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PRECISION REVASCULARIZATION IN ADULT MOYAMOYA DISEASE: HEMODYNAMIC PHENOTYPING, DIRECT AND COMBINED BYPASS, HYPERPERFUSION CONTROL, AND PERSONALIZED SURGICAL TARGETING

Abstract

Background. Adult moyamoya disease is a progressive occlusive cerebrovascular arteriopathy characterized by stenosis of the terminal internal carotid circulation, development of fragile collateral networks, impaired cerebrovascular reserve, and risk of ischemic or hemorrhagic stroke. Surgical revascularization is the principal disease-modifying treatment in symptomatic and hemodynamically compromised patients. However, the optimal strategy cannot be reduced to a universal choice between direct, indirect, and combined bypass because adult moyamoya disease encompasses heterogeneous ischemic, hemorrhagic, asymptomatic, cognitive, and collateral-dominant phenotypes.

Materials and Methods. A structured narrative review was performed using contemporary guidelines, randomized and prospective studies, population-based cohorts, hemodynamic investigations, and surgical series published through August 2026. Evidence was synthesized regarding direct superficial temporal artery–middle cerebral artery bypass, indirect synangiosis, combined revascularization, cerebral perfusion imaging, cerebrovascular reserve, periventricular collateral anatomy, postoperative hyperperfusion, cerebral infarction, cognition, and genetic predictors of revascularization.

Results. Direct bypass provides immediate flow augmentation, whereas indirect procedures depend on delayed extracranial–intracranial neoangiogenesis. Combined surgery offers both mechanisms and may provide broader long-term revascularization in adults. Hemorrhagic moyamoya represents a distinct surgical phenotype in which bypass can reduce rebleeding risk, particularly in patients with high-risk posterior hemorrhage and fragile periventricular collateral pathways. In ischemic moyamoya, surgical selection should integrate symptoms with objective hemodynamic compromise rather than angiographic stenosis alone. Cerebral hyperperfusion syndrome remains a major postoperative complication after direct bypass and is associated with impaired autoregulation, regional perfusion abnormalities, and abrupt redistribution of blood flow. Newer CT perfusion, arterial spin labeling, Flow800, Doppler, and genetic approaches are increasingly capable of predicting postoperative perfusion patterns and neoangiogenesis.

Conclusion. Adult moyamoya surgery is evolving from standardized bypass selection toward precision revascularization. The optimal operation should be determined by clinical phenotype, regional cerebrovascular reserve, collateral architecture, recipient-vessel anatomy, genetic background, and predicted perioperative hemodynamic response. Direct flow augmentation and indirect neoangiogenesis should be regarded as complementary physiological tools rather than competing techniques.

Keywords: moyamoya disease; cerebral revascularization; STA–MCA bypass; combined bypass; indirect bypass; cerebral perfusion; cerebrovascular reserve; cerebral hyperperfusion syndrome; RNF213; precision cerebrovascular surgery.

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ПРЕЦИЗИОННАЯ РЕВАСКУЛЯРИЗАЦИЯ ПРИ БОЛЕЗНИ МОЙАМОЙА У ВЗРОСЛЫХ: ГЕМОДИНАМИЧЕСКОЕ ФЕНОТИПИРОВАНИЕ, ПРЯМОЕ И КОМБИНИРОВАННОЕ ШУНТИРОВАНИЕ, КОНТРОЛЬ ГИПЕРПЕРФУЗИИ И ПЕРСОНАЛИЗИРОВАННОЕ ХИРУРГИЧЕСКОЕ ТАРГЕТИРОВАНИЕ

Аннотация

Актуальность. Болезнь мойамойа у взрослых представляет собой прогрессирующую окклюзирующую цереброваскулярную артериопатию, характеризующуюся стенозированием терминальных отделов внутренней сонной артерии, формированием патологической коллатеральной сети, снижением цереброваскулярного резерва и риском ишемического или геморрагического инсульта. Хирургическая реваскуляризация является основным методом модификации естественного течения заболевания у симптомных и гемодинамически нестабильных пациентов. Однако оптимальная стратегия не может определяться универсальным выбором между прямым, непрямым и комбинированным шунтированием.

Материалы и методы. Проведен структурированный нарративный обзор современных рекомендаций, рандомизированных исследований, проспективных когорт, популяционных исследований, гемодинамических работ и хирургических серий, опубликованных до августа 2026 года. Проанализированы STA–MCA bypass, непрямая реваскуляризация, комбинированные операции, церебральная перфузия, цереброваскулярный резерв, перивентрикулярные коллатерали, послеоперационная гиперперфузия, ишемические осложнения, когнитивные результаты и генетические предикторы.

Результаты. Прямой bypass обеспечивает немедленное увеличение кровотока, тогда как непрямые методики зависят от отсроченного неоангиогенеза. Комбинированная операция объединяет оба механизма и может обеспечивать более широкую долгосрочную реваскуляризацию у взрослых. При геморрагическом фенотипе шунтирование способно снижать риск повторного кровоизлияния, особенно при наличии высокорисковых перивентрикулярных коллатералей. При ишемическом фенотипе показания должны основываться не только на ангиографическом стенозе, но и на объективном снижении гемодинамического резерва. После прямого bypass сохраняется риск церебрального гиперперфузионного синдрома, обусловленного нарушением ауторегуляции и резкой перестройкой регионарного кровотока.

Заключение. Современная хирургия болезни мойамойа у взрослых должна строиться на концепции прецизионной реваскуляризации, объединяющей клинический фенотип, гемодинамику, коллатеральную анатомию, характеристики реципиентных сосудов и риск послеоперационной гиперперфузии.

Ключевые слова: болезнь мойамойа; реваскуляризация; STA–MCA bypass; комбинированное шунтирование; церебральная перфузия; цереброваскулярный резерв; гиперперфузионный синдром; RNF213.

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KATTALARDA MOYAMOYA KASALLIGIDA PRETSIZION REVASKULYARIZATSIYA: GEMODINAMIK FENOTIPLASH, TO‘G‘RIDAN-TO‘G‘RI VA KOMBINATSIYALANGAN BYPASS, GIPERPERFUZIYANI NAZORAT QILISH VA SHAXSIYLASHTIRILGAN JARROHLIK NISHONLASH

Annotatsiya

Dolzarblik. Kattalardagi moyamoya kasalligi terminal ichki uyqu arteriyalari va ularning asosiy shoxlarining progressiv torayishi, patologik kollateral tomirlar rivojlanishi, serebrovaskulyar rezerv pasayishi hamda ishemik yoki gemorragik insult xavfi bilan tavsiflanadigan okklyuziv serebrovaskulyar arteriopatiyadir. Simptomatik va gemodinamik jihatdan beqaror bemorlarda jarrohlik revaskulyarizatsiyasi kasallikning tabiiy kechishini o‘zgartiruvchi asosiy davolash usuli hisoblanadi.

Material va usullar. 2026-yil avgustigacha chop etilgan zamonaviy klinik tavsiyalar, randomizatsiyalangan tadqiqotlar, prospektiv kohortalar, populyatsion ishlar, gemodinamik tadqiqotlar va jarrohlik seriyalari strukturaviy narrativ tahlil qilindi. STA–MCA bypass, bilvosita va kombinatsiyalangan revaskulyarizatsiya, miya perfuziyasi, serebrovaskulyar rezerv, periventrikulyar kollaterallar, giperperfuziya sindromi, ishemik asoratlar va genetik prediktorlar baholandi.

Natijalar. To‘g‘ridan-to‘g‘ri bypass miya qon oqimini darhol oshiradi, bilvosita usullar esa kechikkan neoangiogenezga bog‘liq. Kombinatsiyalangan bypass ikkala mexanizmni birlashtiradi va kattalarda kengroq uzoq muddatli revaskulyarizatsiyani ta’minlashi mumkin. Gemorragik moyamoyada bypass qayta qon ketish xavfini kamaytirishi mumkin. Ishemik variantda operatsiya ko‘rsatmalari angiografik stenozdan tashqari, obyektiv gemodinamik yetishmovchilikka ham asoslanishi lozim. To‘g‘ridan-to‘g‘ri bypassdan keyin serebral giperperfuziya sindromi muhim asorat bo‘lib qolmoqda.

Xulosa. Moyamoya kasalligida zamonaviy jarrohlik taktika klinik fenotip, serebrovaskulyar rezerv, kollateral arxitektura, retsipient arteriyalar va operatsiyadan keyingi gemodinamik javobni birgalikda hisobga olgan holda shaxsiylashtirilishi kerak.

Kalit so‘zlar: moyamoya kasalligi; serebral revaskulyarizatsiya; STA–MCA bypass; kombinatsiyalangan bypass; miya perfuziyasi; serebrovaskulyar rezerv; giperperfuziya; RNF213.

Introduction. Moyamoya disease is a progressive nonatherosclerotic, noninflammatory occlusive arteriopathy involving predominantly the terminal intracranial internal carotid arteries and proximal anterior and middle cerebral circulation, accompanied by compensatory formation of basal collateral networks. The angiographic appearance of these fragile collaterals gave rise to the term “moyamoya,” originally describing a smoke-like vascular pattern [1]. Contemporary understanding has expanded considerably beyond this angiographic definition. Moyamoya is now recognized as a

heterogeneous cerebrovascular disorder involving progressive large-artery stenosis, altered cerebral autoregulation, abnormal collateral remodeling, impaired microvascular reserve, genetic susceptibility, and long-term vulnerability to both cerebral ischemia and intracranial hemorrhage [2–4]. Current Japanese and American recommendations therefore emphasize integrated clinical, angiographic, and hemodynamic assessment rather than diagnosis or treatment based solely on the severity of arterial narrowing [3, 4]. The principal disease-modifying treatment is surgical revascularization because pharmacological therapy cannot reverse the underlying progressive arteriopathy or reconstruct exhausted cerebral blood-flow reserve [3, 4]. Direct superficial temporal artery–middle cerebral artery anastomosis provides immediate extracranial-to-intracranial flow augmentation, whereas indirect procedures such as encephaloduroarteriosynangiosis, encephaloduroarteriomyosynangiosis, or related techniques create a vascularized extracranial tissue interface from which new collaterals progressively develop [11–16]. Combined surgery attempts to exploit both physiological mechanisms by providing immediate direct augmentation and delayed broader neoangiogenesis. Long-term adult series have demonstrated sustained clinical, angiographic, and hemodynamic improvement following combined revascularization [11], while more recent intra-individual analyses indicate that combined bypass can generate a larger revascularization territory and stronger long-term hemodynamic improvement than indirect bypass alone [12]. The superiority of one surgical technique over another cannot, however, be considered independently of age and phenotype. Indirect revascularization is highly effective in many pediatric patients, whereas its biological reliability is more variable in adults because neoangiogenesis develops slowly and may be incomplete [14, 15]. In the multicenter analysis by Zhao and colleagues, favorable neoangiogenesis after indirect bypass occurred in approximately two-thirds of treated hemispheres, while hemorrhagic onset was associated with poorer neovascularization and abundant internal-carotid moyamoya vessels predicted better collateral development [14]. The major neoangiogenic response develops principally during the first postoperative months, although collateral maturation can continue over a longer period [15]. These observations explain why direct or combined techniques are frequently favored in symptomatic adults requiring immediate hemodynamic support [11–15]. Hemorrhagic moyamoya represents a fundamentally different therapeutic phenotype. Intracranial hemorrhage is often attributed to hemodynamic stress on fragile deep collateral pathways, particularly dilated periventricular and choroidal anastomoses. The Japan Adult Moyamoya Trial provided randomized evidence that extracranial–intracranial bypass can reduce recurrent hemorrhagic events in adult hemorrhagic moyamoya [5]. Subsequent prespecified analyses demonstrated that posterior hemorrhage identifies a particularly high-risk population [6]. Further observational analyses implicated choroidal anastomoses and hemodynamic failure as markers of recurrent hemorrhagic risk [7, 8]. The mechanistic surgical objective is therefore not simply to “increase cerebral blood flow” but to reduce abnormal hemodynamic dependence on fragile deep collateral pathways by creating a lower-resistance extracranial supply [5–8].

Ischemic moyamoya presents another decision problem. Angiographic severity does not directly quantify regional metabolic risk. Some patients with advanced stenosis maintain sufficient collateral reserve, whereas others with apparently less severe angiographic disease have markedly impaired cerebrovascular reactivity and recurrent transient ischemic attacks. Perfusion imaging therefore has an increasingly important role in surgical selection. Single-photon emission computed

tomography, positron emission tomography, CT perfusion, arterial spin labeling, and acetazolamide-challenge techniques can evaluate resting cerebral blood flow and cerebrovascular reserve [23–26]. Regional abnormalities in mean transit time, time-to-peak, arterial transit delay, oxygen extraction, or vasodilatory reserve provide physiological information that is not captured by Suzuki stage alone [24–26]. This physiological heterogeneity has direct implications for perioperative risk. Direct anastomosis suddenly introduces relatively high-pressure extracranial flow into a chronically hypoperfused vascular bed with impaired autoregulation. The resulting postoperative state may range from beneficial normalization to focal cerebral hyperperfusion, transient neurological deterioration, seizure, cortical edema, or intracranial hemorrhage [20–23]. Uchino and colleagues demonstrated that postoperative hyperperfusion is not rare in adult moyamoya and is associated with preoperative and perioperative hemodynamic characteristics [20]. More recent studies using arterial spin labeling, CT perfusion, autoregulatory analysis, and clinical variables have attempted to improve prediction of cerebral hyperperfusion syndrome [21–23]. Importantly, postoperative neurological deterioration may also result from ischemia rather than hyperperfusion. Abrupt redistribution of regional flow can create a “watershed shift” in territories remote from the bypass, and perioperative infarction remains a clinically significant complication. Quantitative perfusion analysis has therefore been investigated not only to identify preoperative surgical candidates but also to predict postoperative ischemic injury [24, 25, 32]. Contemporary studies using rapid CT perfusion parameters suggest that larger volumes of critically delayed perfusion may identify adults at elevated postoperative infarction risk [24, 32].

The therapeutic endpoint of revascularization extends beyond stroke prevention. Chronic hemodynamic insufficiency can affect white-matter microstructure, frontal executive networks, processing speed, and cognition even in the absence of overt territorial infarction. Adult studies have identified relationships between cerebral hemodynamic impairment and neurocognitive dysfunction, while postoperative revascularization can be associated with stabilization or improvement in selected cognitive domains [27–29]. These findings suggest that “successful bypass” should not be defined exclusively by graft patency or absence of recurrent stroke [27–29].

Genetic information adds another emerging layer of complexity. RNF213, particularly the p.R4810K founder variant in East Asian populations, is strongly associated with moyamoya susceptibility. Recent surgical studies suggest that RNF213 and additional rare variants may also influence donor-territory angiogenesis and postoperative collateral remodeling [18, 19, 35]. The relationship between genotype and surgical phenotype is not yet sufficiently validated to dictate operative technique, but these observations raise the possibility that future revascularization strategies may incorporate genetic prediction of indirect collateral capacity [18, 19, 35].

The management of asymptomatic adults further demonstrates why a universal surgical algorithm is inappropriate. The prospective AMORE registry showed that clinically asymptomatic moyamoya is not biologically benign; stroke and angiographic progression occur during longitudinal follow-up, but individual risk remains heterogeneous [9]. Consequently, prophylactic surgery for every asymptomatic angiographic case is not justified, and decision-making requires integration of progression, silent infarction, hemodynamic impairment, collateral anatomy, and patient-specific risk [9, 30]. Finally, perioperative timing remains controversial. Some symptomatic adults undergo surgery soon after ischemic presentation because ongoing hemodynamic failure creates recurrent stroke risk,

whereas others are treated after a stabilization interval to reduce perioperative vulnerability. Contemporary observational data indicate that early surgery is not necessarily associated with worse outcome when careful perioperative selection and management are applied, although randomized evidence defining an optimal interval is lacking [31]. Traditional surgical series and contemporary population-level analyses nevertheless agree that the benefits and risks of revascularization differ substantially across ischemic, hemorrhagic, and asymptomatic presentations [10, 13, 31].

Materials and Methods. A structured narrative review was performed using current international and Japanese recommendations, randomized clinical evidence, prospective observational studies, large population-based cohorts, angiographic studies, perfusion-imaging investigations, genetic studies, and major surgical series concerning adult moyamoya disease.

Literature available through August 2026 was evaluated. Particular emphasis was placed on studies addressing ischemic and hemorrhagic adult phenotypes, direct STA–MCA bypass, indirect revascularization, combined surgery, postoperative angiogenesis, periventricular collateral remodeling, cerebral hyperperfusion syndrome, postoperative infarction, regional perfusion imaging, cognition, and genetic predictors. Studies were interpreted according to clinical purpose rather than pooled into a single estimate because surgical techniques, diagnostic criteria, perfusion methods, patient age, presentation type, outcome definitions, and follow-up periods differed substantially among cohorts. The principal conceptual endpoint of the review was defined as precision revascularization, meaning selection of donor artery, recipient artery, bypass type, revascularization territory, and postoperative blood-flow strategy according to the pathophysiological deficit of the individual hemisphere rather than according to moyamoya diagnosis alone.

Results.

Direct Revascularization. The STA–MCA bypass provides immediate augmentation of cortical cerebral blood flow by anastomosing an extracranial donor artery to a cortical MCA branch. This immediate effect is particularly attractive in adults with recurrent ischemic symptoms and severely impaired cerebrovascular reserve because the patient does not need to wait months for indirect neovascularization. Direct bypass also has a mechanistic role in hemorrhagic moyamoya. By reducing the pressure and flow demand imposed on pathological deep collaterals, an extracranial bypass may promote regression of fragile periventricular anastomotic pathways. The major disadvantage is that direct flow augmentation is abrupt. A cortex adapted to chronic hypoperfusion may have severely impaired autoregulatory capacity. Once the bypass is opened, local perfusion can rise rapidly and produce hyperperfusion-related neurological deterioration. The flow delivered by an STA–MCA bypass is also spatially heterogeneous. Retrograde bypass flow may propagate to different depths and territories along recipient cortical arteries, and recent analyses suggest that the depth of retrograde flow is associated with subsequent revascularization behavior [17]. Thus, direct bypass should not be understood simply as a patent or nonpatent conduit. It creates a new hemodynamic network whose effective territory depends on donor capacity, recipient resistance, collateral competition, regional vascular reserve, and postoperative flow redistribution.

Indirect Revascularization. Indirect bypass places vascularized extracranial tissue in contact with the cerebral surface to stimulate spontaneous angiogenesis. Techniques include EDAS, EMS, EDAMS, encephalodurogaleosynangiosis, dural inversion procedures, and multiple burr-hole

approaches. The physiological advantage is gradual augmentation rather than abrupt direct inflow. The principal limitation is latency. A severely ischemic adult remains exposed to stroke during the period before sufficient collateral maturation occurs. Neoangiogenesis is also variable. In the multicenter study of Zhao and colleagues, good neovascularization was observed in 63.2% of analyzed hemispheres. Hemorrhagic presentation was a negative predictor, whereas abundant internal-carotid moyamoya vessels predicted better development of indirect collaterals [14]. Follow-up angiographic studies indicate that the principal period of arterial neoangiogenic development occurs within approximately the first six months, although maturation may continue thereafter [15]. This variability means that an indirect operation technically performed correctly can still produce an inadequate biological response. Future patient selection may therefore increasingly depend on predicting angiogenic capacity before surgery.

Combined Revascularization. Combined bypass attempts to solve the limitations of both isolated techniques. Direct STA–MCA bypass provides immediate perfusion augmentation, while EDAS, EDMS, EDAMS, or another indirect component creates a broad substrate for subsequent collateral growth. Long-term adult series demonstrate sustained expansion of the revascularized area after combined surgery [11]. Combined revascularization can therefore evolve over time rather than remain restricted to the immediate direct-bypass territory. The 2025 intra-individual study by Chung and colleagues is particularly informative because the same patient received combined bypass on one hemisphere and indirect bypass on the contralateral side, reducing interpatient biological confounding. Combined bypass produced larger revascularization areas and stronger long-term improvement in cerebral blood flow and cerebrovascular reserve; delayed postoperative strokes in that small cohort occurred exclusively after indirect-only surgery [12]. These observations favor combined revascularization for many adults, but they do not establish universal superiority. Combined surgery requires a suitable direct donor and recipient, longer operative manipulation, and meticulous perioperative management of immediate flow augmentation.

Table 1. Physiological comparison of adult moyamoya revascularization strategies

Feature	Direct bypass	Indirect bypass	Combined bypass
Onset of flow augmentation	Immediate	Delayed	Immediate + delayed
Mechanism	Surgical anastomosis	Angiogenesis	Anastomosis + angiogenesis
Dependence on neoangiogenic capacity	Low	High	Moderate
Immediate ischemic protection	Highest	Limited initially	High
Hyperperfusion risk	Present	Lower	Present
Revascularization field	Recipient dependent	Potentially broad	Immediate focal + broader long-term
Suitability in adults	High in experienced centers	Selected patients	Frequently attractive

Technical complexity	Microsurgical	Relatively lower	Highest
Main limitation	Hyperperfusion/technical demand	Delayed or inadequate collateralization	More complex perioperative physiology

Hemorrhagic Moyamoya and Collateral Decompression. The Japan Adult Moyamoya Trial fundamentally altered the management of adult hemorrhagic moyamoya by providing randomized evidence supporting surgical revascularization for prevention of recurrent hemorrhage [5]. A prespecified analysis demonstrated that posterior hemorrhage carries a particularly high recurrent bleeding risk and a greater potential surgical benefit [6]. This finding led to increased attention to periventricular collateral pathways. Choroidal, thalamic, and lenticulostriate collateral arteries can become abnormally dilated as they compensate for exhausted anterior circulation inflow. Their distal anastomoses with medullary or cortical arteries are exposed to excessive hemodynamic stress. Nonsurgical JAM analyses identified choroidal anastomosis as an important predictor of recurrent hemorrhage [7], while later work demonstrated persistent periventricular collaterals even after surgery in some patients. The therapeutic goal is therefore collateral decompression. If the bypass provides sufficient alternative cortical blood supply, pathological deep collaterals may regress. This creates a potential imaging biomarker of surgical success beyond simple graft patency.

Ischemic Moyamoya and Hemodynamic Failure. In ischemic moyamoya, the presence of stenosis is not itself sufficient to quantify surgical urgency. The critical variable is whether cerebral tissue retains the ability to increase blood flow in response to metabolic demand. Cerebrovascular reserve is commonly evaluated with acetazolamide-challenge SPECT, PET, arterial spin labeling, or CT perfusion. A hemisphere with normal resting flow but severely impaired reserve may be vulnerable to physiological stress despite apparently adequate baseline perfusion. Conversely, severe angiographic stenosis can coexist with effective collateral compensation. This explains why modern surgical selection increasingly integrates symptoms, silent infarction, perfusion deficit, and CVR. Population-level data from 2024 further support phenotype-specific surgical benefit. In a large adult cohort, bypass surgery was associated with reduced adverse cerebrovascular outcomes, but the pattern of benefit differed between hemorrhagic, ischemic, and asymptomatic presentations [10].

CT Perfusion. CT perfusion provides quantitative or semiquantitative assessment of cerebral blood flow, cerebral blood volume, mean transit time, time to peak, and more recently automated Tmax-based perfusion metrics. In adult moyamoya, prolonged MTT and TTP commonly reflect collateral-dependent delayed flow. The interpretation differs from embolic large-vessel occlusion because tissue may remain viable despite markedly delayed arrival through long collateral pathways. Consequently, thresholds validated for acute ischemic stroke cannot simply be transferred to moyamoya. Nevertheless, serial CTP can quantify postoperative improvement. Studies have demonstrated regional improvements in cerebral perfusion following direct or combined revascularization [24, 25]. Modern RAPID-type processing and regional perfusion metrics are also being investigated for prediction of postoperative cerebral infarction [32].

Table 2. Imaging modalities for precision hemodynamic phenotyping

Modality	Principal information	Main advantage	Main limitation

DSA	Stenosis and collateral architecture	Highest vascular spatial resolution	Invasive
SPECT ± acetazolamide	Resting CBF and CVR	Established functional assessment	Radiation, limited spatial resolution
PET	CBF, metabolism, oxygen extraction	Detailed physiological characterization	Limited availability
CT perfusion	CBF, CBV, MTT, TTP/Tmax	Rapid and quantitative	Radiation and collateral-delay effects
ASL MRI	Noncontrast cerebral perfusion	Repeatable, no radiation	Transit-delay artifacts
DSC MRI	Relative perfusion	Widely available MRI technique	Contrast required
Flow800	Intraoperative cortical flow dynamics	Immediate operative feedback	Surface vessels only
Doppler ultrasonography	Donor/bypass flow characteristics	Noninvasive follow-up	Limited intracranial regional detail

Cerebral Hyperperfusion Syndrome. Cerebral hyperperfusion syndrome is one of the most distinctive complications of direct revascularization in adult moyamoya. Clinical manifestations can include severe headache, aphasia, focal neurological deficit, seizure, cortical edema, and intracranial hemorrhage. The key diagnostic challenge is that postoperative hyperperfusion and postoperative ischemia can produce similar focal neurological symptoms but require fundamentally different hemodynamic responses. Aggressive blood-pressure reduction may be beneficial in symptomatic hyperperfusion but hazardous if the neurological deficit reflects remote hypoperfusion. Therefore, early postoperative perfusion assessment is essential. Uchino et al. demonstrated the value of serial SPECT/PET assessment and identified clinical and hemodynamic characteristics associated with postoperative hyperperfusion [20]. Recent studies have linked CHS to impaired cerebral autoregulation [21], while preoperative perfusion parameters and combined clinical-hemodynamic models have been investigated as predictive tools [22, 23]. The practical implication is that the postoperative blood-pressure target should be individualized rather than fixed.

Watershed Shift and Postoperative Ischemia. Not every neurological deterioration after a patent bypass represents hyperperfusion. Flow entering through a new anastomosis can alter preexisting pressure gradients between adjacent territories. A locally well-perfused region may develop while a more remote watershed territory becomes relatively hypoperfused. This redistribution has been described as a watershed shift phenomenon. Postoperative infarction can also arise from hypotension, hypocapnia, anemia, dehydration, thrombosis, embolism, insufficient bypass flow, or progression of native arterial compromise. Recent perfusion-based prediction studies suggest that quantitative preoperative hypoperfusion burden may help identify patients at increased perioperative ischemic risk [32]. Consequently, perioperative management requires preservation of systemic oxygen delivery and avoidance of excessive fluctuations in blood pressure and carbon dioxide.

Cognitive Outcomes. Moyamoya-associated cerebral dysfunction can occur without major territorial infarction. Chronic frontal hypoperfusion has been associated with executive dysfunction, impaired processing speed, and other subtle neurocognitive deficits. Zeifert and colleagues reported neurocognitive outcomes after cerebral revascularization in adults [27]. Tsunoda and colleagues subsequently demonstrated relationships between frontal lobe hemodynamics and cognitive dysfunction [28]. Diffusion-based studies have also identified microstructural abnormalities in normal-appearing brain tissue, supporting the concept that chronic hemodynamic compromise produces distributed cerebral injury beyond visible infarction [29]. This provides a rationale for including cognitive evaluation as a secondary endpoint in prospective adult moyamoya surgery studies.

Genetic Modifiers of Surgical Revascularization. RNF213 is the most intensively investigated genetic susceptibility locus for moyamoya disease. The p.R4810K founder variant is common among East Asian patients but displays incomplete penetrance. Emerging studies suggest that genetic variation may also influence postoperative vascular remodeling. Ito et al. investigated the relationship between the RNF213 founder variant and postoperative direct and indirect bypass development [18]. Subsequent broader genetic analyses have examined rare RNF213 variants in relation to donor-territory angiogenesis and postoperative periventricular collateral regression [19, 35]. These findings remain exploratory. Genotyping should not currently determine whether an individual adult receives direct or indirect bypass, but genetics may eventually become one component of a multivariable prediction model of angiogenic response.

Asymptomatic Moyamoya. Asymptomatic moyamoya is increasingly identified through modern MRI and MRA. The absence of clinical stroke does not mean absence of disease activity.
The prospective AMORE study demonstrated measurable long-term stroke risk and identified features associated with future events [9]. Nevertheless, the natural risk is lower than in many symptomatic populations, meaning that prophylactic surgery must overcome a relatively low baseline event rate. Potential surgical selection variables include progressive angiographic disease, silent infarction, marked CVR impairment, fragile periventricular collaterals, microbleeds, or significant cognitive dysfunction. Randomized evidence for routine surgery in asymptomatic adults is lacking.

Proposed Precision Revascularization Framework. A precision approach should begin by defining the dominant mechanism of risk. An adult with recurrent TIAs and severely exhausted cerebrovascular reserve has an immediate flow problem. An adult with posterior intracranial hemorrhage and marked choroidal anastomoses has a deep collateral stress problem. An asymptomatic patient with preserved reserve has a progression-monitoring problem. These three patients share the angiographic diagnosis of moyamoya but do not share the same therapeutic objective. For the severely ischemic adult, direct or combined bypass provides immediate hemodynamic augmentation. For hemorrhagic disease, recipient selection may be optimized to reduce flow demand through the pathological collateral territory associated with bleeding. For a patient with adequate reserve but disease progression, surveillance or planned elective surgery may be preferable to urgent intervention.

Table 3. Phenotype-oriented precision revascularization model

Adult phenotype	Dominant pathological problem	Key preoperative assessment	Preferred surgical concept

Recurrent ischemic TIA + low CVR	Flow failure	SPECT/PET/CTP/ASL + DSA	Direct or combined bypass
Ischemic stroke with stable reserve	Tissue recovery + future risk	Infarct burden + CVR + timing	Delayed individualized revascularization
Hemorrhagic posterior phenotype	Fragile deep collaterals	DSA choroidal/periventricular anatomy	Direct/combined collateral-decompression strategy
Hemorrhagic anterior phenotype	Variable collateral stress	DSA + hemodynamics	Individualized bypass
Asymptomatic preserved CVR	Progression risk	Serial MRA/DSA + perfusion	Surveillance in many cases
Asymptomatic impaired CVR	Latent hemodynamic failure	Quantitative CVR	Consider elective surgery
Cognitive/hemodynamic phenotype	Chronic network hypoperfusion	Neuropsychology + perfusion	Consider flow-restorative surgery
Poor predicted indirect angiogenesis	Inadequate collateral response	Age, angiography, possibly genetics	Favor direct component
High CHS-risk phenotype	Autoregulatory failure	ASL/CTP/SPECT + flow metrics	Direct bypass with intensified postoperative monitoring

Discussion. The central conclusion emerging from contemporary adult moyamoya literature is that the historical question “direct or indirect bypass?” is becoming too simplistic. Moyamoya is not a homogeneous stenotic disease, and revascularization is not a homogeneous operation. The disease initially described angiographically by Suzuki and Takaku [1] is now understood through a much broader physiological framework integrating collateral anatomy, hemodynamic reserve, vascular remodeling, cognition, and genetic susceptibility [2–4, 18, 19]. Current Japanese and AHA/ASA recommendations reflect this transition by emphasizing both diagnosis and pathophysiological assessment rather than a purely luminal description [3, 4]. The strongest randomized surgical evidence exists for hemorrhagic adult moyamoya. The JAM Trial demonstrated a preventive effect of bypass against recurrent hemorrhage [5], and the prespecified analysis identified posterior hemorrhage as a higher-risk phenotype [6]. Later work involving choroidal anastomosis and hemodynamic failure provided a plausible vascular mechanism for this observation [7, 8]. These studies collectively transformed bypass in hemorrhagic moyamoya from a nonspecific perfusion procedure into a strategy aimed at unloading fragile pathological collateral pathways [5–8]. This mechanistic interpretation has important implications for recipient selection. A technically successful STA–MCA anastomosis placed in a cortical territory unrelated to the pathological deep collateral network may provide general flow

augmentation but exert less effective hemodynamic decompression of the hemorrhage-prone circulation. Targeted bypass strategies based on the cortical distribution of periventricular collaterals are therefore biologically attractive, although stronger prospective validation remains necessary [7, 36]. Modern collateral registries increasingly focus on postoperative regression of these vessels as an imaging surrogate for successful risk modification [35, 36]. The ischemic phenotype is more complex because the evidence base consists predominantly of observational surgical cohorts rather than randomized trials. Nevertheless, historical adult surgical experience, long-term combined-bypass series, and modern population-level data consistently support revascularization in symptomatic patients with hemodynamic compromise [10–13]. The large 2024 population-based cohort by Lim and colleagues is important because it demonstrated that the association between bypass and outcome differs according to onset phenotype rather than remaining identical across all adult moyamoya presentations [10]. The technique itself must be matched to the time scale of the pathological problem. Direct bypass is uniquely capable of restoring flow immediately. This is advantageous when recurrent symptoms indicate limited reserve, but it also produces the largest acute hemodynamic perturbation. Indirect bypass has a smoother physiological profile but requires time and an effective angiogenic response. Combined surgery provides both mechanisms, making it particularly attractive in adults with severe disease when adequate microsurgical anatomy is available [11–16]. The 2025 intra-individual study provides unusually intuitive evidence because combined and indirect procedures were compared within the same biological patient; the combined hemisphere showed superior long-term perfusion and revascularization metrics [12].

Indirect surgery nevertheless should not be dismissed as ineffective in adults. The multicenter neoangiogenesis study by Zhao et al. demonstrated good collateral formation in 63.2% of treated hemispheres [14], and serial angiographic studies show progressive maturation over the first postoperative months [15]. Thus, the key question is not whether indirect bypass “works in adults,” but which adults possess sufficient angiogenic capacity and can tolerate the latency before the collateral network matures [14, 15]. Recent efforts to predict revascularization patterns may eventually make this selection more objective. The 2026 study by Wipplinger and colleagues identified preoperative vascular characteristics associated with robust postoperative revascularization after combined procedures [17]. Early donor-artery Doppler characteristics have also been studied as markers of later bypass capacity [33]. These approaches suggest that postoperative angiogenesis can increasingly be treated as a predictable biological phenotype rather than an unpredictable consequence of surgery. Genetics may further refine this prediction. RNF213 is already central to disease susceptibility, but studies by Ito and Torazawa suggest that RNF213 genotype and rare variants may correlate with postoperative donor-territory development or regression of pathological collateral pathways [18, 19, 35]. These data are not ready for routine surgical decision-making, but they introduce the concept of genotype-informed bypass selection [18, 19, 35]. The next major component of precision surgery is hemodynamic imaging. The traditional Suzuki angiographic stage describes the evolution of major arterial stenosis and collateral patterns but does not quantify tissue-level reserve. Quantitative perfusion and CVR assessments can identify patients whose vascular compensation is approaching failure [23–26, 30]. CT perfusion has become particularly attractive because it is rapid and produces regional quantitative maps, while ASL avoids both ionizing radiation and exogenous

contrast [23–26]. Yet interpretation must account for delayed collateral transit because extreme time-to-peak abnormalities do not necessarily represent irreversibly ischemic tissue in moyamoya. The hemodynamic literature also explains postoperative hyperperfusion. Uchino et al. demonstrated characteristic preoperative and postoperative perfusion features in patients developing hyperperfusion after revascularization [20]. More recent work has linked CHS to autoregulatory dysfunction and has evaluated preoperative perfusion variables as predictors [21, 22]. ASL-derived microvascular parameters and quantitative CTP increasingly allow noninvasive estimation of hyperperfusion vulnerability [22, 23].

Prediction is important because the clinical response to neurological worsening depends on mechanism. If focal aphasia results from hyperperfusion, controlled blood-pressure reduction may be appropriate. If the same aphasia results from watershed ischemia, aggressive hypotension could enlarge the injury. The management of adult moyamoya therefore requires immediate access to postoperative vascular and perfusion assessment rather than empiric treatment based solely on symptoms [20–23, 32]. Perioperative ischemia remains the opposing risk. Perfusion-based prediction studies indicate that the magnitude and spatial distribution of preoperative hypoperfusion are associated with postoperative infarction [24, 25, 32]. Clinical variables such as vascular risk factors may further modify the perioperative risk profile. Contemporary studies have identified hypertension and smoking as potential perioperative stroke predictors in ischemic-type adult moyamoya, emphasizing that conventional vascular comorbidity remains relevant even in a nonatherosclerotic disease [32, 34]. Surgical timing should therefore be individualized. Reed and colleagues found that early surgery following symptomatic presentation was not necessarily associated with worse outcomes [31]. This supports the concept that a fixed waiting period is less important than neurological stability, infarct evolution, cerebral reserve, and the expertise of the perioperative team. Nevertheless, the absence of randomized timing trials means that a universal “early” or “delayed” rule cannot be justified [31]. The importance of cognition is often underestimated. Studies by Zeifert, Tsunoda, and Hara demonstrate that adult moyamoya can impair cognitive function and normal-appearing white matter even when major disabling infarction is absent [27–29]. Chronic reduction of frontal perfusion may affect executive networks, and revascularization may improve or stabilize cognition in selected patients [27–29]. These findings argue for incorporating formal neuropsychological testing into future surgical trials instead of defining neurological success exclusively as mRS 0–2 or absence of stroke.

Asymptomatic disease further demonstrates the limitations of binary decision-making. The AMORE prospective registry showed that asymptomatic adults have measurable but heterogeneous long-term stroke risk [9]. Morphological and hemodynamic predictors of progression are increasingly being investigated [9, 30]. Surgery for every incidentally diagnosed hemisphere would expose low-risk individuals to unnecessary perioperative complications, whereas simple surveillance may be inadequate in a patient with silent infarction, progressive stenosis, markedly impaired CVR, or fragile hemorrhage-prone collaterals [9, 30]. The most logical next stage is therefore a multivariable surgical model. Such a model would integrate clinical presentation, DSA collateral phenotype, regional CBF, CVR, silent infarct burden, microbleeds, white-matter injury, recipient-artery anatomy, predicted direct bypass capacity, predicted indirect angiogenesis, RNF213 status, and estimated CHS risk. The

output of such a model should not be a generic recommendation of "surgery" or "no surgery." It should provide an operative phenotype.

For example, an adult with recurrent ischemic attacks, severely reduced acetazolamide reserve, a suitable STA donor, and poor predicted indirect neoangiogenesis would be classified as an immediate-flow phenotype and would preferentially receive a substantial direct component [11–17]. An adult with hemorrhage related to posterior choroidal collateral stress would be classified as a collateral-decompression phenotype, requiring bypass placement designed to reduce dependence on the relevant periventricular circulation [5–8, 36]. An asymptomatic adult with preserved reserve and no progression would be categorized as a surveillance phenotype [9]. A patient with high direct-bypass benefit but severe autoregulatory dysfunction would be considered a hyperperfusion-risk phenotype and would require intensive early postoperative perfusion monitoring [20–23].

Table 4. Proposed research framework for a prospective precision-revascularization study

Study component	Proposed design
Population	Adults with definite moyamoya disease requiring unilateral revascularization
Design	Prospective multicenter cohort with phenotype-stratified treatment
Preoperative DSA	Suzuki stage + periventricular collateral mapping
Perfusion	CTP or ASL + CVR assessment
Cognitive assessment	MoCA + executive/neuropsychological battery
Genetics	RNF213 p.R4810K + extended rare-variant panel
Surgical arm	Direct, indirect, or combined based on predefined phenotype
Intraoperative metrics	Bypass flow, Flow800, recipient artery characteristics
Early postoperative imaging	DWI + perfusion within 24–72 hours
Main endpoint	Stroke-free survival without permanent neurological decline
Secondary endpoints	CVR, collateral regression, neoangiogenesis, cognition, QoL
Long-term imaging	DSA/MRA and perfusion at 6–12 months
Primary hypothesis	Phenotype-guided bypass selection improves hemodynamic normalization while reducing CHS and ischemic complications

The proposed study would differ from conventional direct-versus-indirect comparisons because it would recognize that the optimal technique depends on the patient. A randomized comparison assigning adults indiscriminately to direct or indirect surgery risks testing technique independently of biological suitability. The future of moyamoya surgery will likely depend on this transition from procedure comparison to response prediction. Newer imaging studies already quantify regional differences in perfusion and structural injury [24–26, 30]. Genetic studies are beginning to characterize angiogenic capacity [18, 19, 35]. Doppler and angiographic work can estimate donor and revascularization behavior [17, 33]. Hyperperfusion models increasingly integrate preoperative hemodynamics with clinical features [20–23]. The remaining task is to combine these domains into a clinically validated decision architecture. Such precision does not diminish the importance of

microsurgical skill. On the contrary, it increases the importance of matching technical execution to physiological intent. A patent STA–MCA bypass is not necessarily an optimally designed bypass. A large indirect collateral network is not necessarily located in the territory requiring protection. A successful operation should restore blood flow where it is needed, reduce pathological collateral stress where it is dangerous, preserve autoregulatory stability, and produce long-term protection from stroke with minimal neurocognitive cost.

Conclusion. Adult moyamoya disease is a heterogeneous cerebrovascular disorder in which surgical revascularization remains the principal disease-modifying treatment for appropriately selected patients. The optimal operation cannot be determined by angiographic stenosis alone. Direct STA–MCA bypass provides immediate perfusion augmentation and is particularly valuable in adults with severe hemodynamic insufficiency, but it introduces a risk of cerebral hyperperfusion and abrupt flow redistribution. Indirect revascularization provides broader angiogenesis with a lower immediate hemodynamic impact but depends on delayed and biologically variable collateral formation. Combined surgery integrates immediate direct flow with progressive indirect neoangiogenesis and is therefore attractive for many symptomatic adults. Hemorrhagic moyamoya should be approached as a pathological collateral-stress syndrome in which revascularization can reduce dependence on fragile periventricular vessels. Ischemic moyamoya should be approached as a regional cerebrovascular-reserve disorder rather than as an angiographic stenosis alone. Postoperative management must distinguish cerebral hyperperfusion from ischemic watershed shift because these conditions may produce similar clinical manifestations but require different hemodynamic responses. Cognitive dysfunction, silent ischemic injury, genetic susceptibility, and collateral remodeling should increasingly be incorporated into outcome assessment. The future of adult moyamoya surgery is therefore precision revascularization: selection of the appropriate bypass type, recipient territory, flow magnitude, and postoperative management strategy according to the unique hemodynamic and vascular phenotype of each patient.

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