors associated with 30-days postoperative stroke (ischaemic and haemorrhagic) risk

| Variable | Coefficient | Standard Error | P-value | Odds Ratio | 95% Confidence Interval |
|---|---|---|---|---|---|
| **Age** | 1.295 | 0.579 | 0.025* | 3.650 | 1.173-11.359 |
| **DSA score** | 1.294 | 0.415 | 0.002* | 3.648 | 1.618-8.222 |
| **mMRI score** | 2.740 | 0.765 | <0.0001* | 15.494 | 3.462-69.335 |
| **HDR score** | 2.866 | 0.805 | <0.0001* | 17.559 | 3.626-85.037 |

Therefore, taking into account of additional factors identified in this thesis, we proposed the following Stanford-Berlin Moyamoya grading (SBM) system.

Table 8.2. Newly proposed Stanford Berlin Moyamoya (SBM) Grading System

| FACTORS | | SCORE |
|---|---|---|
| **AGE** | ≤18 years | 1 |
| | 19-39 years | 2 |
| | 40-59 years | 3 |
| | ≥ 60 years | 4 |
| | | |
| **DSA** | Steno-occlusive lesion + moyamoya | 1 |
| | Steno-occlusive lesion + moyamoya + ICIC | 2 |
| | Steno-occlusive lesion + moyamoya + ECIC | 3 |
| | | |
| **MMRI** | None | 0 |
| | Ischaemia / atrophy | 1 |
| | DWI +ve infarct | 2 |
| | | |
| **HDR** | Good augmentation | 0 |
| | Impaired augmentation | 1 |
| | Steal phenomenon | 2 |

### 8.2.4 Statistical Analysis

Univariate analysis was performed with Chi square test and Fisher's exact test as appropriate. Multivariable logistic regression model was used to identify variables that independently predicted in-hospital mortality. Odds ratios (OR), 95 % confidence intervals (CI), and p-values were reported.

We evaluated the developed scoring system by the area under the curve (AUC) and receiver operating characteristic (ROC). The area under the curve (AUC) were considered excellent for AUC between 0.9-1, good for AUC between 0.8-0.9, fair for AUC between 0.7-0.8, poor for AUC between 0.6-0.7, and no correlation for AUC between 0.5-0.6.

### 8.2.5 Validation

The Stanford Berlin Moyamoya (SBM) score was developed from the cohort 1991-2014. A separate cohort of 264 adult MMD patients treated at Stanford University Medical Centre between 2015-2018 was used to validate and evaluate the performance of the newly designed SBM score. The demographic data was collected prospectively in the moyamoya database. The individual components of the Stanford Berlin moyamoya scores were assigned by 2 independent assessors (YP, AW), and if disagreement occurred, the senior clinician (GKS) was consulted for a final score.

### 8.2.6 Development of Predictive Modelling

Using R statistical package (Caret as part of R), we attempted to construct a mathematical model that could reliably predict 30-day major post-bypass stroke for MMD patients using popular machine learning algorithm. The entire dataset from 1990-2018 was divided into train and test sets, with 70/30 split in order to allocate the 30-day stroke events proportionally. Missing data imputation was carried out using kNN approach, a standard data imputation technique. 2 machine learning models were used: Dimensionality reduction and Lasso regression, and Gradient Boosted Machine (GBM) regression. (Hastie et al., 2009, Boehmke and Greenwell, 2019, Tibshirani, 1996, Tibshirani, 1997)

## 8.3 Results

### 8.3.1 Outcome measure – 30 day strokes

Of the 84 patients with perioperative strokes, fifty-two patients (6.8%) had a major postoperative stroke with worsening mRS within 30 days postoperatively. The 30-days major stroke risk was 5.3% (41/769) and 2.6% (12/467) after the first and second bypasses respectively, with a 4.2% per procedure major stroke risk. Ten patients had postoperative extraaxial hematoma (subdural or extradural hematoma) requiring evacuation surgery. Five patients (0.6%) died of stroke within 30 days postoperatively. Of the 52 patients with major stroke, 25(48%) improved their mRS (≥ 1 point) at six months follow-up.

Univariate analysis of potential risk factors for postop strokes was previously shown in Chapter 4, Table 4.2. In this chapter, we performed univariate analysis of these potential risk factors based on major postop strokes as defined (Table 8.3).

Table 8.3. Univariate analysis of risk factors associated with 30-days major postoperative ischaemic and haemorrhagic stroke

| | | 30 Day Perioperative Major Stroke | | | | |
|---|---|---|---|---|---|---|
| | | No | | Yes | | p-value |
| | | No. of Patients | Row % | No. of Patients | Row % | |
| **Age Category** | **≤18 yr** | 201 | 98.0% | 4 | 2.0% | <0.001* |
| | **19-39 yr** | 274 | 94.8% | 15 | 5.2% | |
| | **40- 59 yr** | 226 | 88.6% | 29 | 11.4% | |
| | **≥60 yr** | 16 | 80.0% | 4 | 20.0% | |
| **Gender** | **Female** | 509 | 92.9% | 39 | 7.1% | 0.537 |
| | **Male** | 208 | 94.1% | 13 | 5.9% | |
| **Ethnicity** | **Caucasian** | 386 | 93.7% | 26 | 6.3% | 0.601 |
| | **Asian** | 229 | 92.0% | 20 | 8.0% | |
| | **Others** | 102 | 94.4% | 6 | 5.6% | |
| **Family History of MMD** | **No** | 108 | 93.9% | 7 | 6.1% | 0.189 |
| | **Yes** | 27 | 100.0% | 0 | 0% | |
| | | | | | | |
| **Presentations** | | | | | | |
| **Hemorrhagic** | **No** | 620 | 92.8% | 48 | 7.2% | 0.229 |
| | **Yes** | 97 | 96.0% | 4 | 4.0% | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Ischemic** | **No** | 133 | 97.1% | 4 | 2.9% | 0.048* |
| | **Yes** | 584 | 92.4% | 48 | 7.6% | |
| **Headache** | **No** | 380 | 91.6% | 35 | 8.4% | 0.046* |
| | **Yes** | 337 | 95.2% | 17 | 4.8% | |
| **Seizure** | **No** | 634 | 93.4% | 45 | 6.6% | 0.683 |
| | **Yes** | 83 | 92.2% | 7 | 7.8% | |
| | | | | | | |
| **PMHx** | | | | | | |
| **Diabetes** | **No** | 484 | 93.4% | 34 | 6.6% | 0.026* |
| | **Yes** | 70 | 86.4% | 11 | 13.6% | |
| | **Unknown** | 163 | 95.9% | 7 | 4.1% | |
| **Hyperlipidemia** | **No** | 432 | 94.5% | 25 | 5.5% | 0.001* |
| | **Yes** | 114 | 86.4% | 18 | 13.6% | |
| | **Unknown** | 171 | 95.0% | 9 | 5.2% | |
| **Moyamoya Syndrome** | **No** | 630 | 93.1% | 47 | 6.9% | 0.589 |
| | **Yes** | 87 | 94.6% | 5 | 5.4% | |
| **Down Syndrome** | **No** | 695 | 93.2% | 51 | 6.8% | 0.640 |
| | **Yes** | 22 | 95.7% | 1 | 4.3% | |
| **Neurofibromatosis** | **No** | 702 | 93.1% | 52 | 6.9% | 0.292 |
| | **Yes** | 15 | 100.0% | 0 | 0.0% | |
| **Dwarfism** | **No** | 708 | 93.2% | 52 | 6.8% | 0.416 |
| | **Yes** | 9 | 100.0% | 0 | 0.0% | |
| | | | | | | |
| **Radiological Findings** | | | | | | |
| **Suzuki stage** | **2** | 28 | 100.0% | 0 | 0.0% | <0.0001* |
| | **3** | 286 | 97.3% | 8 | 2.7% | |
| | **4** | 344 | 90.8% | 35 | 9.2% | |
| | **5** | 39 | 81.3% | 9 | 18.8% | |
| | **6** | 1 | 100.0% | 0 | 0.0% | |
| **DSA score** | **1** | 16 | 100.0% | 0 | 0.0% | <0.0001* |
| | **2** | 543 | 95.3% | 27 | 4.7% | |
| | **3** | 138 | 84.7% | 25 | 15.3% | |
| **mMRI score** | **0** | 150 | 98.0% | 3 | 2.0% | <0.0001* |
| | **1** | 525 | 93.8% | 35 | 6.3% | |
| | **2** | 23 | 63.9% | 13 | 36.1% | |
| **HDR score** | **0** | 167 | 99.4% | 1 | 0.6% | <0.0001* |
| | **1** | 343 | 94.0% | 22 | 6.0% | |
| | **2** | 79 | 77.5% | 23 | 22.5% | |
| | | | | | | |
| **Types of Surgery** | **Direct** | 652 | 92.6% | 52 | 7.4% | 0.076 |
| **First Bypass** | **Indirect** | 63 | 100.0% | 0 | 0% | |

Based on the univariate analyses, the risk factors associated with major postop strokes are very similar to the risk factors for postop strokes, including older age, ischaemic presentation, comorbidity of diabetes, hyperlipidaemia, the Suzuki stage,

DSA score, mMRI score, and HDR score. With multivariate logistic regression analysis, the risk factors that remained statistically significant were age (p=0.001), mMRI score (p=0.001), HDR score (<0.001), while DSA score showed trend of significance (p=0.094).

**Table 8.4**. Logistic Regression Analysis for risk factors associated with 30-days postoperative major stroke (ischemic and hemorrhagic) risk.

| Variable | Coefficient | Standard Error | p-value | Odds Ratio | 95% Confidence Interval |
|---|---|---|---|---|---|
| **Age** | 0.935 | 0.279 | 0.001* | 2.547 | 1.476-4.397 |
| **Ischaemic presentation** | 1.361 | 1.061 | 0.2 | 3.899 | 0.488-31.164 |
| **Headache presentation** | 0.166 | 0.420 | 0.693 | 1.18 | 0.518-2.687 |
| **Diabetes** | -0.008 | 0.556 | 0.989 | 0.993 | 0.334-2.949 |
| **Hyperlipidaemia** | -0.133 | 0.475 | 0.779 | 0.875 | 0.345-2.222 |
| **Suzuki Stage** | 0.622 | 0.376 | 0.098 | 1.863 | 0.892-3.893 |
| **DSA score** | 0.776 | 0.463 | 0.094 | 2.173 | 0.877-5.384 |
| **mMRI score** | 1.634 | 0.492 | 0.001* | 5.122 | 1.953-13.431 |
| **HDR score** | 1.54 | 0.380 | <0.0001* | 4.664 | 2.216-9.818 |
| **Surgery Types** | -1.227 | 1.119 | 0.273 | 0.293 | 0.033-2.631 |

Table 8.5. A detailed analysis of the multivariate regression analysis on the 30-days postop major stroke risk, the odd ratio for various individual component of the risk factors are listed. DSA score is no longer statistically significant.

| Variable | Odds Ratio | 95% Confidence interval | p-value |
|---|---|---|---|
| **Age** | | | |
| **≤18 yr** | | | 0.024 |
| **19-39 yr** | 2.714 | 0.53-13.891 | 0.231 |
| **40- 59 yr** | 7.167 | 1.399-36.703 | 0.018 |
| **≥60 yr** | 14.583 | 1.688-125.983 | 0.015 |
| | | | |
| **mMRI score** | | | |
| **None** | | | 0 |
| **Ischaemia / atrophy** | 0.889 | 0.179-4.425 | 0.886 |
| **DWI +ve infarct** | 8.072 | 1.306-49.89 | 0.025 |
| | | | |
| **HDR score** | | | |
| **Good augmentation** | | | 0 |
| **Impaired augmentation** | 3.818 | 0.469-31.082 | 0.21 |
| **Steal phenomenon** | 19.555 | 2.285-167.37 | 0.007 |

Based on this multivariate regression model, the strongest risk factor for postop major strokes are the presence of steal phenomenon (OR 19.6), followed by older age (≥60year, OR 14.6), recent DWI+ve infarct (OR 8.1) and age 40-59 (OR 7.2). These factors are highly predictive of postop stroke risks – **S**teal phenomenon (based on

HDR score), **A**ge (over 40 years old), **D**WI +ve infarct, which could be known as the "SAD score".

Table 8.6 Compared the difference between 30-day perioperative stroke and major stroke risks in the various factors listed in Stanford Berlin Moyamoya grading system. With increasing score in each category of the risk factor, the risks of 30-day stroke or 30-day major strokes increased accordingly.

| | | 30Day stroke | | 30Day Major Stroke | |
|---|---|---|---|---|---|
| | | **No. of Patients** | **Row %** | **No. of Patients** | **Row %** |
| **Age Category** | **≤18 yr** | 11 | 5.4% | 4 | 2.0% |
| | **19-39 yr** | 27 | 9.3% | 15 | 5.2% |
| | **40- 59 yr** | 42 | 16.5% | 29 | 11.4% |
| | **≥60 yr** | 4 | 20.0% | 4 | 20.0% |
| **DSA score** | **1** | 0 | 0.0% | 0 | 0.0% |
| | **2** | 44 | 7.7% | 27 | 4.7% |
| | **3** | 40 | 24.5% | 25 | 15.3% |
| **mMRI score** | **0** | 5 | 3.3% | 3 | 2.0% |
| | **1** | 54 | 9.6% | 35 | 6.3% |
| | **2** | 24 | 66.7% | 13 | 36.1% |
| **HDR score** | **0** | 2 | 1.2% | 1 | 0.6% |
| | **1** | 37 | 10.1% | 22 | 6.0% |
| | **2** | 33 | 32.4% | 23 | 22.5% |

### 8.3.2 Stanford Berlin Moyamoya grading system Model Performance

Based on the proposed Stanford Berlin moyamoya grading system, we assigned the scores to all 769 patients with 1250 bypasses (cohort 1991-2014) and correlated with their 30-day major stroke outcome. The following ROC curve analysis (Figure 8.1) and probability distribution (Figure 8.2) was obtained.

The ROC curve analysis between Stanford Berlin moyamoya grade and the risk of 30-day postoperative major stroke, AUC was 0.85, which meant good correlation between the SBM grade and postop major stroke.

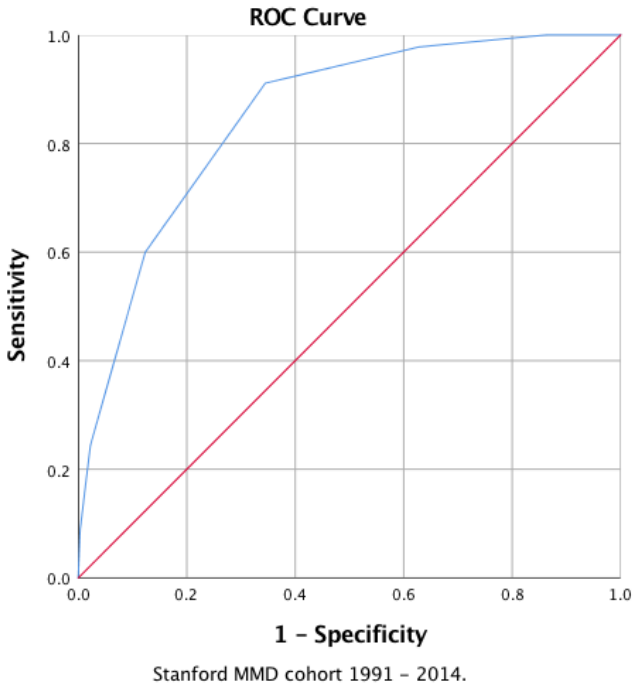



Figure 8.1 ROC curve analysis between Stanford Berlin moyamoya grade and the risk of 30-day postoperative major stroke, AUC was 0.85, which meant good correlation between the SBM grade and postop major stroke. Data generated from 1991-2014 cohort.

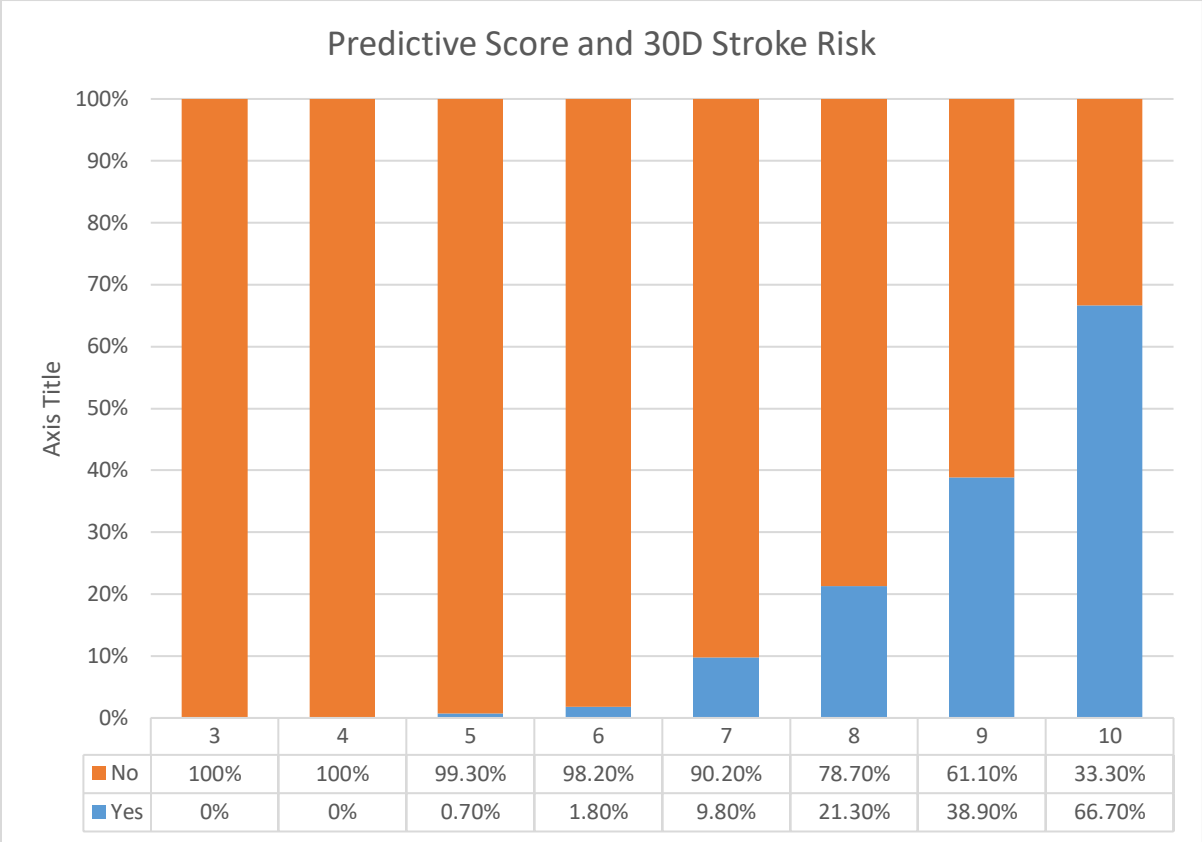



Figure 8.2 Probability distribution of 30 day postoperative major stroke risks with different scores based on the proposed Stanford Berlin moyamoya grading system, data generated from cohort 1991-2014.

The result showed that the higher the Stanford Berlin MMD score (SBMS), the higher the probability of postop major stroke risks. Based on the data, up to SBMS score of 6, the postop stroke risk is very low (less than 2%) but increased to nearly 10% stroke risk with SBMS score of 7, and over 50% with SBMS score of 10. This could be used to stratify the stroke risk to low (SBMS ≤6, 0-2%), moderate (SBMS 7-8, 10-20%), high (SBMS ≥9, >20%).

### 8.3.3 Validation of Stanford Berlin Moyamoya Grading System

In order to validate the newly proposed Stanford Berlin Moyamoya grading system, we identified another cohort of moyamoya patients treated at Stanford University Medical Centre between 2015-2018, consisting of 264 adult patients with 372 bypasses.

Table 8.7 Comparison of baseline characteristics of the cohort from 1991-2014, and validation cohort 2015-2018.

| | | 2015-2018 cohort 264 patients | | 1991-2014 cohort 769 patients | | p-value |
|---|---|---|---|---|---|---|
| | | No. of patients | Column % | No. of patients | Column % | |
| Gender | Female | 202 | 76.50% | 548 | 71.30% | 0.099 |
| | Male | 62 | 23.50% | 221 | 28.90% | |
| Ethnicity | Caucasian | 128 | 48.50% | 412 | 53.60% | 0.131 |
| | Asian | 86 | 32.60% | 249 | 32.40% | |
| | Others | 50 | 18.90% | 108 | 14.00% | |
| Moyamoya syndrome | No | 240 | 90.90% | 677 | 88.00% | 0.202 |
| | Yes | 24 | 9.10% | 92 | 12.00% | |
| Diabetes | No | 220 | 83.30% | 518 | 67.40% | 0.205 |
| | Yes | 44 | 16.70% | 132 | 17.20% | |
| Presentation | | | | | | |
| Haemorrhagic | No | 241 | 90.90% | 668 | 86.90% | 0.06 |
| | Yes | 23 | 8.70% | 101 | 13.10% | |
| Ischaemic | No | 107 | 40.50% | 333 | 43.30% | 0.43 |
| | Yes | 157 | 59.50% | 436 | 56.70% | |
| Headache | No | 98 | 37.10% | 415 | 54.00% | <0.001 |
| | Yes | 166 | 62.90% | 354 | 46.00% | |
| Seizure | No | 220 | 83.30% | 679 | 88.30% | 0.038 |
| | Yes | 44 | 16.70% | 90 | 11.70% | |

Comparing the demographic characteristics between the validation cohort (2015-2018) and the cohort from 1991-2014, there was no significant differences between the 2 groups of patients. The mode of presentation were also similar whereby majority of patients had ischaemic presentation, and small proportion with haemorrhagic presentation. More patients had headache and seizures recorded in the cohort from 2015-2018, but this could be due to increasing awareness amongst clinicians and patients on these symptoms.

Table 8.8 Assessment of the Stanford Berlin MMD Grade on the risk stratification of 30-days postoperative major stroke risks in the validation cohort (2015-2018).

| | | 30 Days Perioperative Major Stroke | | | | |
|---|---|---|---|---|---|---|
| | | No | | Yes | | |
| | | No of Patients | Row % | No of Patients | Row % | P-value |
| Age Score | ≤18 yr | 1 | 100.00% | 0 | 0.00% | 0.11 |
| | 19-39 yr | 114 | 94.20% | 7 | 5.80% | |
| | 40- 59 yr | 116 | 86.60% | 18 | 13.40% | |
| | ≥60 yr | 7 | 87.50% | 1 | 12.50% | |
| DSA Score | 1 | 11 | 91.70% | 1 | 8.30% | 0.397 |
| | 2 | 123 | 91.80% | 11 | 8.20% | |
| | 3 | 89 | 86.40% | 14 | 13.60% | |
| MRI score | 0 | 23 | 100.00% | 0 | 0.00% | 0.003 |
| | 1 | 163 | 92.60% | 13 | 7.40% | |
| | 2 | 51 | 79.70% | 13 | 20.30% | |
| HDR Score | 0 | 68 | 97.10% | 2 | 2.90% | 0.001 |
| | 1 | 102 | 93.60% | 7 | 6.40% | |
| | 2 | 56 | 78.90% | 15 | 21.10% | |

Due to the validation cohort only including adult MMD patients from 2015-2018, there was not enough patients in the paediatric cohort (<18 year old) to study the effect of young age conclusively, only a trend was identified (p=0.11) with age effect and 30-day major stroke risks.

With similar findings as the original cohort from 1990-2014, patients with DWI +ve infarct within 30days of bypass are at a high risk of postop major stroke (20.3%) compared 7.4% of patients with old strokes. Based on this data, we do not perform revascularisation procedure on MMD patients within 30days of an acute infarct.

For patients with haemodynamic compromise, in the presence of steal phenomenon, postop major stroke risk is 21.1% compared to 6.4% for patients with impaired cerebrovascular reserve.

Interestingly, in this validation cohort, the various angiographic scores did not correlate to postop major stroke risks.

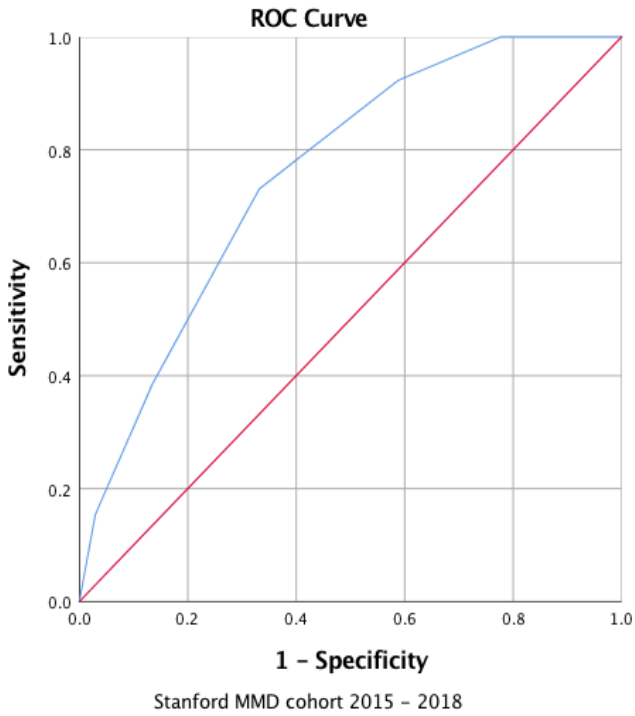
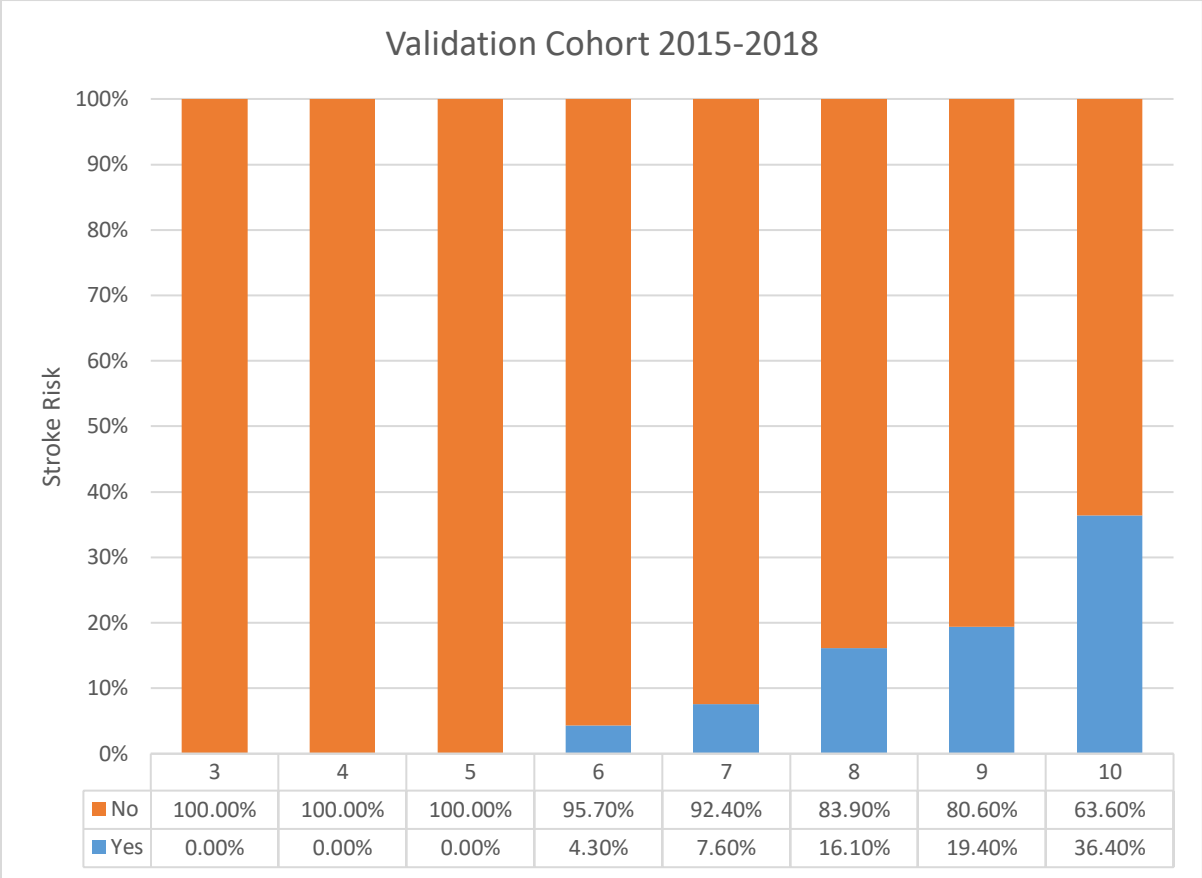



Figure 8.3 Using the validation cohort from 2015-2018, ROC curve analysis between Stanford Berlin moyamoya grade and the risk of 30-day postoperative major stroke, AUC was 0.76, which meant fair to good correlation.




| | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|
| No | 100.00% | 100.00% | 100.00% | 95.70% | 92.40% | 83.90% | 80.60% | 63.60% |
| Yes | 0.00% | 0.00% | 0.00% | 4.30% | 7.60% | 16.10% | 19.40% | 36.40% |

Figure 8.4. Based on the validation cohort, the probability distribution of 30-day postoperative major stroke risks with different scores based on the proposed Stanford Berlin moyamoya grading system.

Based on the data, in keeping with result from initial prediction, up to SBMS score of 6, the postop stroke risk is still considered low (0-4% in the validation cohort), but the risk of major postop strokes increased with advancing SBMS score.

Similar to the findings in cohort 1991-2014, the postop major stroke risk could be stratified to low (SBMS ≤6, 0-5%), moderate (SBMS 7-8, 5-20%), high (SBMS ≥9, >20%).

### 8.3.4 Development of Predictive modelling

Potentially SBMS could be fine-tuned, and assigned the appropriate weighting to the different factors in the Stanford Berlin moyamoya grade, based on machine learning algorithm. In order to develop the predictive modelling, the combined patient cohort from 1991 – 2018, which included 1033 patients, 78 event rate, were split in 70/30 distribution, consisting of:

- Training set 70% of data, 723 patients, 55 events
- Validation set 30% of data, 310 patients, 23 events

Using kNN, standard data imputation technique, the data set was completed. 2 models of machine learning algorithm were used:

- Dimensionality reduction and Lasso regression
- Gradient Boosted Machine (GBM) regression

GBM regression models resulted in greater performance in the prediction of postop major strokes (93% accuracy), compared to Lasso regression model with 80% accuracy.

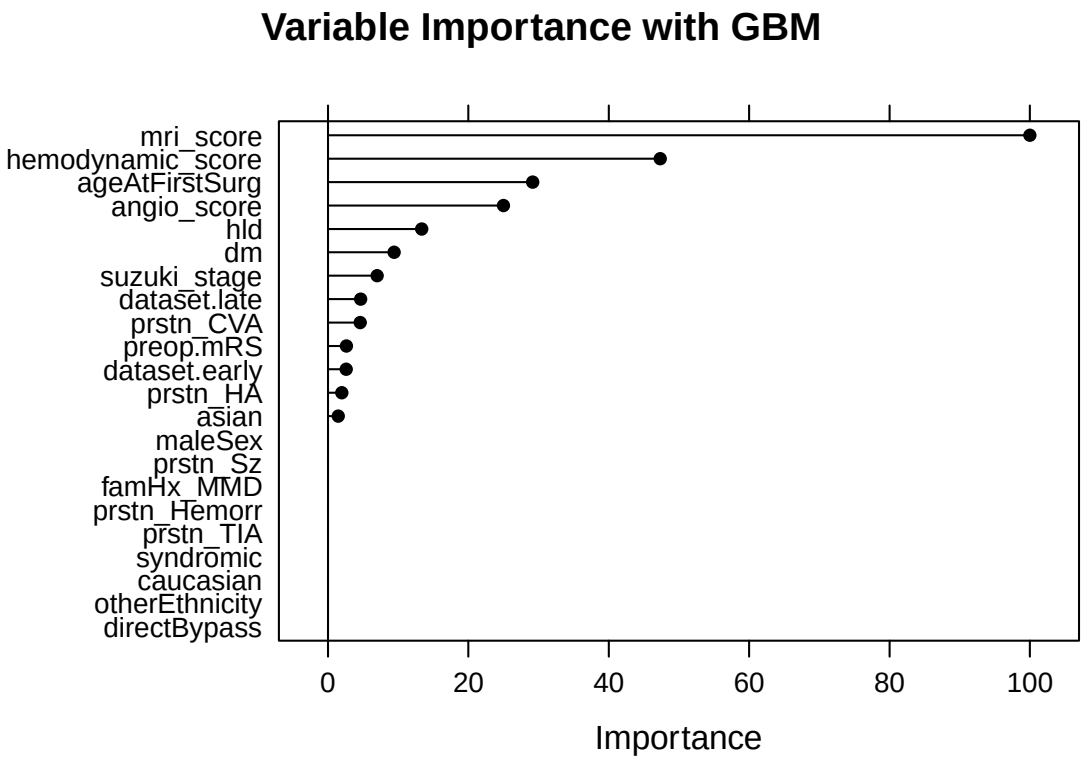
Table 8.9 Predictive accuracy for postoperative major strokes on the validation set, based on GBM regression machine learning models.

| | | **Reference** | |
|---|---|---|---|
| | | **No** | **Yes** |
| **Prediction** | **No** | 284 | 21 |
| | **Yes** | 1 | 2 |

Based on Table 8.9, the GBM regression machine learning models could accurately predict the outcome on 286 / 308 in the validation set, i.e. with 93% accuracy. This model has a very high specificity (99.6%, 284/285), and a negative predictive value of 93% (284/305). However, its positive predictive value is 66.7% (2/3), and lacks sensitivity (8.7%, 2/23).

The GBM regression machine learning models generated an importance matrix plot which listed the factors taken into consideration (based on the weight and importance of the predictive factors) for predicting the risk with or without postoperative major strokes. The top 4 factors listed are MRI score (100%), haemodynamic score (50%), age at first surgery (30%), and DSA score (25%).

Figure 8.5. Importance matrix plot based on GBM model for prediction of 30days major strokes post-bypass.



## 8.4 Discussion

The newly proposed Stanford Berlin Moyamoya (SBM) grading system, incorporating age (1-4), mMRI score (0-2), HDR score (0-2), and DSA score (1-3), is derived from the multivariate regression analyses on risk factors strongly associated with postop stroke risk, and modified from Berlin moyamoya symptomatic grading system. The model was developed from 769 MMD patients with 1250 bypasses from 1991-2014 cohort, and subsequently validated on a separate 2015-2018 cohort of 264 adult patients with 372 bypasses.

Based on the derivation (1991-2014) and validation cohort (2015-2018), similar trend was observed with increasing stroke risk and increasing SBM score. The postop major stroke risk could be stratified to low (SBMS ≤6, 0-5%), moderate (SBMS 7-8, 5-20%), high (SBMS ≥9, >20%).

Based on this multivariate regression model (Table 8.5), the strongest risk factor for postop major strokes are the presence of steal phenomenon (OR 19.6), followed by older age (≥60year, OR 14.6), recent DWI+ve infarct (OR 8.1) and age 40-59 (OR 7.2). These factors are highly predictive of postop stroke risks – **S**teal phenomenon (based on HDR score), **A**ge (over 40 years old), **D**WI +ve infarct, which could be known as the “SAD score”.

Although the SBM grading was validated on the risk of postop major strokes, it could also be applied to patients with strokes that did not result in changes to mRS, i.e. any 30-day postop strokes. Table 8.6 compared the difference between 30-day perioperative stroke and major stroke risks in the various factors listed in Stanford Berlin Moyamoya grading system. With increasing score in each category of the risk factor, the risks of 30-day stroke or 30-day major strokes increased accordingly.

We also employed machine learning algorithm using Gradient Boosted Machine technique to generate a predictive model to predict post-bypass stroke risks, with 93% accuracy, 99% sensitivity. The 4 most important factors identified in the machine learning algorithm were the same 4 factors in the SBM grade system. Therefore we believed that there is a definite clinical role for the SBM grading system, and currently

we are working with experts in artificial intelligence to design a user friendly online calculator for the predictive modelling.

### 8.4.1 Limitations

The newly proposed Stanford Berlin Moyamoya grading system was validated in adult MMD patients from the same institution in a different timeline. Potentially, the SBM grading system should be validated externally with cohorts from other institutions to ensure world-wide clinical applicability.

As the stroke events are relatively rare from the training set, to improve the sensitivity and positive predictive value of the machine learning algorithm, more fine tuning would be required by applying the GBM algorithm in larger cohort of patients, ideally including multicentre cohorts of MMD patients via world-wide collaborative efforts.

## 8.5 Conclusion

The Stanford Berlin Moyamoya grading system, incorporating age, mMRI score, HDR score and DSA score, is now validated and would correlate with postoperative stroke risks. It is a very useful clinical tool for clinical decision making, and to help counsel patients on the post-bypass stroke risks.

# CHAPTER NINE

# MOYAMOYA DISEASE IN THE UK: PERSONAL EXPERIENCE, DEVELOPMENT OF AN INTEGRATED SERVICE AND REGISTRY

## 9.1 Introduction

Moyamoya disease (MMD), typically affects children and young adults. However, the rarity and demography of MMD in the UK may limit access to best medical advice and management. While working in California, USA, I regularly encountered UK MMD patients who self-referred for expert review at Stanford University. However, very few patients could raise the funds required to obtain surgical treatment in USA. After returning back to the UK, we have established an integrated paediatric and adult multi-disciplinary MMD service, registry and patient website to address these concerns.

## 9.2 Methods

We report on the activity and outcomes of the Bristol MMD service using prospective registry data. All adult and paediatric MMD patients referred and managed between January 2017 and December 2020 were included. The paediatric patients are referred and managed at the Bristol Royal Hospital for Children, and under the care of paediatric neurosurgeons. Adult patients are managed at the Bristol Institute of Clinical Neuroscience, Southmead Hospital, under my care.

All patients were discussed in the neurovascular MDT meetings (weekly adult meetings, monthly paediatric meetings) and underwent combinations of MRI / MRA; six-vessel digital subtraction angiography; pre and post-acetazolamide-challenged SPECT.

Patients who had surgery would be followed up in clinic at 3 months, and investigations (MRI brain, DSA, SPECT with/without acetazolamide) carried out at 6 months, 2 years, 5 years, 10 years.

Questionaire study (as shown in Figure 2.1) was prospectively completed preop, at 6 months and 2 years, 5 years, 10 years postop. The outcome of patients with at least 2-years outcome on the questionnaire study, and the imaging follow-up was included.

## 9.3 Results

55 MMD patients from different parts of the UK have been referred to the service (Figure 9.1).

In the 14 paediatric MMD patients, 10 girls, 4 boys; mean age 7, range 3 to 15 years; 2 with familial MMD. 10 of 14 had ischaemic presentations, 2 had developmental delay, and 2 were diagnosed while screening due to underlying clinical conditions (NF1, NF2). 10 of 14 children underwent indirect bypasses (EDAS or burrholes).

41 adults were referred, 29 females, 12 males, mean age 33.4 years, range 19 to 64 years. 33 Caucasians, 8 Asians, 18 had TIAs, 16 had cerebral infarcts, 10 had haemorrhagic presentation. 16 patients underwent direct STA-MCA bypasses or combined bypasses. 1 patient with Down's syndrome underwent bilateral indirect bypass due to very small calibre donor STA vessels. There were no postoperative strokes.

11 adult patients with at least 2 years radiological and questionnaire study outcome was presented in details in Table 9.1, including the baseline demographic, mode of presentation, bypass types. Based on the proposed Stanford Berlin Moyamoya grade, 7 patients are in the low risk category (SBMS ≤6), 4 patients in the moderate risk category (SBMS 7-8), and no patients in the high risk category. No patients had postop strokes within 30-days perioperative period. 3 patients developed TNE postop (3/11, 27%), and recovered within a week postop.

At minimum of 2-years follow-up, patent bypass grafts on angiogram, no new strokes on MRI brain, and improved or good augmentation on SPECT were documented in all 11 patients. 10/11 (91%) of patients had improved mRS, and are functionally independent (mRS0-1) at 2 years. All except 1 patient experienced improvement in headache post bypass, 9 patients were working or studying, 10 patients are independent with self-caring and manages own financial/legal affairs.


Figure 9.1 A geographical representation of the patient cohort referred from different parts of the UK. Created from Google Maps 2021. [online] Available at: https://www.google.com/maps/d/edit?mid=1KGtGVqHQqnLlkeLpX_oJO6QgrdaLgxit&usp=sharing [Accessed 16 Sep. 2021].

Table 9.1. 11 adult MMD patients with at least 2 years radiological and questionnaire study outcome. The baseline demographic, mode of presentation, proposed Stanford Berlin Grade, bypass types, and 2 years outcome are shown.

| Age (yr) | Age score | Sex | Ethnicity | Presentation | DSA score | mMRI score | HDR score | preop mRS | Surgery | 2yr DSA | 2yr SPECT | 2yr MRI brain | 2yr mRS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 37 | 2 | F | Asian | Haemorrhagic | 2 | 1 | 1 | 3 | R direct, L indirect | Patent bypass | Improved | No new strokes | 1 |
| 31 | 2 | F | Asian | Ischaemic | 2 | 1 | 2 | 2 | R direct | Patent bypass | Improved | No new strokes | 0 |
| 32 | 2 | F | Asian | Haemorrhagic | 2 | 1 | 1 | 2 | R direct, L indirect | Patent bypass | Improved | No new strokes | 0 |
| 18 | 1 | F | Caucasian | Ischaemic | 3 | 1 | 1 | 3 | R direct, L direct | Patent bypass | Improved | No new strokes | 1 |
| 26 | 2 | F | Caucasian | Haemorrhagic | 2 | 1 | 1 | 2 | L direct | Patent bypass | Improved | No new strokes | 0 |
| 25 | 2 | M | Caucasian | Seizure, ischaemic, CLN6 Batten's disease, cortical myoclonus | 2 | 1 | 1 | 4 | L direct, R indirect | Patent bypass | Improved | No new strokes | 4 |
| 33 | 2 | M | Caucasian | Ischaemic | 3 | 1 | 2 | 3 | R direct, L direct | Patent bypass | Improved | No new strokes | 1 |
| 23 | 2 | M | Caucasian | Ischaemic | 2 | 1 | NA | 3 | L direct, R direct+EGPS | Patent bypass | Good augmentation | No new strokes | 1 |
| 45 | 3 | M | Caucasian | Ischaemic | 2 | 1 | 2 | 3 | L direct, R direct | Patent bypass | Improved | No new strokes | 0 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | (double barrel) | | | | |
| 55 | 3 | F | Asian | Ischaemic | 2 | 1 | 2 | 2 | R direct, L direct | Patent bypass | Improved | No new strokes | 1 |
| 27 | 2 | F | Caucasian | Haemorrhagic | 2 | 1 | 1 | 2 | R direct, L direct | Patent bypass | Improved | No new strokes | 1 |

### 9.3.1 CASE ILLUSTRATION 1

An 18-year-old female developed dysphasia, dressing apraxia, left-right confusion, and right sided homonymous hemianopia. MRI brain showed acute left parietal infarct, and her symptoms are in keeping with dominant parietal lobe (Gertman's) syndrome.

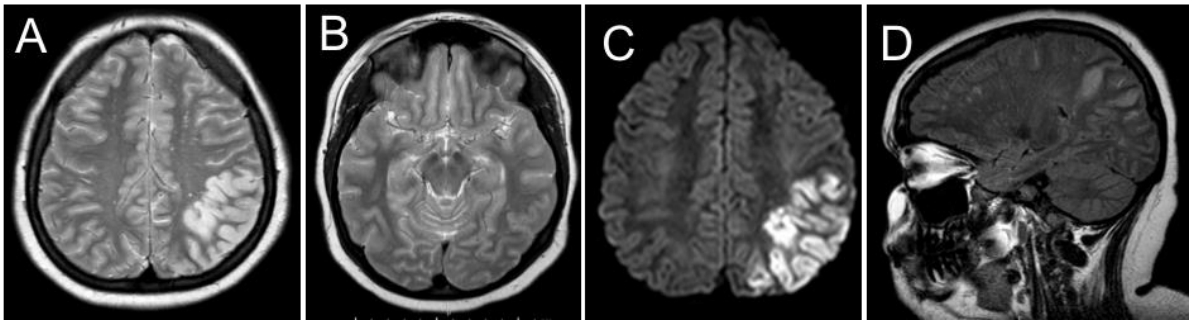



Figure 9.2. (A, B) T2 weighted, axial MRI brain showed ischaemic changes left parietal region, with fragile blood vessels (asterisks) visible in the basal cisterns. (C) DWI sequence axial MRI brain showed left parietal acute infarct. (D) FLAIR sequence sagittal MRI brain showed multiple areas of ischaemic changes.

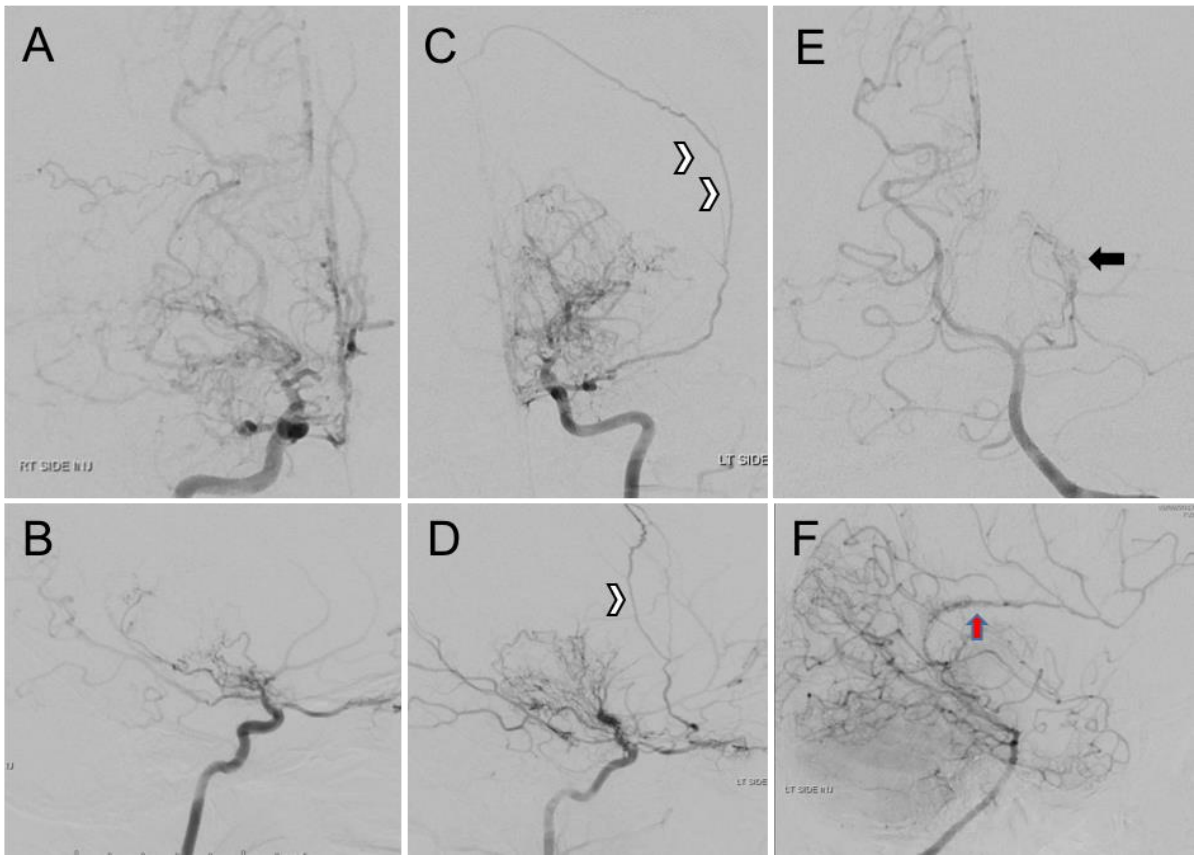


Figure 9.3. Cerebral angiogram. (A,B) AP, lateral R ICA injection showing terminal ICA occlusion with moyamoya vessels collateralisation. (C, D) AP, lateral L ICA injection showing ICA occlusion, moyamoya vessels and reconstitution of circulation by lenticulostriates and the recurrent meningeal branch from the ophthalmic artery (chevron arrow). (E, F) AP, lateral vertebral injection showing left PCA occlusion (black arrow), and anterior cerebral artery supplied extensively via PCA through the posterior pericallosal collateralisation (red arrows).

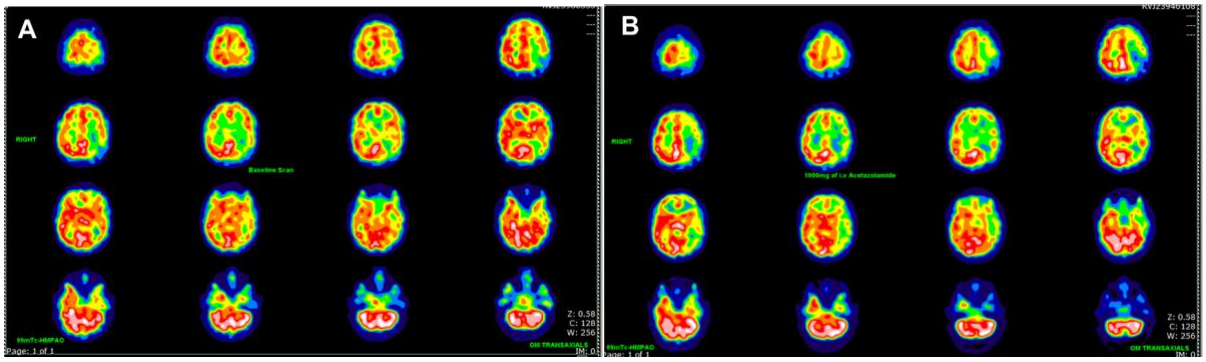



Figure 9.4. NM Brain HMPAO (Ceretec) SPECT Brain Scan. (A) The baseline study demonstrates slightly reduced perfusion in the left hemisphere compared to the right, but most pronounced in the parietal lobe. (B) Following acetazolamide there is a mild reduction in the global cerebral blood flow compared to the cerebellum. There is also a relative shift towards the right hemisphere suggestive of a steal phenomenon from the left hemisphere. This is an abnormal study consistent with moyamoya with reduced cerebral blood flow and impaired cerebrovascular reserve in both cerebral hemispheres but the changes are more marked on the left.

With her ongoing exertion related ischaemic symptoms, she underwent bilateral direct STA-MCA bypasses 6 months after her initial stroke.

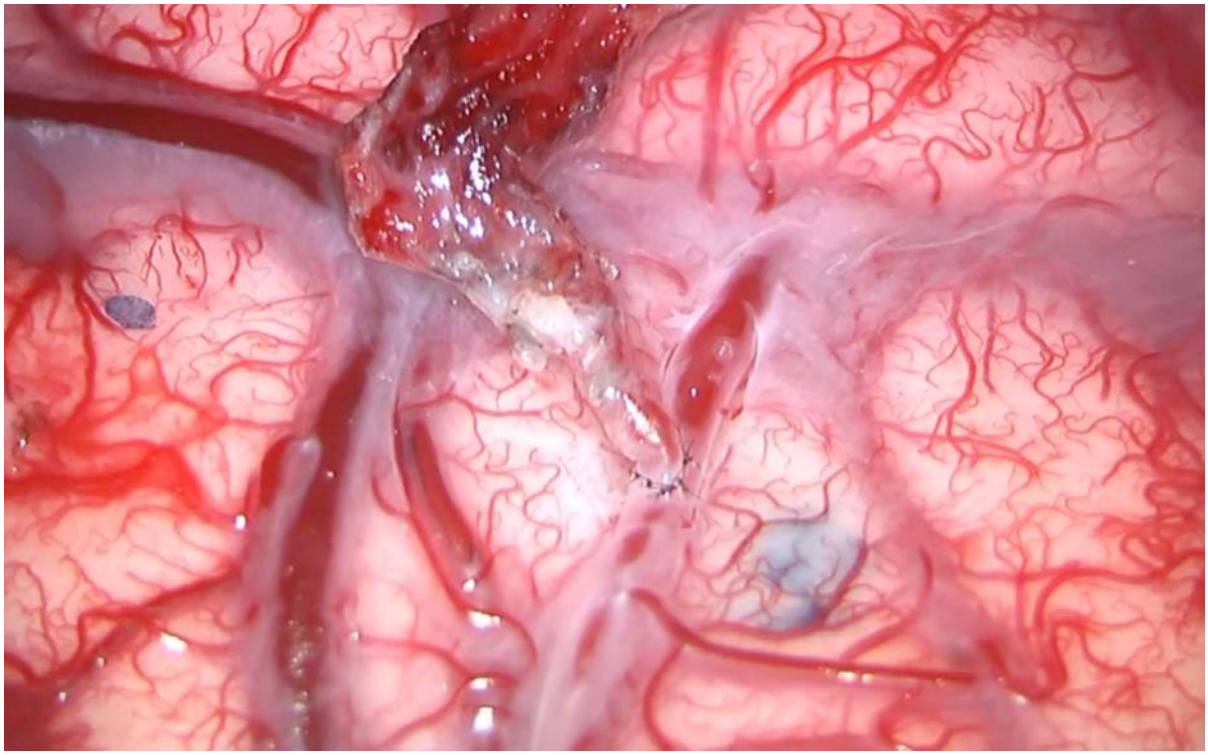


Figure 9.5 Intraop microscopic view of STA-MCA direct bypass

At 6 months and 2-years follow-up, her angiogram showed robust revascularization via the ECIC bypass grafts (Figure 9.6, Figure 9.7), with improvement to the cerebrovascular reserve as shown on the postop SPECT (Figure 9.8).

During her 4 years postoperative follow up, she is well with no neurological deficit. Ongoing long term clinical, radiological (cerebral angiograms, SPECT studies with and without acetazolamide) follow up will be carried out at 10 years and 20 years.

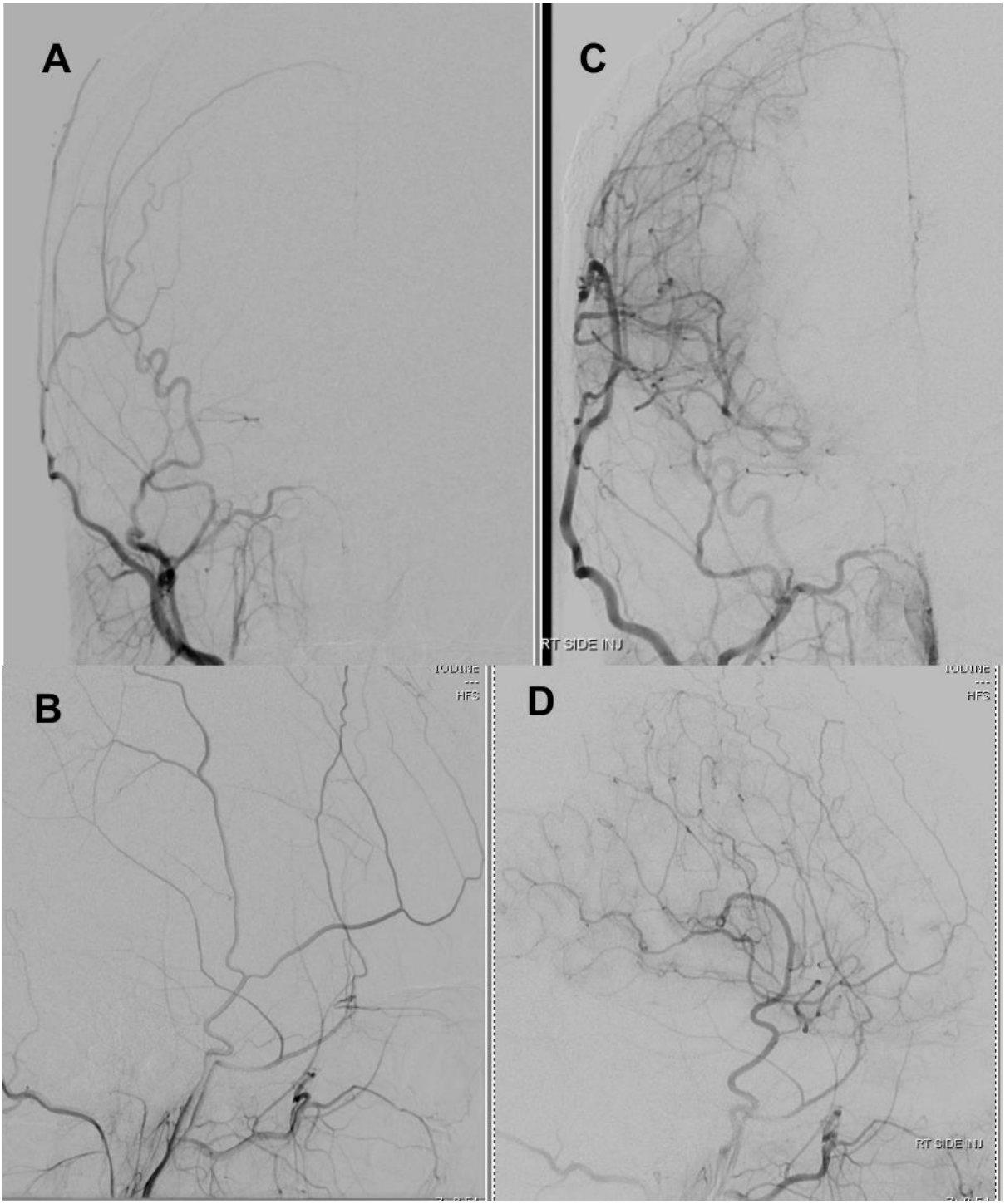



Figure 9.6 (A,B), AP and lateral ECA injection showing STA, middle meningeal arteries supplying the scalp and dura respectively. (C,D) AP and lateral ECA injection at 2 years showing robust extracranial to intracranial collateralization, supplying over 2/3 of the right MCA territory.

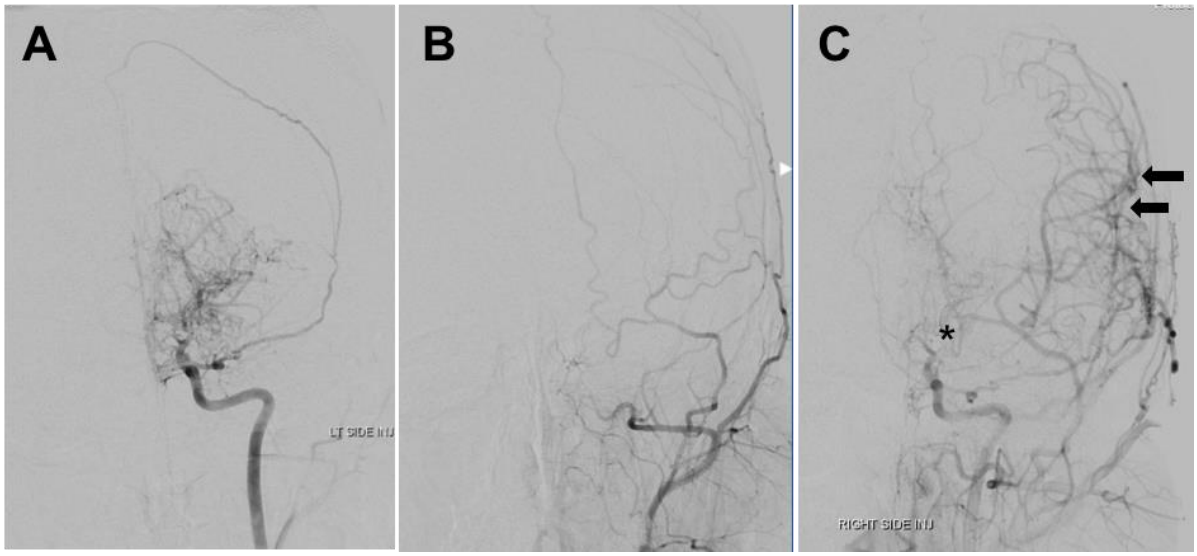



Figure 9.7 (A) Left ICA injection showing L ICA terminal occlusion with moyamoya collateralization. (B) Left ECA injection showing scalp vascularization. (C) Left common carotid injection post revascularization at 2 years showing robust collateralization from left STA-MCA bypass (arrows), and attenuation of the underlying moyamoya vessels (asterisk).

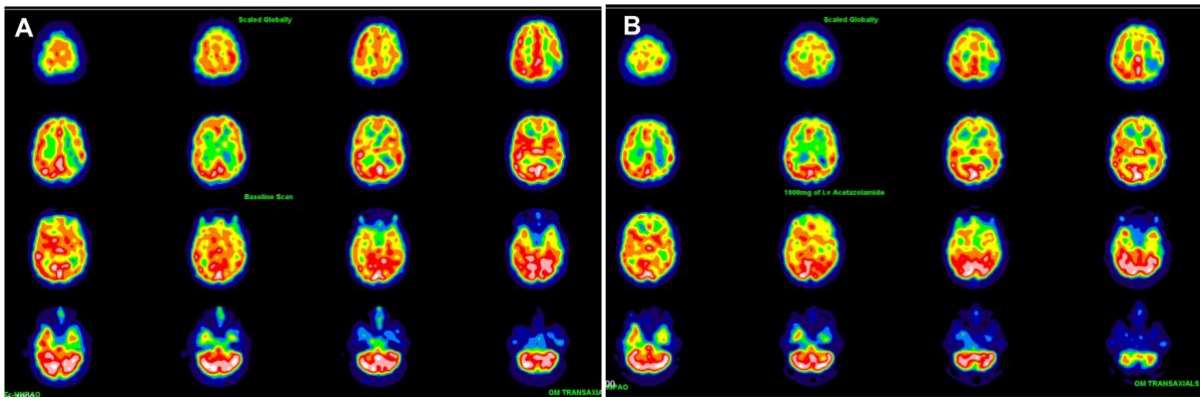



Figure 9.8. Postop SPECT with and without acetazolamide at 2 years showed improved haemodynamic response to acetazolamide.

**9.3.2 Case Illustration 2 -** Progressive R ICA stenoocclusion over 1 year

A 23-year-old male with 5 year history of headache, 6 months of intermittent right arm pins and needles, developed acute speech difficulty, memory impairment and right sided weakness. MRI brain (Figure 9.9) showed a left MCA infarct. His symptoms initially improved but deteriorated again a month later, and was readmitted to hospital for bed rest, and continued on aspirin, atorvastatin. Cerebral angiogram showed left terminal ICA occlusion with moyamoya collateralization (Figure 9.10). The right ICA showed mild stenosis with involvement of the promixal MCA and ACA but overall good right hemispheric perfusion.

He was transferred for review at our institution, and we decided to wait for 4 weeks prior to revascularisation procedure. Postoperatively, he recovered well, with periods of slurred speech (lasted few hours each time), due to TNE. He was also started on Levetiracetam for possible seizures.

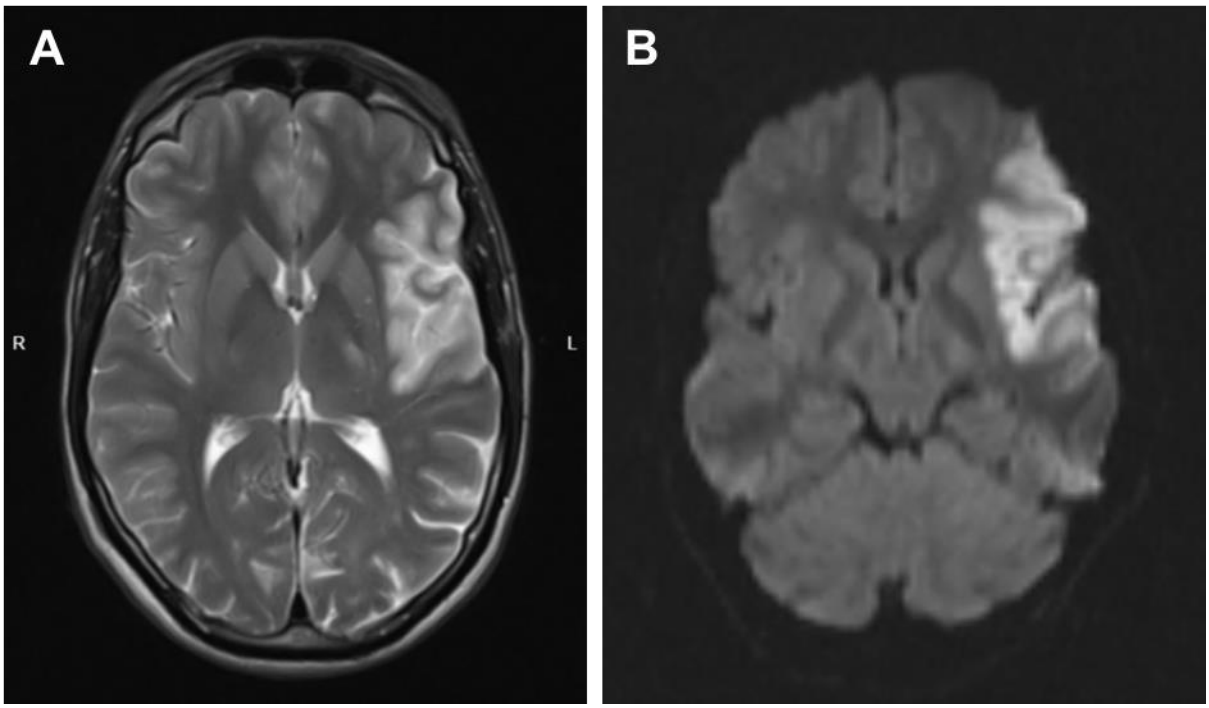



Figure 9.9 (A) MRI brain, T2 weighted and (B) DWI sequence showed an acute left MCA infarct.

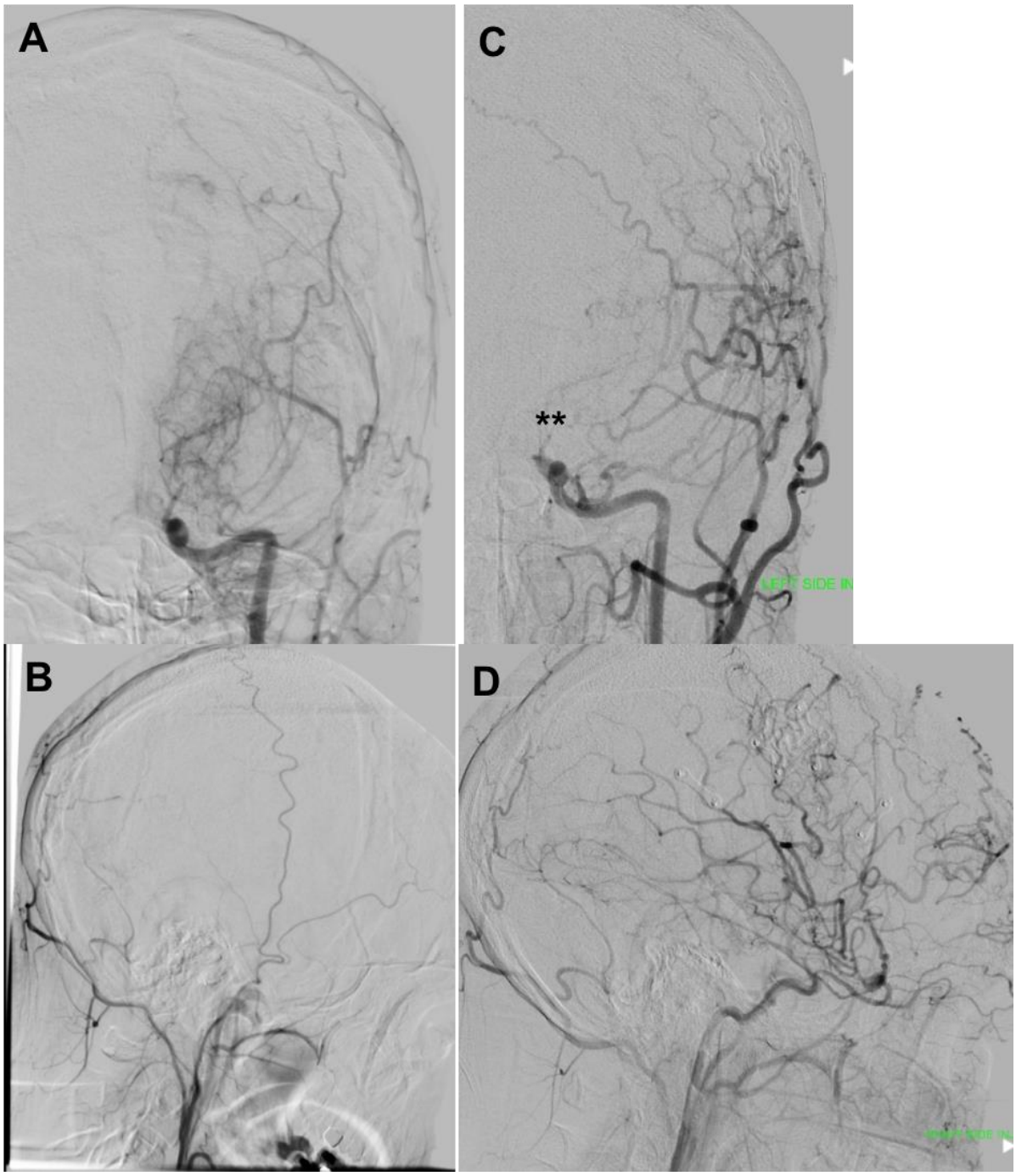



Figure 9.10. (A) L CCA injection, AP view showed occlusion of terminal ICA with moyamoya collateralization. (B) L ECA injection, lateral view showed left parietal STA for bypass harvest. (C) 6 months post bypass. L CCA injection, AP view showed robust collateralisation to the left MCA from left STA-MCA bypass graft, and attenuation of underlying L terminal ICA moyamoya vessels (asterisks). (D) 6months post bypass. L CCA injection, lateral view showed robust revascularisation of the left MCA territory.

At 6-months post bypass, the left direct ECIC bypass provided robust revascularisation to the left MCA territory (Figure 9.10). It was also noted that the right ICA injection showed progression of the terminal ICA, proximal MCA and proximal ACA stenosis (Figure 9.11), but he did not report right hemispheric symptoms.

Several months later, he started reporting left body numbness affecting both his upper and lower limbs, in keeping with ischaemic symptoms affecting his right MCA and ACA territories. Repeat DSA (Figure 9.11) showed occlusion of the right terminal ICA, 12months from the initial left MCA stroke presentation. He then underwent right direct STA-MCA combined with EGPS to revascularise the MCA and ACA territories. Figure 9.12 showed robust right hemispheric collateralization after ECIC bypass and EGPS.

He is now 2 years post bypass, is studying at university, and is hoping to become a physiotherapist.

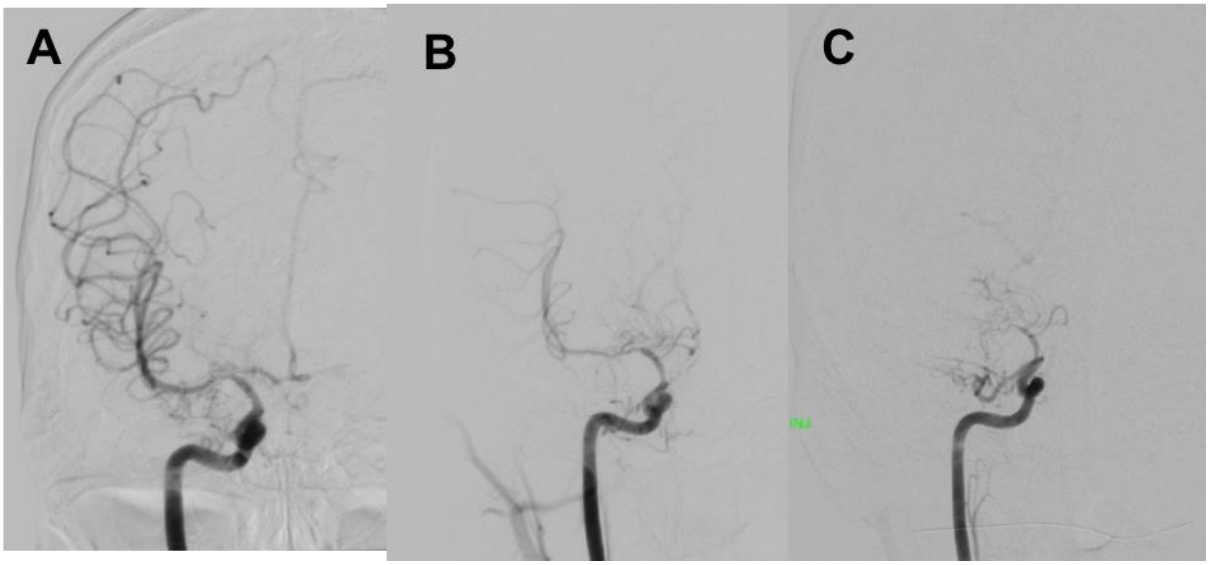



Figure 9.11 (A) Left ICA injection at initial presentation, showing narrowing of terminal ICA, proximal MCA, ACA but with good perfusion of the right hemisphere. (B) 6 months check angiogram showed progression of the right terminal ICA, proximal MCA, ACA stenoocclusion, with (C) complete occlusion of terminal ICA at 12 months.

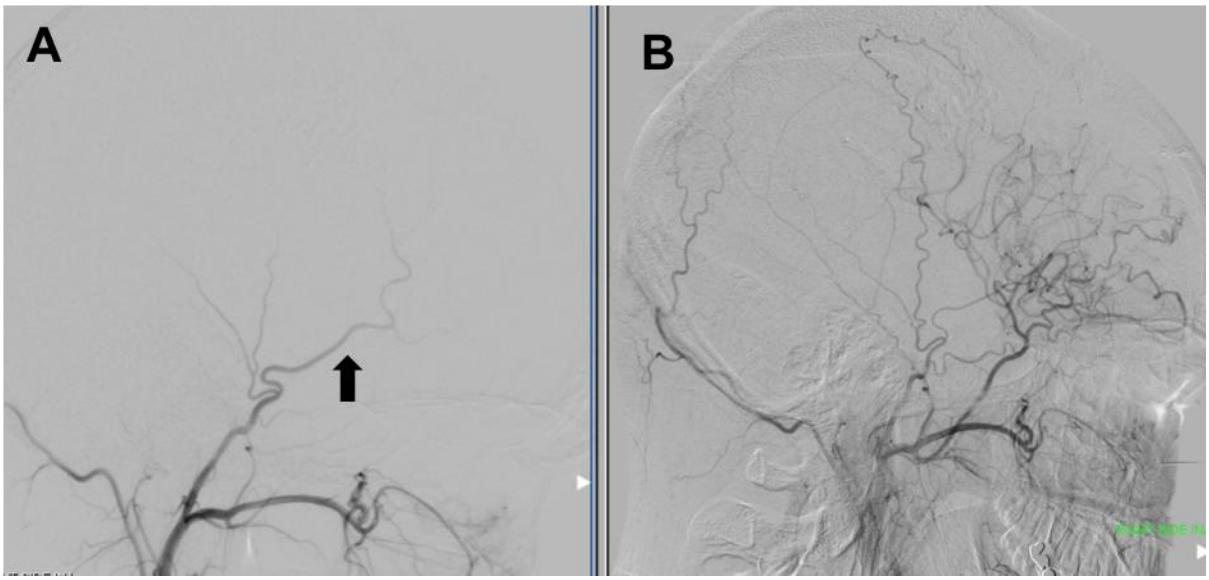



Figure 9.12. (A) pre bypass R ECA injection showed right sided STA, with frontal STA branch available for bypass (arrow). (B) post bypass R ECA injection, lateral projection showing good right hemispheric revascularization.

### 9.4 Conclusion

Our early experience with an integrated MMD service has been encouraging with careful patient selection for revascularization, good symptomatic improvement achieved and no 30-days postoperative strokes. For adult patients with at least 2 years outcome, patent bypass grafts on angiogram, no new strokes on MRI brain, and improved or good augmentation on SPECT were documented in all 11 patients. 91%(10/11) of patients had improved mRS, and are functionally independent (mRS0-1) at 2 years. All except 1 patient experienced improvement in headache post bypass, 9 patients were working or studying, 10 patients are independent with self-caring and manages own financial/legal affairs.

# CHAPTER TEN

# DISCUSSION, CONCLUSION AND FUTURE WORK

## 10.1 Discussion

The goal of surgical revascularization of MMD is to augment cerebral blood flow in patients with an ischemic presentation and to prevent intracranial hemorrhage by decreasing hemodynamic stress in patients with a hemorrhagic presentation. Surgical revascularization methods can be direct, indirect, or a combination of the two bypass approaches. The best choice of bypass method is still controversial. There is currently no definite consensus regarding the surgical treatment of adult or paediatric MMD.

With regards to comparing the various bypass techniques, a recent meta-analysis performed a 3-way comparison of direct bypass (DB), combined bypass (CB) and indirect bypass (IB). Lin et al included a total of 18 studies, and showed that the effect of DB and CB was equivocal, and IB was related to a higher incidence of recurrence stroke. (Lin et al., 2021)

Therefore, we analysed the effect of DB and CB together in our systematic review and meta-analysis, to compare direct and combined versus indirect bypasses with regard to perioperative complications and long-terms stroke risk, angiographic revascularization in pediatric and adult patients with MMD.

A total of 2490 studies were identified. 20 reporting 2982 patients were eventually included in our meta-analysis. Pooled mean age was 37.5 years and 7.4 years in adult and pediatric patients respectively. For both adult and paediatric patients, perioperative stroke rate (8.8% in adults, 7.5% in paediatrics) was comparable between direct/combined bypass and indirect bypass. No difference was found in perioperative mortality between direct/combined bypass and indirect bypass for adult patients (0.3%), and paediatric patients (0.1%). Our meta-analysis showed that both direct and indirect bypasses have similar rates of perioperative complications in pediatric and adult patients, however there was no comparative data to report long term (>5 years) stroke risk, angiographic revascularization between direct/combined bypass and indirect bypass.

The fundamental question of whether to perform surgical revascularization for moyamoya patients was addressed in 5 meta-analyses, and all the studies showed that revascularization was superior to medical treatment alone (Table 3.3, Chapter 3)

With network meta-analysis gaining popularity as a research tool, Ding et al included 9 comparative studies to compare the management of patients with haemorrhagic MMD. They used Bayesian hierarchical models to perform pairwise comparisons among DB, IB and conservative treatment, and concluded that direct bypass is the optimal strategy for treating haemorrhagic MMD to reduce recurrent strokes (including ischaemic and haemorrhagic stroke), but not in reducing mortality. (Ding et al., 2018)

Very little is known about MMD in the western population. This study from 769 patients with 1250 revascularisations treated at Stanford Univesity Medical Center (1991-2014) showed that most of the patients are Caucasians, and small proportion of Hispanics and African-Americans. The bimodal peak age distribution and female predominance is very similar to the demographics from Eastern MMD. As shown previously (Guzman et al., 2009), most adult MMD from the west presented with cerebral ischaemia (80%), in contrast to nearly 50% with haemorrhagic presentation in the Asian series (Miyamoto et al., 2014a, Hung et al., 1997, Miao et al., 2010). Paediatric MMD has a higher proportion of non-caucasian, non-asian, and patients with moyamoya syndrome compared to the adult MMD cohort. Besides, haemorrhagic presentation is less common in children compared to adults.

With a generally poor natural history of untreated or medically treated MMD (8-13% stroke risk per year) (Miyamoto et al., 2014a), surgical revascularisations to reduce stroke risks are good treatment choices. However, extracranial to intracranial bypasses are considered high risk procedures, and now rarely performed in the UK.

In this study, 92 strokes (ischaemic and haemorrhagic) in 84 patients were encountered after a total of 1250 bypasses, therefore there is a 7.3% per procedure stroke risk. However, this is not a universal 30-days postoperative stroke risk. In children (<18 years old), the stroke risk is 5% per patient, while in over 60 years old, the risk can be as high as 20% per patient. Furthermore, we also identified several other risk factors including the angiographic findings (presence or absence of ICIC or

ECIC collateralization), MRI findings (old or recent strokes prior to bypass), and haemodynamic reserve (impaired cerebrovascular reserve or steal phenomenon during acetazolamide challenge to simulate increased cerebral metabolic demand) that would also to be taken into account to determine the postoperative stroke risks. We found that patients with recent DWI +ve infarct within a month of surgery has the highest postop stroke risk. Therefore, generally we will not attempt cerebral revascularisations within a month of acute stroke as a result of this study.

In the long-term study with up to 25 years follow-up, we are very reassured that 80% of MMD patients post revascularisation remained in excellent physical, social and functional wellbeing. Of the patients who experienced preoperative headache, 84% of those who completed the quality of life questionnaire study reported resolution or improvement of their headache. Furthermore, 83% remained in employment or education, and 75% are living independently or has set up family of their own.

The long term stroke risk is 0.6% per patient year based on a mean follow-up of over 7 years in 730 patients. Again, age plays an important role in the long term stroke risk. Based on the Kaplan Meier logrank analyses, up to 25 years, 1% of paediatric cohort compared to 5% of adults developed long term strokes. There was no association between 30-day perioperative stroke risk and long term stroke risks.

In paediatric group, the bypass types were not associated with long term stroke risk; whereas in the adult population, indirect bypass was associated with nearly 3 times higher long term stroke risk and also higher chance of needing repeat revascularization.

It is interesting to note that TNE rate is consistent at about 20% regardless of gender, ethnicity, mode of presentations, comorbidities, preoperative radiological findings, and lower at 10% for paediatrics, patients with moyamoya syndrome, and those with indirect bypasses. The aetiology is still uncertain, either due to global cerebral hyperperfusion (Fujimura et al 2007, Fujimura et al 2009, Kim et al 2008) or local hypoperfusion (Mukerji et al 2015), after changes in cerebral blood flow to ischaemic brain post revascularisations. Regardless of the pathophysiology, there are no DWI

changes on postoperative MRI, and patients' symptoms generally resolved within 6 weeks postop.

In a small group of patients, repeat revascularisation is required due to persistent or new symptoms secondary to inadequate collateralization post initial bypass surgery. In these 57 patients, 38 had previous indirect procedures and 19 had previous direct bypass of the same hemisphere. In this study, 70% of the repeat surgeries were performed on patients with previous revascularisations at another institution, and two-thirds of patients had previous indirect bypasses. With the ongoing debate between direct or indirect bypass, we also compare and contrast the clinical and radiological outcome of repeat revascularization in MMD patients with previous indirect or direct bypasses.

For patients who needed repeat revascularization, there was a greater proportion of females in the previous direct bypass group (84%) compared with the cohort with previous indirect bypass (60%). Even though the sex distribution for moyamoya disease in the first decade of life is equally common in males and females, with a subsequent strong female predominance with a ratio of 2-3:1 thereafter (Baba et al 2008), this would still not explain the observed difference. A similar gender difference observation in moyamoya disease was made in one previous study (Khan et al 2012). They showed that the 5-year cumulative risk of adverse postoperative events (despite successful revascularization) on Kaplan Meier analysis, was 11.4% in female patients versus 5.3% in male patients ($p = 0.05$), but that difference was no longer statistically significant after multivariate analysis. Although inconclusive, intriguing hypotheses were raised that perhaps the natural history of moyamoya disease is more aggressive in women than in men, and the risk from surgical revascularization for moyamoya disease is higher in women than in men. However, the result from this mini-thesis in chapter 3 doesn't support that gender difference play a role in the surgical risk or MMD disease severity.

Reports on repeat revascularization post-direct bypass in the English literature are very rare (Hori et al 2016), presumably due to its extreme rarity and the effectiveness of direct bypass in providing adequate collateralization after the first procedure. Our study showed another added benefit of direct bypass with a lower rate of repeat

revascularization (1% in the direct bypass group and 4% in the indirect bypass group). Other well established advantages of direct bypass compared to indirect bypass include the establishment of augmented flow immediately following surgery, a more consistent and higher extent of angiographic collateralization (Arias et al., 2015a, Matsushima et al., 1998), superiority in restoring cerebrovascular reserve capacity post-bypass (Czabanka et al., 2011a), more patients with symptomatic improvement, less recurrent ischemic risk and more patients with stroke-free survival (Kazumata et al., 2014b, Bang et al., 2012, Houkin et al., 2000).

Furthermore, over 50% of repeat revascularizations could be achieved with direct procedures, however, the choice of procedure depends on the operative findings and the status of donor and recipient vessels. In large area of repeat revascularisation, omental-cranial transposition is ideal, whereas for focal area in the presence of a small STA branch, EDAS or EMS could be used as good indirect methods. At the latest follow up, over 80% of patients in both groups are well, free from stroke or TIA symptoms, with excellent radiological results.

Following the publication of our results, a recent study on surgical treatment of failed revascularisation from Germany included 308 MMD patients with 405 surgically treated hemispheres. Of the 405 hemispheres treated, 15 patients (3.7%) underwent repeat revascularization. Contrary to our finding, in that series, time to repeat revascularization in 60% of patients was within 1 year of first surgery, and the most common cause of repeat revascularisation was symptomatic bypass occlusion. Intermediate-flow bypass using a radial artery graft was most commonly used for repeat revascularization in 9/15 (60%). (Lucia et al., 2021)

For patients with moyamoya syndrome, we showed that their underlying radiological characteristics, 30-days postoperative adverse outcome rates, and long term stroke risk did not differ significantly compared to patients with classical MMD. However, some of the differences noted include MMS is more common in the paediatric age group, has fewer Asian, with more seizure presentations compared to patients with classical MMD. We also presented the largest reported surgical series of patients with MOPD II and moyamoya disease, and found that despite the challenging nature of surgery for these patients, it is feasible at expert centers, and good long-term

outcomes are possible. Long-term surveillance with vascular imaging is also extremely important in view of the progressive nature of these intracranial vascular anomalies, and we have to be mindful of the other associated medical conditions due to their underlying diagnosis.

Not all MMD patients are the same. In terms of grading MMD severity, the existing MMD classification system proposed by Suzuki et al (Suzuki et al 1969) was based on angiographic findings, but DSA would not provide important information including hemodynamic cerebrovascular insufficiency and recurrent ischemic events. While developing a hemispheric symptomatology grading system for MMD, the Berlin group incorporated DSA, MRI and CVRC using Xenon-CT, and showed that 21% of grade I, 63% of grade II and 93% of grade III hemispheres were clinically symptomatic (Czabanka et al 2011). We validated their findings on our cohort of 96 patients (192 hemispheres), and showed that 33% of grade I, 92% of grade II, 100% of grade III hemispheres were clinically symptomatic.

There are still limitations amongst the proposed scoring system, as age was not taken into account, the hemispheres were assessed individually (while patients should be assessed globally), and identified risk factors from this thesis was not accountable in the Berlin grading system. Furthermore, due to regulatory issues and some of the disadvantages of Xenon-CT (which include relatively long acquisition time, prone to motion artifacts, some patients cannot tolerate inhalation of Xenon through a face mask during the procedure), currently, others methods to assess CVRC are used including hemodynamic MR perfusion studies, SPECT. It is therefore important that our study showed despite the changes in methodology for CVRC assessment over the last 25 years, the grading for normal augmentation, impaired cerebrovascular reserve or steal can be applicable across the different imaging modalities.

Therefore, together with the perioperative stroke risk factors identified from our recent work in the multivariate regression analysis, and the validated Berlin symptomatic grading system (Czabanka et al., 2011c, Czabanka et al., 2016), we proposed the Stanford Berlin Moyamoya (SBM) grading system.

Table 10.1. Newly proposed Stanford Berlin Moyamoya (SBM) Grading System

| FACTORS | | SCORE |
|---|---|---|
| **AGE** | ≤18 years | 1 |
| | 19-39 years | 2 |
| | 40-59 years | 3 |
| | ≥ 60 years | 4 |
| | | |
| **DSA** | Steno-occlusive lesion + moyamoya | 1 |
| | Steno-occlusive lesion + moyamoya + ICIC | 2 |
| | Steno-occlusive lesion + moyamoya + ECIC | 3 |
| | | |
| **MMRI** | None | 0 |
| | Ischaemia / atrophy | 1 |
| | DWI +ve infarct | 2 |
| | | |
| **HDR** | Good augmentation | 0 |
| | Impaired augmentation | 1 |
| | Steal phenomenon | 2 |

### 10.1.1 SBM model performance (1991-2014 cohort)

The ROC curve analysis between SBM grade and the risk of 30-day postoperative major stroke, AUC=0.85, i.e good correlation. Based on probability distribution, up to SBM score 6, the postop stroke risk is very low (less than 2%); SBM score 7-8:10-20% stroke risk; SBM score ≥9, >20% stroke risk. (Figure 8.1, Figure 8.2, Chapter 8)

### 10.1.2 SBM validation (2015-2018 cohort)

ROC curve analysis between SBM grade and the risk of 30-day postoperative major stroke, AUC was 0.76, i.e. fair to good correlation. Based on probability distribution, the postop major stroke risk could be stratified to low (SBMS ≤6, 0-5%), moderate (SBMS 7-8, 5-20%), high (SBMS ≥9, >20%). (Figure 8.3, Figure 8.4, Chapter 8)

### 10.1.3 Development of predictive modelling for 30-day postop stroke risks

From 1991–2018, 1033 patients, 78 event rate, were split in 70/30 distribution, into training vs validation set. Using Gradient Boosted Machine(GBM) regression machine learning algorithm, 93% accuracy and 99.6% specificity was obtained, with 66.7% positive predictive value.

## 10.2 Conclusion

Based on the findings in this thesis and long term outcome, 80-90% of patients with moyamoya disease in the western world are symptomatically and functionally cured after extracranial-intracranial bypasses.

The newly proposed Stanford Berlin Moyamoya grading system, incorporating age, mMRI score, HDR score and DSA score, is simple, user friendly, and able to stratify postoperative stroke risks. Using SBM grade, post bypass stroke risk could be stratified to low (SBM ≤6, 0-5%), moderate (SBM 7-8, 5-20%), high (SBM ≥9, >20%).

## 10.3 Future work

The Stanford Berlin Moyamoya grading was validated in a separate cohort of MMD patients, but would ideally need further validation in other cohorts of MMD patients from other centres to ensure its world-wide clinical applicability.

On the machine learning logarithm to predict postoperative stroke risks, as the stroke events are relatively rare from the training set, to improve the sensitivity and positive predictive value of the machine learning algorithm, more fine tuning would be required, ideally including multicentre cohorts of MMD patients via world-wide collaborative efforts. We are also working with the expertise from INSIGNEO Institute, at the University of Sheffield, to incorporate their expertise in the predictive model development.

The knowledge learnt from this thesis is applied on my own clinical practice. We have since set up the UK moyamoya service, developed a multidisciplinary team and accepted referrals from different parts of the UK, created a website for patient information, and performed ECIC bypasses for UK patients with good outcome so far. The Stanford Berlin Moyamoya grading system is a very useful clinical tool for clinical decision making, and to help counsel patients on the post-bypass stroke risks.

# CHAPTER ELEVEN

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# CHAPTER TWELVE

# APPENDICES

Supplementary Table 12.1. Full search phrases used for the 3 respective databases.

| **Ovid MEDLINE** | | 1049 articles |
|---|---|---|
| **Moyamoya concept** | | |
| 1 | exp Moyamoya disease/ | |
| 2 | moyamoya.tw | |
| 3 | 1 or 2 | |
| **Surgery concept** | | |
| 4 | exp Cerebral Revascularisation/ | |
| 5 | revascular*.tw | |
| 6 | exp Temporal Arteries/ | |
| 7 | superficial temporal arter*.tw | |
| 8 | STA.tw | |
| 9 | exp Middle Cerebral Artery/ | |
| 10 | MCA.tw | |
| 11 | exp Anastomosis, Surgical/ | |
| 12 | bypass.tw | |
| 13 | anastomos*.tw | |
| 14 | STA-MCA.tw | |
| 15 | direct bypass.tw | |
| 16 | encephaloduroarteriosynangiosis.tw | |
| 17 | EDAS.tw | |
| 18 | encephaloduroarteriomyosynangiosis.tw | |
| 19 | EDAMS.tw | |
| 20 | indirect bypass.tw | |

| | |
|---|---|
| 21 | pial.tw |
| 22 | synangiosis.tw |
| 23 | combined surgery.tw |
| 24 | intracranial.tw |
| 25 | exp Neurosurgical Procedures/ |
| 26 | exp Neurosurgery/ |
| 27 | 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 |
| **Outcome concept** | |
| 28 | exp Cerebrovascular circulation/ |
| 29 | exp Cerebral angiography/ |
| 30 | angiographic.tw |
| 31 | outcome*.tw |
| 32 | 30 AND 31 |
| 33 | exp Stroke/ |
| 34 | secondary stroke.tw |
| 35 | neurologic deficit*.tw |
| 36 | exp Mortality/ |
| 37 | mortality.tw |
| 38 | 28 or 29 or 32 or 33 or 34 or 35 or 36 or 37 |
| 39 | 3 and 27 and 38 |
| **Embase** | 1436 articles |
| **Moyamoya concept** | |
| 1 | exp Moyamoya disease/ |
| 2 | moyamoya.tw |

| | |
|---|---|
| 3 | 1 or 2 |
| **Surgery concept** | |
| 4 | exp Cerebral Revascularisation/ |
| 5 | revascular*.tw |
| 6 | exp Temporal Artery/ |
| 7 | superficial temporal arter*.tw |
| 8 | STA.tw |
| 9 | exp Middle Cerebral Artery/ |
| 10 | MCA.tw |
| 11 | exp Anastomosis/ |
| 12 | exp Brain Artery Bypass/ |
| 13 | bypass.tw |
| 14 | anastomos*.tw |
| 15 | STA-MCA.tw |
| 16 | direct bypass.tw |
| 17 | encephaloduroarteriosynangiosis.tw |
| 18 | EDAS.tw |
| 19 | encephaloduroarteriomyosynangiosis.tw |
| 20 | EDAMS.tw |
| 21 | indirect bypass.tw |
| 22 | pial.tw |
| 23 | synangiosis.tw |
| 24 | combined surgery.tw |
| 25 | intracranial.tw |
| 26 | exp Neurosurgery/ |

| | |
|---|---|
| | |
| 27 | 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 |
| **Outcome concept** | |
| 28 | exp Brain circulation/ |
| 29 | exp Brain angiography/ |
| 30 | angiographic.tw |
| 31 | outcome*.tw |
| 32 | 30 AND 31 |
| 33 | exp cerebrovascular accident/ |
| 34 | secondary stroke.tw |
| 35 | neurologic deficit*.tw |
| 36 | exp Mortality/ |
| 37 | mortality.tw |
| 38 | 28 or 29 or 32 or 33 or 34 or 35 or 36 or 37 |
| 39 | 3 and 27 and 38 |
| **Cochrane Controlled Register of Trials CENTRAL** | 82 articles |
| **Moyamoya concept** | |
| 1 | MeSH descriptor: [Moyamoya Disease] explode all trees |
| 2 | (“Moyamoya”):ti,ab,kw |
| 3 | (“moyamoya disease”):ti,ab,kw |
| 4 | #1 OR #2 OR #3 |
| **Surgery concept** | |
| 5 | MeSH descriptor: [Cerebral Revascularization] explode all trees |
| 6 | MeSH descriptor: [Temporal Arteries] explode all trees |
| 7 | (superficial temporal arter*):ti,ab,kw |

| | |
|---|---|
| 8 | (STA):ti,ab,kw |
| 9 | MeSH descriptor: [Middle Cerebral Artery] explode all trees |
| 10 | (MCA):ti,ab,kw |
| 11 | MeSH descriptor: [Anastomosis, Surgical] explode all trees |
| 12 | MeSH descriptor: [Neurosurgical Procedures] explode all trees |
| 13 | #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 |
| **Outcome concept** | |
| 14 | MeSH descriptor: [Cerebrovascular Circulation] explode all trees |
| 15 | MeSH descriptor: [Cerebral Angiography] explode all trees |
| 16 | MeSH descriptor: [Stroke] explode all trees |
| 17 | MeSH descriptor: [Neurologic Manifestations] explode all trees |
| 18 | MeSH descriptor: [Mortality] explode all trees |
| 19 | #14 OR #15 OR #16 OR #17 OR #18 |
| 20 | #4 AND #15 AND #21 |

Supplementary Table 12.2. Joanna Briggs Institute quality assessment checklist for prevalence studies.

| | Question no. | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **Overall** |
| Yu (2019) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Zhao (2019) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Zheng (2019) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Deng (2018) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Jang (2017) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Teo (2017) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Czabanka (2016) | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Sadashiva (2016) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Liu (2015) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Abla (2013) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Gross (2013) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Bang (2012) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Choi (2012) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Kim (2012) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Lee (2012) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Ng (2011) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Hyun (2010) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Guzman (2009) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Matsushima (1998) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Ishikawa (1997) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

1. Was the sample frame appropriate to address the target population?
2. Were study participants sampled in an appropriate way?
3. Was the sample size adequate?
4. Were the study subjects and the setting described in detail?
5. Was the data analysis conducted with sufficient coverage of the identified sample?
6. Were valid methods used for the identification of the condition?
7. Was the condition measured in a standard, reliable way for all participants?
8. Was there appropriate statistical analysis?
9. Was the response rate adequate, and if not, was the low response rate managed appropriately?

Supplementary Table 12.3. Joanna Briggs Institute quality assessment checklist for case series.

| | Question no. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **Overall** |
| Yu (2019) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Zhao (2019) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Zheng (2019) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Deng (2018) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Jang (2017) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Teo (2017) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Czabanka (2016) | ✓ | ✓ | ✓ | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Sadashiva (2016) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Liu (2015) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Abla (2013) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Gross (2013) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Bang (2012) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Choi (2012) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Kim (2012) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Lee (2012) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Ng (2011) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Hyun (2010) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Guzman (2009) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Matsushima (1998) | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Ishikawa (1997) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series?
3. Were valid methods used for identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

# STANFORD UNIVERSITY

*Stanford, CA 94305 [Mail Code 5579]*

David D. Oakes, M.D. (650) 723-5215
CHAIR, PANEL ON MEDICAL HUMAN SUBJECTS (650) 725-8013

## Certification of Human Subjects Approvals

**Date:** February 11, 2016

**To:** Mario K.C Teo, M.D., Neurosurgery
Tej Deepak Azad MD/MS, Year 3

**From:** David D. Oakes, M.D., Administrative Panel on Human Subjects in Medical Research

**Protocol** Retrospective Chart Review of Moyamoya Disease

**Protocol ID:** 36691 **IRB Number:** 6208 (Panel: 8)

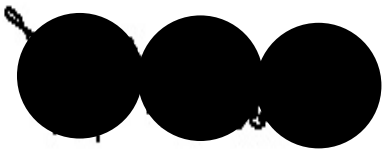
The IRB approved human subjects involvement in your research project on 02/11/2016. **'Prior to subject recruitment and enrollment, if this is: a Cancer-related study, you must obtain Cancer Center Scientific Review Committee (SRC) approval;** a CTRU study, you must obtain CTRU approval; a VA study, you must obtain VA R and D Committee approval; and if a contract is involved, it must be signed.'

The expiration date of this approval is 01/31/2019 at Midnight. If this project is to continue beyond that date, you must submit an updated protocol in advance for the IRB's re-approval. If this protocol is used in conjunction with any other human use it must be re-approved. Proposed changes to approved research must be reviewed and approved prospectively by the IRB. No changes may be initiated without prior approval by the IRB, except where necessary to eliminate apparent immediate hazards to subjects. (Any such exceptions must be reported to the IRB within 10 working days.) Unanticipated problems involving risks to participants or others and other events or information, as defined and listed in the Report Form, must be submitted promptly to the IRB. (See Events and Information that Require Prompt Reporting to the IRB at http://humansubjects.stanford.edu.)

All continuing projects and activities must be reviewed and re-approved on or before Midnight of the expiration date. The approval period will be less than one year if so determined by the IRB. It is your responsibility to resubmit the project to the IRB for continuing review and to report the completion of the protocol to the IRB within 30 days.

Please remember that all data, including all signed consent form documents, must be retained for a minimum of three years past the completion of this research. Additional requirements may be imposed by your funding agency, your department, or other entities. (See Policy 1.9 on Retention of and Access to Research Data at http://doresearch.stanford.edu/policies/research-policy-handbook)

This institution is in compliance with requirements for protection of human subjects, including 45 CFR 46, 21 CFR 50 and 56, and 38 CFR 16.



David D. Oakes, M.D., Chair

**Approval Period:** 02/11/2016 THROUGH 01/31/2019

**Review Type:** EXPEDITED - NEW

**Funding:** None

**Expedited Under Category:** 5

**Assurance Number:** FWA00000935 (SU), FWA00000934 (SHC)

# STANFORD UNIVERSITY

*Stanford, CA 94305 [Mail Code 5579]*

David D Oakes, M.D. (650) 723-5215
CHAIR, PANEL ON MEDICAL HUMAN SUBJECTS (650) 725-8013

## Certification of Human Subjects Approvals

**Date:** January 8, 2019

**To:** Mario K.C Teo, M.D., Neurosurgery
Tej Deepak Azad MD/MS, Year 3

**From:** David D Oakes, M.D., Administrative Panel on Human Subjects in Medical Research

**eProtocol Title:** Retrospective Chart Review of Moyamoya Disease

**eProtocol #:** 36691 **IRB 8 (Registration #:** 6208)

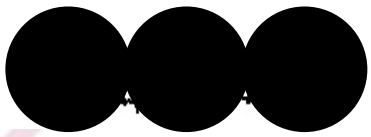
The IRB approved human subjects involvement in your research project on 01/08/2019. **'Prior to subject recruitment and enrollment, if this is: a Cancer-related study, you must obtain Cancer Center Scientific Review Committee (SRC) approval;** a CTRU study, you must obtain CTRU approval; a VA study, you must obtain VA R and D Committee approval; and **if a contract is involved, it must be signed.**'

This protocol has been approved under the Extended Approval Process and **approval does not expire**. Proposed changes to approved research must still be reviewed and approved prospectively by the IRB. No changes may be initiated without prior approval by the IRB, except where necessary to eliminate apparent immediate hazards to subjects. (Any such exceptions must be reported to the IRB within 10 working days.) Unanticipated problems involving risks to participants or others and other events or information, as defined and listed in the Report Form, must be submitted promptly to the IRB. (See Events and Information that Require Prompt Reporting to the IRB at http://humansubjects.stanford.edu.) It is your responsibility to report the completion of the protocol to the IRB within 30 days.

Please remember that all data, including all signed consent form documents, must be retained for a minimum of three years past the completion of this research. Additional requirements may be imposed by your funding agency, your department, HIPAA, or other entities. (See Policy 1.9 on Retention of and Access to Research Data at http://doresearch.stanford.edu/policies/research-policy-handbook)

This institution is in compliance with requirements for protection of human subjects, including 45 CFR 46, 21 CFR 50 and 56, and 38 CFR 16.

Waiver of Individual Authorization for recruitment under 45 CFR 164.512(i)(2)(ii)(A),(B),(C), pursuant to information provided in the HIPAA section of the protocol application.



David D Oakes, M.D., Chair

**Approval Period:** 01/08/2019 - (Does Not Expire)

**Review Type:** EXPEDITED - MODIFICATION

**Funding:** None

**Expedited Under Category:** 5

**Assurance #:** FWA00000935 (SU), FWA00000934 (SHC)

Stanford MEDICINE | Center for Clinical Informatics

Stanford University School of Medicine

Stanford Center for Clinical Informatics

# Moyamoya Database

## Data Dictionary Codebook

01/14/2015 2:15pm

| # | Variable / Field Name | Field Label<br>*Field Note* | Field Attributes (Field Type, Validation, Choices, Calculations, etc.) |
|---|---|---|---|
| Instrument: **Demographics** | | | |
| 1 | record_id | Record ID | text |
| 2 | mrn | MRN | text, Required, Identifier |
| 3 | last_name | Last name | text, Required, Identifier |
| 4 | first_name | First name | text, Identifier |
| 5 | sex | Sex | radio<br>0, Female<br>1, Male |
| 6 | date_of_birth | Date of birth<br>*MM/DD/YYYY* | text |
| 7 | age_at_presentation | Age at presentation<br>*years* | text |
| 8 | age_at_diagnosis | Age at diagnosis<br>*years* | text |
| 9 | demographics_complete | Complete? | dropdown<br>0, Incomplete<br>1, Unverified<br>2, Complete |
| Instrument: **Clinical Characteristics** | | | |
| 10 | diagnosis | Diagnosis<br>*Should select two* | checkbox<br>0, diagnosis___0, MMD<br>1, diagnosis___1, atypical<br>2, diagnosis___2, unilateral<br>3, diagnosis___3, bilateral |
| 11 | repeat_revascularization | Repeat revascularization? | yesno<br>1, Yes<br>0, No |
| 12 | presentation | Presentation | checkbox<br>0, presentation___0, Hemorrhage<br>1, presentation___1, TIAs<br>2, presentation___2, Stroke<br>3, presentation___3, Headache |

| | | | |
|---|---|---|---|
| | | | 3 presentation___3 Headache |
| 13 | duration_of_headache_befor<br>Show the field ONLY if: [presentation(3)] = '1' | Duration of headache before diagnosis<br>*enter in months* | text |
| 14 | hypertension_pre_operative | Hypertension, pre-operatively? | yesno<br>1 Yes<br>0 No |
| 15 | systolic_blood_pressure<br>Show the field ONLY if: [hypertension_pre_operative] = '1' | Systolic Blood Pressure | radio<br>0 130-140<br>1 140-150<br>2 >150 |
| 16 | other_relevant_symptoms | Other relevant symptoms? | notes |
| 17 | clinical_characteristics_complete | Complete? | dropdown<br>0 Incomplete<br>1 Unverified<br>2 Complete |

Instrument: **Pre-op Imaging**

| | | | |
|---|---|---|---|
| 18 | digital_subtraction_angiog | Digital Subtraction Angiography | checkbox<br>0 digital_subtraction_angiog___0 unilate ica occlusi<br>1 digital_subtraction_angiog___1 bilatera ica occlusi<br>2 digital_subtraction_angiog___2 unilate M1 occlusi<br>3 digital_subtraction_angiog___3 bilatera M1 occlusi<br>4 digital_subtraction_angiog___4 unilate A1 occlusi<br>5 digital_subtraction_angiog___5 bilatera A1 occlusi<br>6 digital_subtraction_angiog___6 unilate A1 & M occlusi<br>7 digital_subtraction_angiog___7 bilatera A1 & M occlusi<br>8 digital_subtraction_angiog___8 dissect<br>9 digital_subtraction_angiog___9 posteri circulat dx<br>10 digital_subtraction_angiog___10 Other |
| 19 | other_dsa | Other DSA? | notes |

| | | | |
|---|---|---|---|
| | Show the field ONLY if: [digital_subtraction_angiog(10)] = '1' | | |
| 20 | mri_flair_changes | MRI FLAIR changes | notes |
| 21 | mri_dwi | MRI DWI? | notes |
| 22 | mri_perfusion | MRI Perfusion | notes |
| 23 | cerebrovascular_reserve | Cerebrovascular reserve | radio<br>0 good augmentation<br>1 no augmentation<br>2 other |
| 24 | other_cv_reserve<br>Show the field ONLY if: [cerebrovascular_reserve] = '2' | Other CV reserve | text |
| 25 | cerebrovascular_reserve_ca | Cerebrovascular reserve capacity | radio<br>0 steal phenomenon (>-5%)<br>1 no steal phenomenon (< -5%) |
| 26 | preop_imaging_complete | Complete? | dropdown<br>0 Incomplete<br>1 Unverified<br>2 Complete |
| Instrument: **Operative Characteristics** | | | |
| 27 | date_of_surgery | Date of Surgery<br>*MM/DD/YYYY* | text |
| 28 | site | Site<br>*Select 2; If nothing written likely MCA* | radio<br>0 Left<br>1 Right<br>2 ACA<br>3 MCA |
| 29 | type | Type | radio<br>0 Direct<br>1 Indirect<br>2 Omental flap |
| 30 | complications | Complications | checkbox<br>0 complications___0 Postop infarction<br>1 complications___1 TND<br>2 complications___2 DWI changes<br>3 complications___3 Postop clot<br>4 complications___4 Postop infection |
| 31 | operative_characteristics_complete | Complete? | dropdown<br>0 Incomplete<br>1 Unverified<br>2 Complete |

| | | | |
|---|---|---|---|
| Instrument: **Follow up** | | | |
| 32 | follow_up_duration | Follow up duration?<br>*enter in months* | text |
| 33 | follow_up_outcome | Follow up outcome | text |
| 34 | mrs | MRS | text |
| 35 | blood_pressure_resolved | Blood pressure resolved | yesno<br>1 Yes<br>0 No |
| 36 | headache_resolved | Headache resolved? | yesno<br>1 Yes<br>0 No |
| 37 | associated_conditions | Associated conditions? | notes |
| 38 | follow_up_complete | Complete? | dropdown<br>0 Incomplete<br>1 Unverified<br>2 Complete |
| Instrument: **Long term follow up** | | | |
| 39 | dsa_bypass_grafts_patent | Six month DSA - Bypass grafts patent? | yesno<br>1 Yes<br>0 No |
| 40 | dsa_collaterals | Six month DSA - collaterals? | yesno<br>1 Yes<br>0 No |
| 41 | dsa_progression | Six month DSA - progression? | yesno<br>1 Yes<br>0 No |
| 42 | mri_evidence_of_new_infarc | Six month MRI - Evidence of new infarcts | yesno<br>1 Yes<br>0 No |
| 43 | location_of_new_infarcts<br>Show the field ONLY if: [mri_evidence_of_new_infarc] = '1' | Six month - Location of new infarcts? | text |
| 44 | six_month_mri_perfusion | Six month MRI perfusion | notes |
| 45 | three_yr_dsa_bypass_grafts | Three yr DSA - bypass grafts patent? | yesno<br>1 Yes<br>0 No |
| 46 | three_yr_dsa_collaterals | Three yr DSA - Collaterals? | yesno<br>1 Yes<br>0 No |

| | | | |
|---|---|---|---|
| 47 | three_yr_dsa_progression | Three yr DSA - Progression? | yesno<br>1 Yes<br>0 No |
| 48 | three_yr_mri_evidence_of_n | Three yr MRI - Evidence of new infarcts? | yesno<br>1 Yes<br>0 No |
| 49 | three_yr_location_of_new_i<br>Show the field ONLY if: [three_yr_mri_evidence_of_n] = '1' | Three yr MRI - location of new infarcts? | text |
| 50 | ten_yr_dsa_bypass_grafts_p | Ten yr DSA - bypass grafts patent? | yesno<br>1 Yes<br>0 No |
| 51 | ten_yr_dsa_collaterals | Ten yr DSA - Collaterals? | yesno<br>1 Yes<br>0 No |
| 52 | ten_yr_dsa_progression | Ten yr DSA - Progression? | yesno<br>1 Yes<br>0 No |
| 53 | ten_yr_mri_evidence_of_new | Ten yr MRI - Evidence of new infarcts? | yesno<br>1 Yes<br>0 No |
| 54 | ten_yr_mri_location_of_new<br>Show the field ONLY if: [three_yr_mri_evidence_of_n] = '1' | Ten yr MRI - location of new infarcts | text |
| 55 | twenty_year_dsa_bypass_gra | Twenty yr DSA - bypass grafts patent? | yesno<br>1 Yes<br>0 No |
| 56 | twenty_yr_dsa_collaterals | Twenty yr DSA - Collaterals? | yesno<br>1 Yes<br>0 No |
| 57 | twenty_yr_dsa_progression | Twenty yr DSA - progression? | yesno<br>1 Yes<br>0 No |
| 58 | twenty_yr_mri_evnence_of_n | Twenty yr MRI - Evidence of new infarcts? | yesno<br>1 Yes<br>0 No |
| 59 | twenty_yr_mri_location_of<br>Show the field ONLY if: [twenty_yr_mri_evnence_of_n] = '1' | Twenty yr MRI - location of new infarcts? | yesno<br>1 Yes<br>0 No |

| | | | |
|---|---|---|---|
| 60 | long_term_follow_up_complete | Complete? | dropdown<br>0, Incomplete<br>1, Unverified<br>2, Complete |

# Demographics

Record ID _____

MRN _____

Last name _____

First name _____

Sex
◯ Female
◯ Male

Date of birth _____
(MM/DD/YYYY)

Race
☐ Caucasian
☐ Asian/Pacific Islander
☐ African-American
☐ Hispanic
☐ Native American
☐ Other

Age at presentation _____
(years)

Age at diagnosis _____
(years)

Other demographic comments _____

# Clinical Characteristics

Handedness
- ◯ Right
- ◯ Left
- ◯ Ambidextrous

Diagnosis
- ☐ MMD
- ☐ atypical
- ☐ unilateral
- ☐ bilateral
- ☐ unilateral progressed to bilateral

(Should select two)

Presentation
- ☐ Hemorrhage
- ☐ TIAs
- ☐ Stroke
- ☐ Headache
- ☐ Seizure

Number of TIAs _____

TIA symptoms _____

Duration of headache before diagnosis _____
(enter in months)

Preoperative modified Rankin Score
- ◯ 0 (no sx)
- ◯ 1 (sx, but no activity limit)
- ◯ 2 (activity limit, but independent)
- ◯ 3 (activity limit, req help, but walks indep)
- ◯ 4 (req bodily needs or walking assist)
- ◯ 5 (bedridden, incontinent, req constant care)
- ◯ 6 (dead)

Preoperative neurological exam normal?
- ◯ Yes
- ◯ No

Preoperative neurological exam description _____

Co-existing syndromes
- ☐ Down syndrome
- ☐ Neurofibromatosis 1
- ☐ Neurofibromatosis 2
- ☐ Sickle cell disease
- ☐ Vasculitis
- ☐ Dwarfism
- ☐ Glycogen Storage Disorder Type 1a
- ☐ Hurler
- ☐ Alagille
- ☐ Russell-Silver
- ☐ Atherosclerosis
- ☐ Hyperthyroidism
- ☐ Homocysteinuria
- ☐ Fibromuscular dysplasia
- ☐ Polycystic Kidney Disease
- ☐ Marfan Syndrome
- ☐ Thalassemia
- ☐ Fe deficiency anemia
- ☐ Protein S or Protein C deficiency
- ☐ Homocystinemia
- ☐ AntiPhospholipid Syndrome
- ☐ Thrombophillia
- ☐ Systemic Lupus Erythro
- ☐ Other (specify below)

Other significant history

- ☐ Hx CNS infection
- ☐ Hx Cranial Therapeutic Irradiation
- ☐ Hx OCP
- ☐ Hx of Cocaine or Amphetamine Use

Smoker

- ◯ Yes
- ◯ No

Body mass index (kg/m2) _____

Hypertension, pre-operatively?

- ◯ Yes
- ◯ No

Systolic Blood Pressure

- ◯ 130-140
- ◯ 140-150
- ◯ >150

SBP _____
(systolic)

DBP _____

Hypertension being treated?

- ◯ Yes
- ◯ No

Hypertension medications _____

Thyroid disease

- ◯ Yes
- ◯ No

Coronary artery disease

- ◯ Yes
- ◯ No

Prior myocardial infarction

- ◯ Yes
- ◯ No

Diabetes

- ◯ Yes
- ◯ No

Renal artery stenosis

- ◯ Yes
- ◯ No

Renal artery ultrasound or angiography performed?

- ◯ Yes
- ◯ No

Renal artery imaging description _____

Hyperlipidemia

- ◯ Yes
- ◯ No

Peripheral vascular disease

- ◯ Yes
- ◯ No

Other relevant symptoms, syndromes, or comments _____

# Family History

Family history of moyamoya
◯ Yes
◯ No

Family members with moyamoya _____

Family history of early Coronary Artery Disease in first-degree relatives.
◯ Yes
◯ No

Family history of stroke at < 50 years in first-degree relatives
◯ Yes
◯ No

Family members with stroke at < 50 years old _____

Other family history comments _____

# Pre-op Imaging

Any pre-existing cerebral lesion
◯ Yes
◯ No

Infarction
◯ Yes
◯ No

Infarction side
◯ Left
◯ Right
◯ Both

Infarction type
☐ Watershed
☐ Territory
☐ Multiple territory
☐ Other

Infarction location
_____

Intracerebral hemorrhage
◯ Yes
◯ No

Intracerebral hemorrhage side
◯ Left
◯ Right
◯ Both

Intracerebral hemorrhage type
☐ Intraparenchymal
☐ Intraventricuar
☐ Subarachnoid
☐ Subdural
☐ Epidural
☐ Other

Intracerebral hemorrhage location
_____

Moyamoya vessels
◯ Absent
◯ Minimal
◯ Marked

ICA findings
☐ Left Occluded
☐ Left Stenosed
☐ Left Patent
☐ Right Occluded
☐ Right Stenosed
☐ Right Patent

ICA occlusion location
_____

ACA findings
☐ Left Occluded
☐ Left Stenosed
☐ Left Patent
☐ Right Occluded
☐ Right Stenosed
☐ Right Patent

ACA occlusion location
_____

MCA findings
☐ Left Occluded
☐ Left Stenosed
☐ Left Patent
☐ Right Occluded
☐ Right Stenosed
☐ Right Patent

MCA occlusion location
_____

PCA findings

- ☐ Left Occluded
- ☐ Left Stenosed
- ☐ Left Patent
- ☐ Right Occluded
- ☐ Right Stenosed
- ☐ Right Patent

PCA occlusion location _____

Any vascular dissection?

- ◯ Yes
- ◯ No

Dissection location _____

Suzuki stage

- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6

Other DSA comments _____

MRI FLAIR changes _____

MRI DWI? _____

MR NOVA findings _____

Type(s) of preoperative cerebrovascular reserve imaging performed

- ☐ None
- ☐ Xenon CT with Diamox
- ☐ MR perfusion with Diamox

Pre-Diamox Xenon CT abnormality description _____

Post-Diamox Xenon CT abnormality description _____

ASL: Pre-Diamox Left frontoparietal territory CBF (mL blood/100g brain) _____

ASL: Pre-Diamox Left frontal lobe CBF (mL blood/100g brain) _____

ASL: Pre-Diamox Left MCA territory CBF (mL blood/100g brain) _____

ASL: Pre-Diamox Left PCA territory CBF (mL blood/100g brain) _____

ASL: Pre-Diamox Left cerebellum CBF (mL blood/100g brain) _____

ASL: Pre-Diamox Right frontoparietal territory CBF (mL blood/100g brain) _____

ASL: Pre-Diamox Right frontal lobe CBF (mL blood/100g brain) _____

ASL: Pre-Diamox Right MCA territory CBF (mL blood/100g brain) _____

ASL: Pre-Diamox Right PCA territory CBF (mL blood/100g brain) _____

ASL: Pre-Diamox Right cerebellum CBF (mL blood/100g brain) _____

ASL: Post-Diamox Left frontoparietal territory CBF (mL blood/100g brain) _____

ASL: Post-Diamox Left frontal lobe CBF (mL blood/100g brain) _____

ASL: Post-Diamox Left MCA territory CBF (mL blood/100g brain) _____

ASL: Post-Diamox Left PCA territory CBF (mL blood/100g brain) _____

ASL: Post-Diamox Left cerebellum CBF (mL blood/100g brain) _____

ASL: Post-Diamox Right frontoparietal territory CBF (mL blood/100g brain) _____

ASL: Post-Diamox Right frontal lobe CBF (mL blood/100g brain) _____

ASL: Post-Diamox Right MCA territory CBF (mL blood/100g brain) _____

ASL: Post-Diamox Right PCA territory CBF (mL blood/100g brain) _____

ASL: Post-Diamox Right cerebellum CBF (mL blood/100g brain) _____

Cerebrovascular reserve capacity

◯ no steal phenomenon (< -5%)
◯ steal phenomenon (>-5%)

Preoperative steal description _____

Any region of delayed Tmax on PWI?

◯ Yes
◯ No

Delayed Tmax on PWI description _____

Other preoperative imaging comments _____

# Surgery 1 Operative Characteristics

Total number of moyamoya surgeries. Include all surgeries at Stanford (i.e. those documented in this database) plus outside hospitals. _____

Date of Surgery 1 at Stanford _____ (MM/DD/YYYY)

Side of surgery 1
- ◯ Left
- ◯ Right

Procedure performed in surgery 1
- ☐ STA-MCA
- ☐ Occipital-MCA
- ☐ MMA-MCA
- ☐ EDAS
- ☐ EDAMS
- ☐ EDMS
- ☐ EMS
- ☐ EDPS
- ☐ Omentum
- ☐ Carotid Endarterectomy
- ☐ Other (describe below)

Is surgery 1 a repeat revascularization surgery?
- ◯ Yes
- ◯ No

Reason surgery 1 is a repeat operation _____

STA diameter (mm) _____

MCA diameter (mm) _____

MAP pre-occlusion (mm Hg) _____

MAP post-bypass (mm Hg) _____

End-tidal CO2 pre-anastomosis (mm Hg) _____

End-tidal CO2 post-bypass (mm Hg) _____

Intraoperative hematocrit _____

STA cut max (mL/min) _____

STA post-anastomosis max (mL/min) _____

MCA total pre-anastomosis max (mL/min) _____

MCA proximal post-anastomosis max (mL/min) _____

MCA distal post-anastomosis max (mL/min) _____

MCA total post-anastomosis max (mL/min) _____

Occlusion time surgery 1 (minutes) _____

Intraoperative adverse events
- ☐ None
- ☐ Hypotension
- ☐ Hypocapnic episodes
- ☐ Other

Estimated blood loss (mL) _____

Other surgery 1 comments _____

# Surgery 1 Early 30 day Postoperative

Infection
◯ Yes
◯ No

Infection description _____

Transient Neurological Event
◯ Yes
◯ No

Number of TNEs _____

Post-op day onset of first TNE _____

TNE description _____

TNE duration _____

Transient Ischemic Attack
◯ Yes
◯ No

TIA description _____

Any permanent or long-term deficit experienced
◯ Yes
◯ No

Deficit description _____

Symptomatic Infarction
◯ Yes
◯ No

Number of symptomatic infarctions in 30-day postop period _____

Post-op day onset of first infarction _____

Infarction side relative to surgery side
◯ Ipsilateral
◯ Contralateral
◯ Both

Infarction type
☐ Watershed
☐ Territory
☐ Multiple Territory
☐ Other

Infarction location _____

Infarction symptoms _____

Maximum grade _____

Intracerebral hemorrhage
◯ Yes
◯ No

Hemorrhage side relative to surgery side
◯ Ipsilateral
◯ Contralateral
◯ Both

Hemorrhage type
☐ Intraparenchymal
☐ Intraventricular
☐ Subarachnoid
☐ Subdural
☐ Epidural

Hemorrhage location _____

Edematous lesion

◯ Yes
◯ No

Edematous lesion location

_____

Length of stay (days)

_____

Modified Rankin Score at discharge

◯ 0 (no sx)
◯ 1 (sx, but no activity limit)
◯ 2 (activity limit, but independent)
◯ 3 (activity limit, req help, but walks indep)
◯ 4 (req bodily needs or walking assist)
◯ 5 (bedridden, incontinent, req constant care)
◯ 6 (dead)

Other comments on early postoperative course, imaging etc

_____

# Surgery 2 Operative Characteristics

Date of Surgery 2 _____
(MM/DD/YYYY)

Side of surgery 2
◯ Left
◯ Right

Procedure performed in surgery 2
☐ STA-MCA
☐ Occipital-MCA
☐ MMA-MCA
☐ EDAS
☐ EDAMS
☐ EDMS
☐ EMS
☐ EDPS
☐ Omentum
☐ Carotid Endarterectomy
☐ Other (describe below)

Is surgery 2 a repeat revascularization surgery?
◯ Yes
◯ No

Reason surgery 2 is a repeat operation _____

STA diameter (mm) _____

MCA diameter (mm) _____

MAP pre-occlusion (mm Hg) _____

MAP post-bypass (mm Hg) _____

End-tidal CO2 pre-anastomosis (mm Hg) _____

End-tidal CO2 post-bypass (mm Hg) _____

Intraoperative hematocrit _____

STA cut max (mL/min) _____

STA post-anastomosis max (mL/min) _____

MCA total pre-anastomosis max (mL/min) _____

MCA proximal post-anastomosis max (mL/min) _____

MCA distal post-anastomosis max (mL/min) _____

MCA total post-anastomosis max (mL/min) _____

Occlusion time surgery 2 (minutes) _____

Intraoperative adverse events
☐ None
☐ Hypotension
☐ Hypocapnic episodes
☐ Other

Estimated blood loss (mL) _____

Other surgery 2 comments _____

# Surgery 2 Early 30 Day Postoperative

Infection
◯ Yes
◯ No

Infection description _____

Transient Neurological Event
◯ Yes
◯ No

Number of TNEs _____

Post-op day onset of first TNE _____

TNE description _____

TNE duration _____

Transient Ischemic Attack
◯ Yes
◯ No

TIA description _____

Any permanent or long-term deficit experienced
◯ Yes
◯ No

Deficit description _____

Symptomatic Infarction
◯ Yes
◯ No

Number of symptomatic infarctions in 30-day postop period _____

Post-op day onset of first infarction _____

Infarction side relative to surgery side
◯ Ipsilateral
◯ Contralateral
◯ Both

Infarction type
☐ Watershed
☐ Territory
☐ Multiple Territory
☐ Other

Infarction location _____

Infarction symptoms _____

Maximum grade _____

Intracerebral hemorrhage
◯ Yes
◯ No

Hemorrhage side relative to surgery side
◯ Ipsilateral
◯ Contralateral
◯ Both

Hemorrhage type
☐ Intraparenchymal
☐ Intraventricular
☐ Subarachnoid
☐ Subdural
☐ Epidural

Hemorrhage location _____

Edematous lesion

◯ Yes
◯ No

Edematous lesion location

_____

Length of stay (days) (if not discharged between surgeries, count from first surgery during this hospitalization)

_____

Modified Rankin Score at discharge

◯ 0 (no sx)
◯ 1 (sx, but no activity limit)
◯ 2 (activity limit, but independent)
◯ 3 (activity limit, req help, but walks indep)
◯ 4 (req bodily needs or walking assist)
◯ 5 (bedridden, incontinent, req constant care)
◯ 6 (dead)

Other comments on early postoperative course, imaging etc

_____

# Surgery 3 Operative Characteristics

Date of Surgery 3 _____
(MM/DD/YYYY)

Side of surgery 3
◯ Left
◯ Right

Procedure performed in surgery 3
☐ STA-MCA
☐ Occipital-MCA
☐ MMA-MCA
☐ EDAS
☐ EDAMS
☐ EDMS
☐ EMS
☐ EDPS
☐ Omentum
☐ Carotid Endarterectomy
☐ Other (describe below)

Is surgery 3 a repeat revascularization surgery?
◯ Yes
◯ No

Reason surgery 3 is a repeat operation _____

STA diameter (mm) _____

MCA diameter (mm) _____

MAP pre-occlusion (mm Hg) _____

MAP post-bypass (mm Hg) _____

End-tidal CO2 pre-anastomosis (mm Hg) _____

End-tidal CO2 post-bypass (mm Hg) _____

Intraoperative hematocrit _____

STA cut max (mL/min) _____

STA post-anastomosis max (mL/min) _____

MCA total pre-anastomosis max (mL/min) _____

MCA proximal post-anastomosis max (mL/min) _____

MCA distal post-anastomosis max (mL/min) _____

MCA total post-anastomosis max (mL/min) _____

Occlusion time surgery 3 (minutes) _____

Intraoperative adverse events
☐ None
☐ Hypotension
☐ Hypocapnic episodes
☐ Other

Estimated blood loss (mL) _____

Other surgery 3 comments _____

# Surgery 3 Early 30 Day Postoperative

Infection
◯ Yes
◯ No

Infection description _____

Transient Neurological Event
◯ Yes
◯ No

Number of TNEs _____

Post-op day onset of first TNE _____

TNE description _____

TNE duration _____

Transient Ischemic Attack
◯ Yes
◯ No

TIA description _____

Any permanent or long-term deficit experienced
◯ Yes
◯ No

Deficit description _____

Symptomatic Infarction
◯ Yes
◯ No

Number of symptomatic infarctions in 30-day postop period _____

Post-op day onset of first infarction _____

Infarction side relative to surgery side
◯ Ipsilateral
◯ Contralateral
◯ Both

Infarction type
☐ Watershed
☐ Territory
☐ Multiple Territory
☐ Other

Infarction location _____

Infarction symptoms _____

Maximum grade _____

Intracerebral hemorrhage
◯ Yes
◯ No

Hemorrhage side relative to surgery side
◯ Ipsilateral
◯ Contralateral
◯ Both

Hemorrhage type
☐ Intraparenchymal
☐ Intraventricular
☐ Subarachnoid
☐ Subdural
☐ Epidural

Hemorrhage location _____

Edematous lesion

◯ Yes
◯ No

Edematous lesion location

_____

Length of stay (days, counted from first surgery during this hospitalization)

_____

Modified Rankin Score at discharge

◯ 0 (no sx)
◯ 1 (sx, but no activity limit)
◯ 2 (activity limit, but independent)
◯ 3 (activity limit, req help, but walks indep)
◯ 4 (req bodily needs or walking assist)
◯ 5 (bedridden, incontinent, req constant care)
◯ 6 (dead)

Other comments on early postoperative course, imaging etc

_____

# Surgery 4 Operative Characteristics

Date of Surgery 4 _____
(MM/DD/YYYY)

Side of surgery 4
◯ Left
◯ Right

Procedure performed in surgery 4
☐ STA-MCA
☐ Occipital-MCA
☐ MMA-MCA
☐ EDAS
☐ EDAMS
☐ EDMS
☐ EMS
☐ EDPS
☐ Omentum
☐ Carotid Endarterectomy
☐ Other (describe below)

Is surgery 4 a repeat revascularization surgery?
◯ Yes
◯ No

Reason surgery 4 is a repeat operation _____

STA diameter (mm) _____

MCA diameter (mm) _____

MAP pre-occlusion (mm Hg) _____

MAP post-bypass (mm Hg) _____

End-tidal CO2 pre-anastomosis (mm Hg) _____

End-tidal CO2 post-bypass (mm Hg) _____

Intraoperative hematocrit _____

STA cut max (mL/min) _____

STA post-anastomosis max (mL/min) _____

MCA total pre-anastomosis max (mL/min) _____

MCA proximal post-anastomosis max (mL/min) _____

MCA distal post-anastomosis max (mL/min) _____

MCA total post-anastomosis max (mL/min) _____

Occlusion time surgery 4 (minutes) _____

Intraoperative adverse events
☐ None
☐ Hypotension
☐ Hypocapnic episodes
☐ Other

Estimated blood loss (mL) _____

Other surgery 4 comments _____

# Surgery 4 Early 30 Day Postoperative

Infection
◯ Yes
◯ No

Infection description _____

Transient Neurological Event
◯ Yes
◯ No

Number of TNEs _____

Post-op day onset of first TNE _____

TNE description _____

TNE duration _____

Transient Ischemic Attack
◯ Yes
◯ No

TIA description _____

Any permanent or long-term deficit experienced
◯ Yes
◯ No

Deficit description _____

Symptomatic Infarction
◯ Yes
◯ No

Number of symptomatic infarctions in 30-day postop period _____

Post-op day onset of first infarction _____

Infarction side relative to surgery side
◯ Ipsilateral
◯ Contralateral
◯ Both

Infarction type
☐ Watershed
☐ Territory
☐ Multiple Territory
☐ Other

Infarction location _____

Infarction symptoms _____

Maximum grade _____

Intracerebral hemorrhage
◯ Yes
◯ No

Hemorrhage side relative to surgery side
◯ Ipsilateral
◯ Contralateral
◯ Both

Hemorrhage type
☐ Intraparenchymal
☐ Intraventricular
☐ Subarachnoid
☐ Subdural
☐ Epidural

Hemorrhage location _____

Edematous lesion

◯ Yes
◯ No

Edematous lesion location

_____

Length of stay (days, counted from first surgery during this hospitalization)

_____

Modified Rankin Score at discharge

◯ 0 (no sx)
◯ 1 (sx, but no activity limit)
◯ 2 (activity limit, but independent)
◯ 3 (activity limit, req help, but walks indep)
◯ 4 (req bodily needs or walking assist)
◯ 5 (bedridden, incontinent, req constant care)
◯ 6 (dead)

Other comments on early postoperative course, imaging etc

_____

# Early 30 Day postoperative imaging

Any new lesion on postop imaging? (besides expected surgical change)
◯ Yes
◯ No

Imaging modalities within the first 30 days postop
☐ None
☐ MRI
☐ CT

Description of postop imaging lesion or improvement _____

# Long term follow up

Date of last follow up
_____
(MM/DD/YYYY)

Did any of the following adverse events occur? (after the early 30-day postoperative period)
☐ Stroke
☐ ICH
☐ Death
☐ Transient Neurological Event (TNE)
☐ Other
☐ Transient Ischemic Attack (TIA)

TIA description
_____

If unilateral, did patient experience contralateral progression?
◯ Yes
◯ No

Describe contralateral progression
_____

Stroke date?
_____
(MM/DD/YYYY)

Recovery after stroke?
◯ Yes
◯ No

ICH date?
_____
(MM/DD/YYYY)

Recovery from ICH?
◯ Yes
◯ No

Death date?
_____
(MM/DD/YYYY)

Explain 'Other' post-operative adverse event
_____

Headache improved at last follow up?
◯ Yes
◯ No

TIA improved at last follow up?
◯ Yes
◯ No

BP improved at last follow up?
◯ Yes
◯ No
(blood pressure )

Outside scans available?
◯ Yes
◯ No

6 month follow up available?
◯ Yes
◯ No

Six month DSA - Bypass grafts patent?
◯ Yes
◯ No

Six month DSA - Number of collaterals?
◯ Increased
◯ Stable
◯ Decreased

Six month DSA - progression?
◯ Yes
◯ No

Six month MRI - Evidence of new infarcts
◯ Yes
◯ No

Six month - Location of new infarcts?
_____

Six month MRI perfusion _____

Six month mRS
- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6

Three yr follow up available?
- ◯ Yes
- ◯ No

Three yr DSA - bypass grafts patent?
- ◯ Yes
- ◯ No

Three yr DSA - Number of collaterals?
- ◯ Increased
- ◯ Stable
- ◯ Decreased

Three yr DSA - Progression?
- ◯ Yes
- ◯ No

Three yr MRI - Evidence of new infarcts?
- ◯ Yes
- ◯ No

Three yr MRI - location of new infarcts? _____

Three year mRS
- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6

Ten year follow up available?
- ◯ Yes
- ◯ No

Ten yr DSA - bypass grafts patent?
- ◯ Yes
- ◯ No

Ten yr DSA - Number of collaterals?
- ◯ Increased
- ◯ Stable
- ◯ Decreased

Ten yr DSA - Progression?
- ◯ Yes
- ◯ No

Ten yr MRI - Evidence of new infarcts?
- ◯ Yes
- ◯ No

Ten yr MRI - location of new infarcts _____

Ten year mRS
- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6

Twenty yr follow up available?
- ◯ Yes
- ◯ No

Twenty yr DSA - bypass grafts patent?
- ◯ Yes
- ◯ No

Twenty yr DSA - Number of Collaterals?
- ◯ Increased
- ◯ Stable
- ◯ Decreased

Twenty yr DSA - progression?
- ◯ Yes
- ◯ No

Twenty yr MRI - Evidence of new infarcts?
- ◯ Yes
- ◯ No

Twenty yr MRI - location of new infarcts?
- ◯ Yes
- ◯ No

Other follow up time point?
- ◯ Yes
- ◯ No

Other Follow up year?
_____
(after surgery)

Other year bypass grafts patent?
- ◯ Yes
- ◯ No

Other year Number of Collaterals?
- ◯ Increased
- ◯ Stable
- ◯ Decreased

Other year Progression?
- ◯ Yes
- ◯ No

Other year evidence of new infarcts
- ◯ Yes
- ◯ No

Other - location of new infarcts?
_____

Other year mRS?
- ◯ 0
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6