し、Q-recon NDB を作成した。

Q-recon NDB では、定量解析の時に用いられる 7mm(FWHM)の Gauss Filter 処理の他に、Gauss Filter プログラムで 12mm(FWHM)、18mm(FWHM)のフィルタによる処理を加えたものを含め、3 種類の Q-recon NBD(Q-7mm, Q-12mm, Q-18mm)を作成した。T-recon NDB と、これらの 3 つの Q-recon NDB の平均画像（Mean）と標準偏差画像(S.D.)について、視覚的な比較、直線回帰式による相関関係から、T-recon NBD に近似する Q-recon NBD の Gauss Filter 処理条件について検討した。

2. 各 NDB を用いた高次脳機能障害典型症例の IMZ SPECT 統計画像の比較：

典型症例の IMZ SPECT 収集データについて、T-recon NDB を用いた 3D-SSP 解析画像、Q-recon NBD(Q-7mm, Q-12mm, Q-18mm)の NDB を用いた 3D-SSP 解析画像を作成し、これらについて比較検討した。

I. 研究結果

1. T-recon NDB と Q-recon NDB（Q-7mm, Q-12mm, Q-18mm）の平均画像（Mean）と標準偏差画像(S.D.)の比較結果：

図 1 に、上段から、T-recon、Q-7mm、Q-12mm、Q-18mm の平均画像（Mean）を示す。Q-recon NDB に見られる IMZ の平均的分布については、明らかな差はないが、画像の滑らかさから、T-recon NDB と Q-recon NDB (12mm)が一致していた。

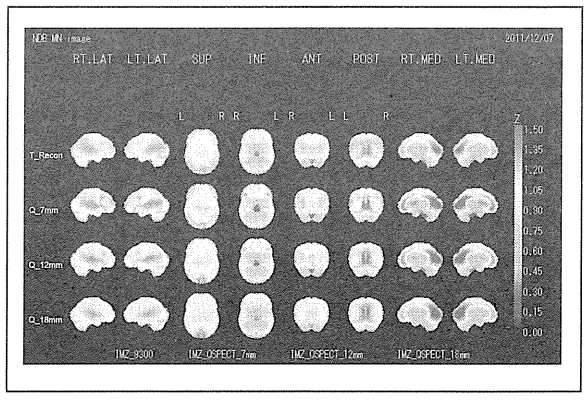

図 1

図 2 に、T-recon NDB の平均画像（Mean）と Q-recon NBD(Q-7mm、Q-12mm、Q-18mm)の平均画像（Mean）との相関関係を示す。いずれも高い相関関係が見られるが、過大評価や過少評価が少ない点で、T-recon と Q-12mm との相関関係が優れていた。

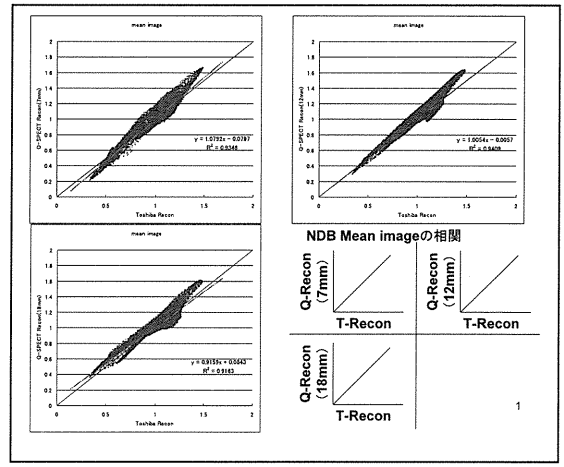

図 2

図 3 に、上段から、T-recon、Q-7mm、Q-12mm、Q-18mm の標準偏差画像(S.D.)を示す。Q-recon NDB に見られる標準偏差については、Gauss Filter の FWHM が 7mmから 18mmへと大きくなるほど画像が滑らかとなり、全体的に減少することが確認された。標準偏差の分布の程度から、T-recon NDB と Q-recon NDB (Q-12mm)が一致していた。

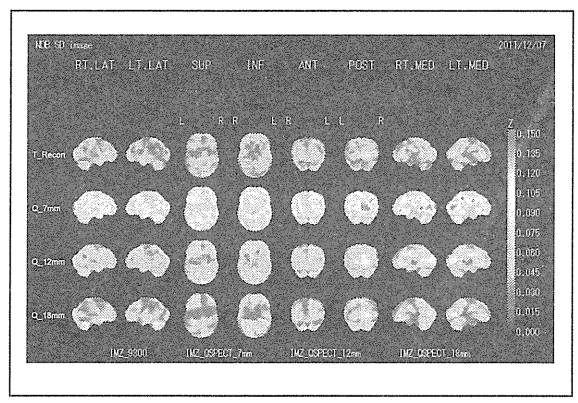

図 3

図４に、T-recon NDB の標準偏差画像(S.D.)と Q-recon NBD(Q-7mm、Q-12mm、Q-18mm)の標準偏差画像(S.D.)との相関関係を示す。T-recon と Q-12mm および Q-18mm との相関関係が優れていた。

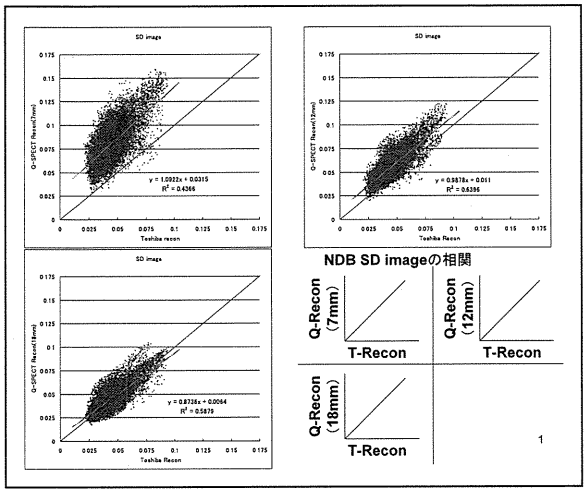

図４

2. 各 NDB を用いた高次脳機能障害典型症例の IMZ SPECT 統計画像の比較結果：

図５に、高次脳機能障害典型症例の IMZ SPECT に対して、上段から、T-recon、Q-7mm、Q-12mm、Q-18mm の各 NDB を用いた 3D-SSP 解析画像を示す。Q-12mm の解析画像が、T-recon と同等と評価された。

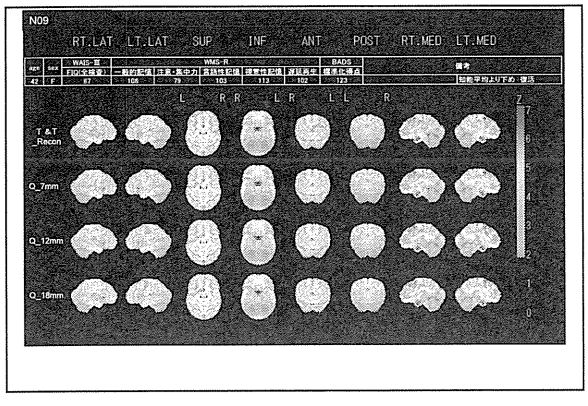

図５

J. 考察

行政的診断基準 [5]により高次脳機能障害と判定されたもやもや病症例を対象として、その責任病巣を探索的に見出すことを目的として、IMZ SPECT 統計画像解析が実施されてきた。これまでの研究成果として、SEE Level 3 解析を用いて脳回ごとの皮質神経細胞の脱落の程度を詳細に解析したところ、両側前頭葉 MGF および ACG に高率に皮質神経細胞の脱落所見が見出された [4]。また、両側 MFG あるいは ACG における extent ratio が 10%以上となる皮質神経細胞の脱落所見は、行政的診断基準による高次脳機能障害に共通して見られる特異的画像所見と考えられ、器質的脳損傷が明確でない高次脳機能障害の診断に有用と考えられた。

探索研究により、高次脳機能障害の診断におけ IMZ-SPECT 統計画像解析の有用性が確認されたが、この診断法を普遍化するためには多施設共同研究による検証が欠かせない。しかし、IMZ-SPECT 統計画像解析では、SPECT 機種ごとに NDB が必要となること、更に異なる SPECT 機種で得られた統計画データを統合的に解析することが出来ないこと、などが多施設共同研究を進める上での大きな問題点であった。

今回の研究では、これまでの SPECT 定量画像解析において、SPECT 機種間差を補正できることが証明されている QSPECT パッケージ（国循研究センター研究所　飯田秀博らが開発）を用いて NDB を再構成し、3D-SSP 統計画像解析を行なったところ、Gauss Filter 処理の調整によって、従来の SPECT 装置に附属する workstation 処理と同等の解析が得られることが判明した。また、QSPECT により再構成された NDB は、QSPECT 収集に対応する全ての SPECT 機種に対して使用できることから、SPECT 機種ごとに NDB を作成する必要がないこと、QSPECT により再構成された NDB を用いた 3D-SSP 統計画像解析データは、データを収集した SPECT の機種に関わらず

統合的に解析可能であること、などが新たな知見として得られた。これらの新たな知見により、高次脳機能障害の診断における IMZ-SPECT 統計画像解析の有用性に関する多施設共同研究を進める上での主要な問題点は解決出来る見通しとなった。今後の多施設共同研究のためのプロトコールの作成が急がれる。

QSPECT パッケージを用いた SPECT 画像解析は、SPECT 定量画像解析の標準化に続いて、SPECT 統計画像解析の標準化にも大きく貢献するものと考えられた。

K. 結論

もやもや病における高次脳機能障害例では、両側内側前頭回（MFG）や前方帯状回（ACG）の皮質神経細胞脱落が IMZ SPECT 統計画像 SEE Level 3 解析により捉えられる。

SPECT 定量画像解析のために開発された QSPECT パッケージを用いて NDB を再構成し統計画像解析を行なったところ、従来と同等の評価が得られること、機種間差を超えた統合解析が可能であることが判明した。

SPECT 統計画像解析の標準化は、高次脳機能障害の診断における IMZ-SPECT 統計画像解析の有用性に関する多施設共同研究を進める上でも極めて重要な成果である。

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M. 知的財産権の出願・登録状況

特になし

平成23年度厚生労働科学研究費補助金（難治性疾患克服研究事業）
分担研究報告書

もやもや病成人出血発症例の治療方針に関する研究

京都大学医学研究科脳神経外科
宮本　享、　高橋　淳

研究要旨

出血発症もやもや病に対するバイパス手術の再出血予防効果を明らかにすることを目的に、2001年度から無作為振分け試験（JAM trial）を行っている。平成20年6月に目標登録症例数80例（手術群42例、非手術群38例）に到達し、新規登録を停止した。平成24年4月現在、手術群6例、非手術群13例がprimary end pointに達した（到達率：手術群3.2%/年、非手術群8.3%/年）。多くの登録症例で登録から5年（観察期間）を経過し、現在観察期間内で追跡しているのは3例である。全症例が観察期間を満了するのは平成25年6月の予定である。

A. 研究目的

出血発症もやもや病に対するバイパス手術の再出血予防効果を明らかにすることを目的とする。

B. 研究方法

多施設間共同臨床試験として登録5年・追跡5年のprospective randomized trialを行う。[倫理面への配慮] 参加各施設の医の倫理委員会の審議と登録前のinformed consentを必須とする。

頭蓋内出血発作を1年以内に認めたモヤモヤ病確定診断例で、ADLがmodified Rankin disability scale 0〜2のものを対象とし、事務局による登録条件のチェックの後、保存的治療を行う「非手術群」とSTA-MCA anastomosisを行う「手術群」へのrandomizationを行う。登録時、登録6ヶ月後、1年後、その後1年毎に規定の諸検査（脳循環測定を含む）を行いながら臨床経過を観察する。「再出血発作」、「ADLを悪化させる虚血発作」、「その他の死亡ならびに重篤なADL悪化」、「内科医の判断による手術への移行（虚血発作頻発等）」が研究のend pointである。目標症例数は160例（手術群、非手術群各80例）とするが、研究開始より5年経過時点で見直しを行う。

C. 研究結果

平成13年1月より11の症例登録施設により症例登録を開始し、本症の呼称としてJapan Adult Moyamoya (JAM) trialを採択した。登録施設数はその後増加し23施設となった。登録開始から5年が経過した平成18年1月時点で目標症例数の見直しが行われ、新たな目標症例数は80例に再設定されたが、平成20年6月にこの症例数に到達し新規登録を終了した。80症例の内訳は手術群42例、非手術群38例であり、**平成24年4月時点で手術群6例、非手術群13例がprimary end pointに到**

達した。観察期間を加味して算出された primary end point 到達率は**手術群 3.2%/年、非手術群 8.3%/年**である。登録状況を表 1 に、また end point 到達症例の詳細を表 2 に示す。

表 1.　JAM trial 登録状況

	A 群	P 群	計
手術群	24	18	42
非手術群	21	17	38
計	45	35	80

表 2.　Primary end point 到達症例

(1) 手術群

性別	出血部位	登録からの期間	原因
F	A	3 ヶ月	再出血
M	P	8 ヶ月	脳幹梗塞死
M	A	9 ヶ月	再出血
F	A	1.4 年	再出血
F	A	2.3 年	再出血
F	A	4.8 年	再出血

(2) 非手術群

性別	出血部位	登録からの期間	原因
F	P	7 ヶ月	再出血
F	P	7 ヶ月	再出血
M	P	8 ヶ月	再出血
F	P	1.2 年	再出血
F	P	1.7 年	再出血
M	A	2.0 年	再出血
F	P	2.4 年	再出血
F	P	3.3 年	再出血
F	A	3.5 年	再出血
F	P	4.0 年	再出血
F	A	4.5 年	虚血発作増強
M	P	4.98 年	再出血
F	P	3.9 年	再出血

統計解析（2012 年 4 月 1 日現在）

○Mean follow-up period: 4.28 年

○Primary end point 到達率

手術群　：0.032/patient-year

非手術群：0.083/ patient-year

(Log rank 検定 p=0.0502)

○再出血（secondary end point）率

手術群　：0.027/patient-year

非手術群：0.076/patient-year

(Log rank 検定 p=0.0432)

全登録症例（８０例）の現状は下記のようになっている。

●観察終了（５年満了または endpoint）：77 人（手術群 40，非手術群 37）

○観察期間内出血：17 人

(手術群 5，非手術群 12)

○観察期間内虚血：２人

(手術群１，非手術群１)

○観察期間中脱落（victim of murder）：１人

(手術群１)

○観察期間終了後出血：9 人

(手術群 5，非手術群 4)

○有害事象なし：48 人

(手術群 28，非手術群 20)

●観察継続中（５年未満かつ endpoint 該当事象なし）：3 人（手術群 2，非手術群 1）

観察期間内と観察期間終了後を合わせると、登録 80 人中 26 人（全症例の 32.5%）が再出血発作を起こしていた。群別内訳は手術群 10 人、非手術群 16 人である。

(参考)副次研究について

平成 14 年度からは副次研究である JAM (supplement)および non-randomized data base の登録が開始されている。さらに片側性モヤモヤ病出血発症例を対象とした non-randomized data base への登録研究も開始されている。

1)　JAM(supplement)

JAM(supplement)はより重篤な出血発症例において再出血予防に関するbypassの効果を解明するための、補完的な別立てのprospective randomized controlled trialである。study designはJAM trialとほぼ同一であるが、対象はmodified Rankin disability scale 3のみを対象として同様にrandomizationを行い、再出血発作とそれよるmorbidity/ mortalityだけをend pointとする研究である。

なお、統計学的な解析にあたってはJAMtrialおよびJAM(supplement)を独立して個別に検討するが、再出血率について両者を加えてで解析することとした。

JAM(supplement)は各施設医の倫理委員会での承認が得られた施設から登録可能となり、現在3症例が登録されている。

3) non-randomized data base

modified Rankin disability scale 4ないし5は本人の意思確認が難しくrandomized trialの実施には問題があり、またexclusionを含めてJAM trialのpreallocation biasを少しでも少なくするために、本data baseを作りinformed consentを得て登録後、神経症状、再発作などについての年次報告を行うこととした。現在28症例が登録されている。

4) Unilateral moyamoya non-randomized data base

片側性モヤモヤ病においても出血発症例があり上記のnon-randomized data baseに準じて臨床経過を観察する。現在の登録例はない。

[研究参加施設]

中村記念病院、北海道大学医学部附属病院、札幌医科大学医学部附属病院、東北大学医学部附属病院、長岡中央総合病院、岩手医科大学付属病院、秋田県立脳血管研究センター、東京女子医科大学病院、北里大学病院、千葉大学医学部附属病院、群馬大学医学部附属病院、名古屋第二赤十字病院、名古屋市立大学医学部附属病院、岐阜大学医学部付属病院、京都大学医学部附属病院、奈良県立医科大学付属病院、天理よろず相談所病院、国立循環器病センター、徳島大学医学部付属病院、中国労災病院、倉敷中央病院、国立病院九州医療センター、長崎大学医学部附属病院

D. 考察

もやもや病は日本で多く報告されてきたが、出血発症例に対するバイパス手術の再出血予防効果を科学的に立証した研究は国際的にもなく、本研究によりその「治療指針を明らかにすることは学術的に有意義であると共に社会的責務である。

目標症例数である80例に到達し、現在登録症例の経過観察を続けている。現在までに18例のprimary end point到達が確認され、観察期間を加味した年間出血率は前述の如く非手術群のほうが手術群よりも高い傾向にある。観察期間内追跡例は残り3例となっており、最終的に統計学的有意差が証明されるか否かが注目される。

結論

JAM trialに80症例（手術群42例、非手術群38例）の登録が行われ、平成24年4月現在、手術群6例、非手術群13例がprimary end pointに達した。現時点での到達率は手術群3.2%/年、非手術群8.3%/年である。登録事業開始5年後にあたる平成18年1月に目標症例数の再設定が行われ、現在すでにこれに到達して新規登録を終了している。最終的には平成25年6月に全症例の追跡終了となる見込みである。

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F. 知的財産権の出願・登録状況

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ウイリス動脈輪閉塞症の診断・治療に関する研究班　名簿

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Significance of Focal Cerebral Hyperperfusion as a Cause of Transient Neurologic Deterioration After Extracranial-Intracranial Bypass for Moyamoya Disease: Comparative Study With Non-Moyamoya Patients Using *N*-Isopropyl-p-[^{123}I]Iodoamphetamine Single-Photon Emission Computed Tomography

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BACKGROUND: Superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis prevents cerebral ischemic attack by improving cerebral blood flow in patients with occlusive cerebrovascular disease and hemodynamic compromise. Recent evidence suggests that focal cerebral hyperperfusion is a potential complication of this procedure for moyamoya disease.

OBJECTIVE: To clarify the exact differences in the incidence and clinical manifestations of this phenomenon between patients with and without moyamoya disease.

METHODS: *N*-isopropyl-p-[^{123}I]iodoamphetamine single-photon emission computed tomography was performed 1 and 7 days after STA-MCA anastomosis on 121 hemispheres from 86 consecutive patients with moyamoya disease (2-67 years of age; mean, 34.3 years) and on 28 hemispheres from 28 non-moyamoya patients (12-67 years of age; mean, 56.5 years). The incidence of symptomatic hyperperfusion, defined as a significant focal increase in cerebral blood flow at the site of the anastomosis that is responsible for the apparent neurological signs, was compared between groups.

RESULTS: Symptomatic cerebral hyperperfusion including mild focal neurological signs was seen in 25 patients with moyamoya disease (26 hemispheres, 21.5%) but in none of the patients without moyamoya disease ($P = .0069$). Multivariate analysis revealed that moyamoya disease was significantly associated with the development of symptomatic cerebral hyperperfusion ($P = .0008$). All patients with symptomatic hyperperfusion were relieved by intensive blood pressure control, and no patients suffered from permanent neurological deficit caused by hyperperfusion.

CONCLUSION: Symptomatic cerebral hyperperfusion is a potential complication of STA-MCA anastomosis, especially in patients with moyamoya disease. Accurate diagnosis and adequate management of hyperperfusion are recommended, especially in patients with moyamoya disease.

KEY WORDS: Cerebral hyperperfusion, Extracranial-intracranial bypass, Moyamoya disease, Surgical complication

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ABBREVIATIONS: EC-IC, extracranial-intracranial; **ICH,** intracerebral hemorrhage; **^{123}I-IMP-SPECT,** **N**-isopropyl-p-[^{123}I]iodoamphetamine single-photon emission computed tomography; **MRA,** magnetic resonance angiography; **SAH,** subarachnoid hemorrhage; **STA-MCA,** superficial temporal artery–middle cerebral artery

Cerebrovascular reconstruction surgery including carotid endarterectomy or extracranial-intracranial (EC-IC) bypass for patients with atherosclerotic steno-occlusive cerebrovascular diseases can cause a rapid increase in cerebral blood flow (CBF) in the chronic ischemic brain, resulting in complications such as

cerebral hyperperfusion syndrome. Cerebral hyperperfusion syndrome after carotid endarterectomy is characterized by unilateral headache, face and eye pain, seizures, and focal symptoms that occur secondary to cerebral edema or intracerebral hemorrhage (ICH).[1-4] Patients with poorer cerebrovascular reactivity are known to have higher risk for hyperperfusion syndrome.[4-7] In contrast, cerebral hyperperfusion syndrome after EC-IC bypass for atherosclerotic occlusive cerebrovascular disease is rare and mostly manifests as mild focal neurological deficit,[8,9] except for 1 case of acute hyperperfusion with massive ICH after high-flow EC-IC bypass.[10]

Moyamoya disease is a chronic, occlusive cerebrovascular disease with unknown origin characterized by bilateral stenoocclusive changes at the terminal portion of the internal carotid artery and an abnormal vascular network at the base of the brain.[11] EC-IC bypass such as superficial temporal artery–middle cerebral artery (STA-MCA) anastomosis is generally the standard surgical treatment for moyamoya disease to prevent cerebral ischemic attacks.[12-15] Despite the favorable long-term outcome,[12-15] increasing evidence suggests that focal cerebral hyperperfusion may cause transient neurological deterioration[12,16-22] or delayed ICH[23] during the acute stage after EC-IC bypass for moyamoya disease. These results strongly suggest that patients with moyamoya disease are more vulnerable to cerebral hyperperfusion compared with patients with other occlusive cerebrovascular diseases. However, the differences in the incidence and clinical manifestation of cerebral hyperperfusion between patients with and without moyamoya disease have not been evaluated.

The present prospective study performed *N*-isopropyl-p-[^{123}I]iodoamphetamine single-photon emission computed tomography (^{123}I-IMP-SPECT) 1 and 7 days after STA-MCA (M4) anastomosis in 121 hemispheres of 86 consecutive patients with moyamoya disease and 28 hemispheres of 28 patients without moyamoya disease to compare the incidences of symptomatic cerebral hyperperfusion.

PATIENTS AND METHODS

Inclusion Criteria

The postoperative changes in CBF and clinical course were investigated in 86 consecutive patients (moyamoya group; male/female = 24/62; age, 2-67 years; mean age, 34.3 years) with moyamoya disease surgically treated in 121 hemispheres by the same surgeon (M.F.) from March 2004 to June 2009. For comparison, the postoperative changes in CBF and clinical course were also investigated in 28 patients (non-moyamoya group; male/female = 24/4; age, 12-67 years; mean age, 56.3 years), including 27 adult patients with atherosclerotic occlusive cerebrovascular disease and 1 pediatric patient with MCA occlusion probably caused by dissection, who were surgically treated in 28 affected hemispheres. Inclusion criteria of this study, corresponding to our surgical indications for STA-MCA anastomosis, included all of the following: the presence of ischemic symptoms, apparent hemodynamic compromise by SPECT, independent activity of daily living (modified Rankin scale scores, 0-2), and absence of major cerebral infarction. All hemispheres that did not match these criteria were excluded from the initial surgery. Once hemodynamic compromise was confirmed, the patients underwent revascularization surgery. All patients in the moyamoya group underwent STA-MCA (M4) anastomosis with or without encephalo-duro-myo-synangiosis.[12,16] All patients in the non-moyamoya group underwent STA-MCA (M4) anastomosis without indirect pial synangiosis. All patients in the moyamoya group satisfied the diagnostic criteria of the Research Committee on Spontaneous Occlusion of the Circle of Willis of the Ministry of Health, Labor, and Welfare, Japan, except for 4 patients with "probable moyamoya disease" with unilateral involvement. All patients were strictly followed up in our institutes for > 6 months with a mean follow-up period of 45.6 months.

Postoperative CBF Measurement and Diagnosis of Hyperperfusion

The CBF was routinely measured by ^{123}I-IMP-SPECT 1 and 7 days after surgery in all patients in both groups. The CBF was quantified by the autoradiographic method; the CBF in each subregion of the cerebral cortex was automatically calculated by the Three-Dimensional Stereotactic Region of Interest Template software (version 2) provided by Daiichi Radio-Isotope (Tokyo, Japan), and the diagnosis of cerebral hemodynamics was made by 2 specialized radiologists blinded to the clinical condition of the patients.[12,20] Within 2 days after surgery, 1.5- or 3-T magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) were routinely performed.[19] MRI included diffusion-weighted images, fluid-attenuated inversion recovery images, T1-/T2-weighted images, and T2*-weighted images. The diagnostic criteria for symptomatic cerebral hyperperfusion included all of the following[12,20]: the presence of a significant focal increase in CBF at the site of the anastomosis (qualitative observation of focal intense increase in CBF confined to 1 major vascular territory), which is responsible for the apparent neurological signs including focal neurological deficit and/or severe headache resulting from hemorrhagic changes; apparent visualization of STA-MCA bypass by MRA and the absence of any ischemic changes by diffusion-weighted imaging; and the absence of other pathologies such as compression of the brain surface by the temporal muscle inserted for indirect pial synangiosis, ischemic attack, and seizure.

The occurrence of symptomatic cerebral hyperperfusion after revascularization surgery was evaluated by ^{123}I-IMP-SPECT in the acute stage. The mortality and morbidity resulting from cerebral hyperperfusion were also evaluated 3 months after revascularization surgery. We investigated the correlation between postoperative CBF changes and clinical presentation in both groups and compared the incidence of symptomatic cerebral hyperperfusion between the moyamoya group and non-moyamoya group.

Statistical Analysis

The incidence of symptomatic cerebral hyperperfusion was compared between the moyamoya and non-moyamoya groups by χ^2 test. Because age and history of intracranial hemorrhage were known to be related to symptomatic cerebral hyperperfusion after STA-MCA anastomosis for moyamoya disease,[12] multivariate statistical analysis of the factors related to development of symptomatic cerebral hyperperfusion, including disease subtype, age, sex, operated side, and history of intracranial hemorrhage, was performed with a logistic regression model. The incidence of any cerebral hyperperfusion (both symptomatic and asymptomatic) was also compared between the moyamoya and non-

moyamoya groups. Correlation between age and development of symptomatic cerebral hyperperfusion was evaluated in the moyamoya group by the Student *t* test. Systolic blood pressure 1 day after surgery was compared between the moyamoya group and non-moyamoya group by the Student *t* test.

RESULTS

Moyamoya Group

Among the 86 consecutive patients with 121 operated hemispheres, 25 patients (26 hemispheres, 21.5% of 121 operated hemispheres) suffered from temporary neurological deterioration, including mild focal neurological signs, resulting from postoperative focal cerebral hyperperfusion from 2 to 14 days after surgery (Table 1). Postoperative MRI/MRA showed no ischemic changes, and the thick high signal intensity of the STA on the operated hemisphere was evident in all 26 hemispheres. Postoperative SPECT revealed significant intense increases in CBF at the sites of anastomosis on all 26 hemispheres. As Table 2 summarizes, 21 patients (22 hemispheres, 18.2%) suffered from transient focal neurological deficit caused by focal hyperperfusion that mimicked ischemic attack, which started from 2 to 9 days after surgery and was sustained for several days. The anatomic location and the temporal profile of hyperperfusion were completely in accordance with the transient neurological signs in these 21 patients. Four patients (4 hemispheres, 3.3%) complained of severe headache and suffered from cerebral hyperperfusion syndrome associated with subarachnoid hemorrhage (SAH) in 3 patients (2.5%) or with ICH at the right frontal subcortex in 1 patient (0.83%). Symptoms were relieved by intensive blood pressure control with the use of the free radical scavenger edaravone (Mitsubishi Pharma Co, Tokyo, Japan), although 1 patient with ICH required rehabilitation to relieve transient left hemiparesis for 2 months.[23] One patient with significant bilateral flow compromise manifesting as SAH required ligation of the STA-MCA bypass 2 days after the first-stage surgery to control postoperative cerebral hyperperfusion and was rescued by marked development of pial synangiosis without complication. No patient suffered from permanent neurological deficit caused by cerebral hyperperfusion. No patients suffered from delayed neurological deterioration resulting from cerebral hyperperfusion during the follow-up period. Cerebral hyperperfusion, both asymptomatic and symptomatic, was detected by SPECT in 60.3% (73 of 121 hemispheres) in the moyamoya group.

Among 86 consecutive patients with 121 operated hemispheres in the moyamoya group, no patient suffered from perioperative cerebral infarction, except for 3 patients (2.5%) presenting with pseudolaminar necrosis in the part of the cerebral cortex supplied by the STA-MCA bypass in the subacute stage, which did not affect their long-term neurological status. All patients with the onset of transient ischemic attack obtained disappearance or improvement of ischemic attack during the follow-up period. One ischemia-onset patient (0.83%) suffered from ICH on the ipsilateral thalamus 3 years after successful revascularization surgery, and she suffered deteriorated modified Rankin scale score from 0 to 3 after hemorrhage. Two hemorrhage-onset patients suffered from rebleeding (1.65%), 1 from contralateral ICH and 1 from SAH, both of which did not affect their neurological status. The patency of the STA-MCA bypass was confirmed in all 86 patients with 121 operated hemispheres by postoperative MRA.

TABLE 1. Incidence of Symptomatic Cerebral Hyperperfusion After Extracranial-Intracranial Bypass

	Moyamoya	Non-Moyamoya
Hemispheres, n (patients, n)	121 (86)	28 (28)
Age (mean), y	2–67 (34.3)	12–67 (56.5)
Male/female, n	24/62	24/4
Symptomatic hyperperfusion, n (%)	26 (21.5)[a]	0 (0)

[a]Significantly higher (P = .0069).

Non-Moyamoya Group

Among 28 patients with 28 operated hemispheres in the non-moyamoya group, no patient (0 of 28, 0%) suffered from symptomatic cerebral hyperperfusion. No patient suffered from perioperative cerebral infarction by postoperative MRI, and the patency of STA-MCA bypass was confirmed by MRA in all 28 patients. No patient suffered cerebral ischemic events such as transient ischemic attack and recurrent stroke during the follow-up period. One patient presented with simple partial seizure of his right upper extremity several hours after left STA-MCA anastomosis, whereas ^{123}I-IMP-SPECT 1 day after surgery demonstrated only mild increase in CBF at the left fronto-parietal lobe. On the basis of the effect of seizure on subsequent flow study and equivocal finding of ^{123}I-IMP-SPECT, we did not include this case as symptomatic cerebral hyperperfusion. No other patients in the non-moyamoya group suffered from seizure postoperatively. Cerebral hyperperfusion, both asymptomatic and symptomatic, was detected by SPECT in 67.9% (19 of 28 hemispheres) in the non-moyamoya group.

Statistical Analysis

The incidence of symptomatic cerebral hyperperfusion was significantly higher in the moyamoya group (26 of 121, 21.5%) compared with the non-moyamoya group (0 of 28, 0%; P = .0069). The incidence of hemorrhagic cerebral hyperperfusion was 3.3% (4 of 121) in the moyamoya group, whereas no hemorrhagic complication occurred in the non-moyamoya group (0 of 28), although there was no statistical significance between groups (P = .33). There was no significant difference in the incidence of any cerebral hyperperfusion, both asymptomatic and symptomatic, between the moyamoya group (73 of 121, 60.3%) and non-moyamoya group (19 of 28, 67.9%; P = .46). Multivariate analysis revealed that the disease subtype of moyamoya disease was significantly associated with the development of

TABLE 2. Incidence of Symptomatic Cerebral Hyperperfusion After Extracranial-Intracranial Bypass in 86 Patients With Moyamoya Disease[a]

	Hemisphere, n (Incidence, %)	Symptomatic Period, d	Brain Damage Caused by Hyperperfusion	Permanent Neurological Deficit Caused by Hyperperfusion
Symptomatic hyperperfusion	26 (21.5)			
Focal neurological deficit	22 (18.2)	2–14	None	None
SAH	3 (2.5)	1–2	None	None
ICH	1 (0.8)	≥ 4	Minimum	None

[a]ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

symptomatic cerebral hyperperfusion (P = .0008), as shown in Table 3. Age was also found to be associated with symptomatic cerebral hyperperfusion by multivariate analysis (P = .033), probably because of the younger age distribution in the moyamoya group compared with the non-moyamoya group. There was no significant association of sex (P = .41), side of the operated hemisphere (P = .49), and past history of hemorrhage (P = .19) with the occurrence of symptomatic hyperperfusion (Table 3).

Because of the apparently different age distributions in the moyamoya and non-moyamoya groups (Table 1), the correlation between age and development of symptomatic cerebral hyperperfusion was examined only in the moyamoya group. Among 86 patients with moyamoya disease, patients with symptomatic hyperperfusion were relatively older (mean, 38.9 years of age) than those without symptomatic hyperperfusion (mean, 32.8 years of age), but the difference was not significant (P = .12). Systolic blood pressure 1 day after surgery was 131.8 mm Hg in the moyamoya group and 126.8 mm Hg in the non-moyamoya group (no statistical difference; P = .069).

REPRESENTATIVE CASES

Case 1: Moyamoya Disease

This 9-year-old boy, presenting with minor completed stroke in the right temporo-occipital lobe, was found to have moyamoya disease. He underwent STA-MCA anastomosis with encephalo-duro-myo-synangiosis on the left hemisphere 4 months after revascularization surgery on the right hemisphere. The recipient artery at the M4 segment of the temporal branch of the MCA was explored, and anastomosis was performed between the stump of the STA (1.0 mm in diameter) and the M4 segment (0.8 mm in diameter) that supplied the left temporal lobe. The temporary occlusion time was 19 minutes. ^{123}I-IMP-SPECT 1 day after surgery revealed focal intense increase in CBF at the site of the anastomosis (arrows in Figure 1A). Postoperative MRI 1 day after surgery showed no evidence of ischemic change, and MRA demonstrated thick high signal intensity of the STA (arrow in Figure 1B). Two days after surgery, he suffered from fluctuating aphasia. Repeated MRI ruled out cerebral ischemia and compression of the brain surface. On the basis of the diagnosis of symptomatic cerebral hyperperfusion, his systolic blood pressure was controlled under 110 mm Hg, which improved his symptom. His aphasia resolved 5 days after surgery, and ^{123}I-IMP-SPECT 7 days after surgery showed normalization of CBF on the left hemisphere. He was discharged without neurological deficit 16 days after surgery, and there was no cerebrovascular event during the follow-up period of 3 months.

TABLE 3. Multivariate Analysis of Symptomatic Cerebral Hyperperfusion After Extracranial-Intracranial Bypass

Risk Factors	Symptomatic Cerebral Hyperperfusion: Yes	Symptomatic Cerebral Hyperperfusion: No	P
Mean age, y	38.8 ± 14.92	40.52 ± 18.68	.0330
Male sex, n (%)	6 (23.1)	52 (42.3)	.4064
Left hemisphere, n (%)	12 (46.15)	65 (52.84)	.4910
History of hemorrhage, n (%)	4 (15.38)	5 (4.07)	.1876
Moyamoya disease, n (%)	26 (100)	95 (77.2)	.0008

Case 2: Atherosclerotic Right MCA (M1) Occlusion

This 66-year-old woman, presenting with minor completed stroke in the right hemisphere, was proven to have severe hemodynamic compromise of the affected hemisphere. She underwent STA-MCA anastomosis on the affected hemisphere 6 months after the onset of stroke. The recipient artery at the M4 segment of the temporal branch of the MCA was explored, and anastomosis was performed between the stump of the STA (1.0 mm in diameter) and the M4 segment (1.0 mm in diameter) that supplied the temporal lobe. The temporary occlusion time was 18 minutes. ^{123}I-IMP-SPECT 1 day after surgery revealed focal increase in CBF at the site of the anastomosis (arrows in Figure 2A). Postoperative MRI 2 days after surgery showed no evidence of ischemic change, and MRA demonstrated the high signal intensity of ipsilateral STA (arrow in Figure 2B). Blood pressure was maintained in the normal range, and she did not present neurological sign perioperatively. There was no cerebrovascular event during the follow-up period of 4 months.

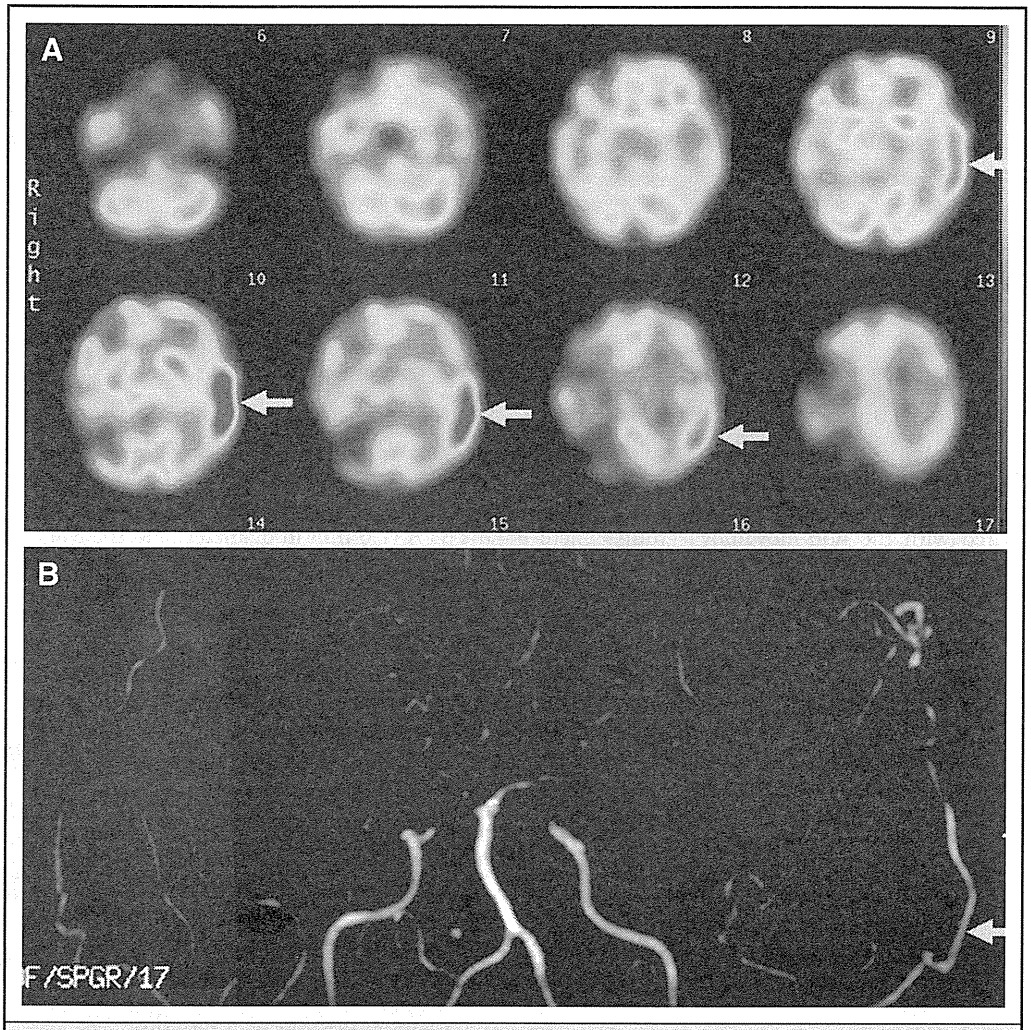

FIGURE 1. *Case 1: a 9-year-old boy with moyamoya disease presenting with cerebral infarction.* **A,** *N-isopropyl-p-[^{123}I] iodoamphetamine single-photon emission computed tomography 1 day after left superficial temporal artery–middle cerebral artery (STA-MCA) anastomosis with pial synangiosis. Marked increase in cerebral blood flow at the site of the anastomosis was evident (arrows in* **A***) in accordance with the manifestation of aphasia.* **B,** *magnetic resonance angiography 1 day after STA-MCA anastomosis with pial synangiosis demonstrating STA-MCA bypass as a thick high-signal sign (arrow in* **B***).*

Follow-up MRA 3 months after surgery showed apparently patent STA.

DISCUSSION

In the present study, we demonstrated for the first time that patients with moyamoya disease have significantly higher risk for symptomatic hyperperfusion as a potential complication of EC-IC bypass compared with other occlusive cerebrovascular diseases treated by the same procedure. Accurate diagnosis by flow study and proper management of hyperperfusion is recommended, especially in patients with moyamoya disease, because the management of hyperperfusion is contradictory to that of cerebral ischemia.

Incidence and Clinical Manifestation of Symptomatic Cerebral Hyperperfusion After EC-IC Bypass

Symptomatic cerebral hyperperfusion after EC-IC bypass for atherosclerotic occlusive cerebrovascular disease is rare and generally manifests as mild focal neurological deficit, which resolves within 2 weeks.[8,9] Heros et al[8] first suggested the involvement of cerebral hyperperfusion in 5 patients with atherosclerotic ischemic disease who presented with temporary neurological deterioration after STA-MCA bypass among 134 patients (3.7%). All 5 patients had resolved symptoms within 2 weeks after surgery. Kuroda and colleagues[9] also reported on a 64-year-old woman with atherosclerotic internal carotid artery occlusion who presented with transient aphasia caused by hyperperfusion from 2 to 7 days after STA-MCA anastomosis. Our results showed that

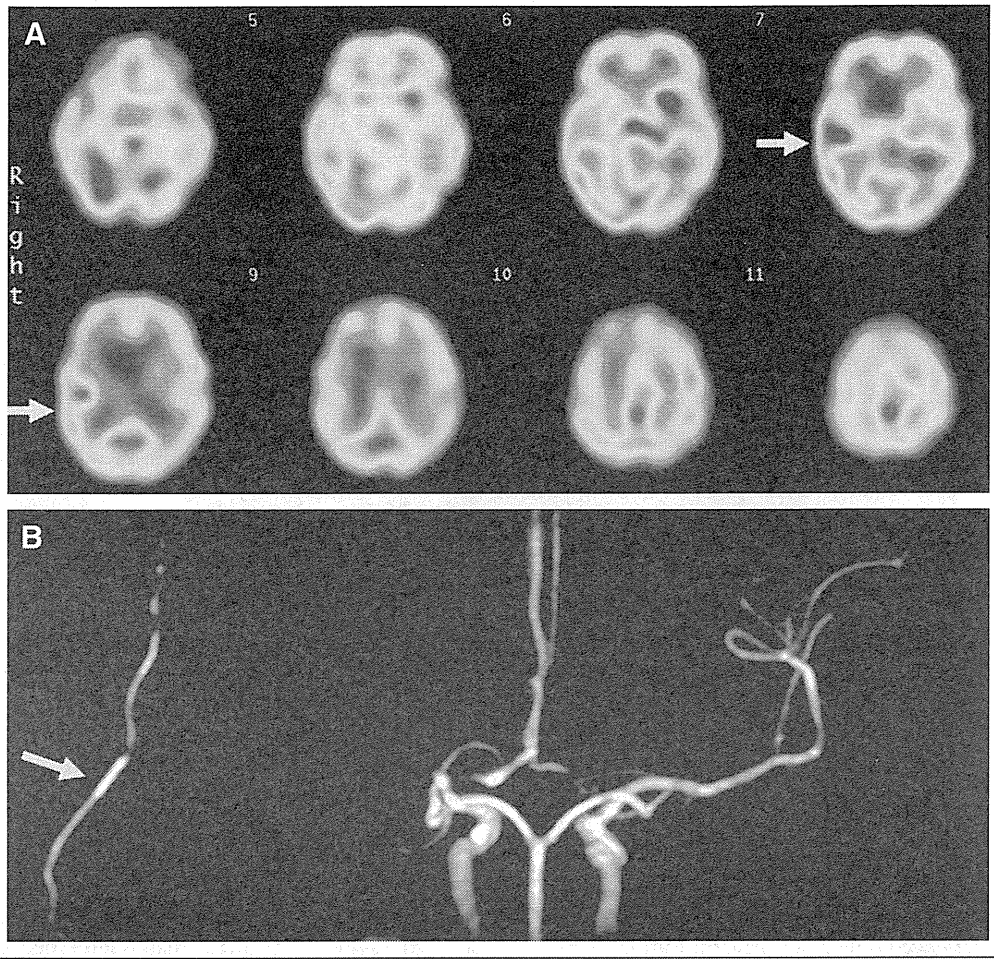

FIGURE 2. *Case 2: a 66-year-old woman with atherosclerotic right M1 occlusion presenting with minor completed stroke.* **A**, *N-isopropyl-p-[^{123}I]iodoamphetamine single-photon emission computed tomography 1 day after right superficial temporal artery–middle cerebral artery (STA-MCA) anastomosis. Focal increase in cerebral blood flow at the site of the anastomosis was evident (arrows in* **A**). **B**, *magnetic resonance angiography 1 day after STA-MCA anastomosis demonstrating STA-MCA bypass as a thick high-signal sign (arrow in* **B**). *Blood pressure was maintained in the normal range, and she did not present with neurologic sign perioperatively.*

no patients in the non-moyamoya group (0 of 28, 0%) suffered from symptomatic cerebral hyperperfusion after STA-MCA anastomosis. Regarding high-flow bypass, Stiver and Ogilvy[10] reported on a 48-year-old woman with severe right supraclinoid internal carotid artery and proximal M1 stenosis who suffered from acute hyperperfusion with massive ICH after high-flow EC-IC bypass. EC-IC bypass for atherosclerotic occlusive disease, as long as the low-flow bypass is selected, is considered to have relatively low risk for cerebral hyperperfusion, and symptoms are thought to be self-limiting in most cases.

In contrast to atherosclerotic patients, however, increasing evidence suggests that cerebral hyperperfusion is a cause of transient neurological deterioration[12,16-22] or delayed ICH[23] during the acute stage after EC-IC bypass for moyamoya disease. The incidence of temporary neurological deterioration probably caused by hyperperfusion is reported to be 16.7% to 28.1%[12,18,22] when mild focal neurological signs are included. Our most recent report, the only study in which a time sequential flow study was conducted in all cases, indicated that the incidence of symptomatic cerebral hyperperfusion was as high as 24.5% (25 of 102 consecutive surgeries),[12] although the exact difference in the incidence and clinical presentation of hyperperfusion between moyamoya patients and non-moyamoya patients was unclear.

In the present study, symptomatic cerebral hyperperfusion including mild focal neurological sign was seen in 25 patients with moyamoya disease (26 hemispheres, 21.5%) but in no

patients in the non-moyamoya group (0%; $P = .0069$). All patients with symptomatic hyperperfusion were treated with intensive blood pressure control, and no patient suffered from permanent neurological deficit resulting from cerebral hyperperfusion, although 4 patients with moyamoya disease had hemorrhagic hyperperfusion (4/121, 3.3%), including 3 patients with SAH and 1 with ICH,[23] which makes us aware of the substantial risks for surgical morbidity resulting from hyperperfusion in moyamoya patients. Regarding the time course of symptomatic cerebral hyperperfusion, focal neurological sign may manifest from postoperative day 2 and could prolong for several days, whereas SAH could occur on the day after revascularization surgery.[12,16] Intensive blood pressure control relieves symptoms caused by hyperperfusion, which may also help the diagnosis of hyperperfusion, whereas the focal neurological signs may fluctuate for a couple days before complete resolution. Thus, we recommend routine CBF measurement for patients with high risk of postoperative hyperperfusion such as moyamoya patients and patients with atherosclerotic ischemic disease associated with marked hemodynamic compromise.

We previously reported that adult-onset and/or hemorrhage-onset moyamoya patients had higher risk for symptomatic cerebral hyperperfusion.[12] In the present study, patients with symptomatic hyperperfusion were relatively older (mean, 38.9 years) than those without symptomatic hyperperfusion (mean, 32.8 years) in the moyamoya group, but we did not find a statistical difference, in contrast to our previous study. Relatively small numbers of pediatric cases in our series and our recent case with symptomatic cerebral hyperperfusion in a child (representative case 1) with marked preoperative hemodynamic compromise might have diluted the results in the present series. Nevertheless, we experienced only 2 pediatric moyamoya patients with symptomatic cerebral hyperperfusion, both presenting with mild neurological signs without hemorrhage, and we consider that accurate diagnosis of cerebral hyperperfusion is clinically important, especially for adult-onset moyamoya disease.

Underlying Mechanism of the Occurrence of Cerebral Hyperperfusion in Patients With Moyamoya Disease

The reason why moyamoya patients had higher risk for symptomatic cerebral hyperperfusion is undetermined. Because the vulnerability of the blood-brain barrier in patients subjected to chronic ischemia is thought to be one of the important factors for cerebral hyperperfusion,[4] it is conceivable that a similar mechanism regarding blood-brain barrier maintenance, which may facilitate hemorrhage in patients with moyamoya disease, could also contribute to the occurrence of postoperative cerebral hyperperfusion. Because reactive oxygen species have been implicated in cerebral ischemia/reperfusion injury,[24] excessive production of reactive oxygen species during revascularization may also affect vascular permeability and thus result in transient neurological deterioration and/or hemorrhagic complications.[24,25] Regarding the downstream molecules related to reperfusion injury, recent studies using dura mater, arachnoid membrane, and serum obtained from the patients with moyamoya disease demonstrated that the expression of vascular endothelial growth factor[26] and matrix metalloproteinase-9,[25] both of which have a potential role to increase the permeability of the blood-brain barrier, is significantly increased in moyamoya patients compared with healthy control subjects. These observations raise the possibility that the increased expression of vascular endothelial growth factor and matrix metalloproteinase-9 in patients with moyamoya disease[25,26] may contribute, at least in part, to the vulnerability to cerebral hyperperfusion in moyamoya patients compared with the patients in the non-moyamoya group. Our results showed that there was no difference in the incidence of any cerebral hyperperfusion (symptomatic and asymptomatic) between the moyamoya and non-moyamoya groups, whereas moyamoya patients showed much higher incidence of symptomatic hyperperfusion compared with non-moyamoya patients. These findings strongly suggest a lower threshold for symptoms in the setting of hyperperfusion in moyamoya disease rather than in the hemodynamics. The issues regarding underlying mechanism of symptomatic cerebral hyperperfusion remain to be elucidated in a future study. By delineating the deleterious cascades of cerebral hyperperfusion, prophylactic blockade of these molecules in high-risk patients may be helpful in avoiding unfavorable complications, including postoperative cerebral hyperperfusion after EC-IC bypass, which could be a new therapeutic approach in combination with revascularization surgery for moyamoya disease.

Besides the intrinsic biological background of moyamoya disease, characteristic angioarchitecture of the pial artery may explain the underlying mechanism that facilitates postoperative cerebral hyperperfusion in patients with moyamoya disease. Kim and colleagues[18] speculate that poorer network formation between the pial arteries may lead to the poorer hemodynamic distribution after revascularization surgery and thus result in focal cerebral hyperperfusion after EC-IC bypass, especially in moyamoya disease. Our most recent study using a novel intraoperative infrared monitoring system on the brain surface demonstrated that the increase in the brain surface temperature around the site of the anastomosis immediately after surgical revascularization was significantly higher in patients who subsequently presented with symptomatic hyperperfusion,[20] suggesting that poorer distribution of the blood flow from STA may result in focal hyperemia and thus cause symptomatic cerebral hyperperfusion. Further study with a larger number of patients with moyamoya disease and with atherosclerotic ischemic disease may address this important issue.

CONCLUSION

Symptomatic cerebral hyperperfusion is a potential complication of EC-IC bypass, especially in patients with moyamoya disease. Accurate diagnosis and proper management of hyperperfusion are recommended, especially in patients with moyamoya disease.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

In this study, the authors report the differential risk for symptomatic cerebral hyperperfusion after revascularization for moyamoya disease compared with atherosclerotic disease. Whereas 21.5 % of the 121 moyamoya hemispheres suffered transient neurological symptoms attributable to focal hyperperfusion, none of the 28 patients with atherosclerosis demonstrated symptomatic hyperperfusion. Interestingly, imaging evidence of hyperperfusion was present in approximately two-thirds of patients in both groups, suggesting that the phenomenon is not uncommon but that the moyamoya group has a lower threshold for developing symptoms in this setting. Future studies to quantitatively assess the extent of hyperperfusion and correlation with intraoperative and postoperative bypass flow measurements will be important to provide further insights into this phenomenon.

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Fujimura et al present their large extracranial-intracranial arterial bypass experience and a comparison of the incidence of perioperative hyperperfusion syndrome, diagnosed by neurologic findings and abnormalities on *N*-isopropyl-p-[^{123}I]iodoamphetamine single-photon emission computed tomography, between those with moyamoya disease and those with nonmoyamoya, atherosclerotic occlusive disease. Interestingly, hyperperfusion was seen in 26 of 121 operated hemispheres for moyamoya disease and 0 of 28 hemispheres in the nonmoyamoya group. Hyperperfusion syndrome was confirmed in these patients by the presence of neurologic symptoms, absence of ischemic changes on magnetic resonance imaging, and concomitant hyperperfusion visualized in the region of the bypass on single-photon emission computed tomography imaging. In addition, subarachnoid hemorrhage and intracerebral hemorrhage were seen in a minority of patients with moyamoya disease undergoing extracranial-intracranial bypass and in none of those with atherosclerotic disease.

The authors present an elegant study that suggests a true difference in susceptibility to hyperperfusion in patients with moyamoya disease compared with those with vascular occlusive disease secondary to atherosclerotic disease. Hyperperfusion syndrome appears to be an increasingly recognized cause of neurologic deficit in the immediate postoperative period after cerebral revascularization, likely secondary to improved diagnostic imaging techniques and better understanding of this previously considered rare entity. A solid understanding of this diagnosis is particularly relevant, given that the treatment for hyperperfusion is the opposite of that for ischemia, and an unfortunate misdiagnosis may result in symptom exacerbation by inappropriate hemodynamic alterations if ischemia is wrongly suspected. Further research is essential to establish useful management guidelines for the successful prevention of cerebral hyperperfusion after revascularization; however, we commend the authors on their efforts to further illuminate the management nuances of this challenging disease.

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Efficacy of Prophylactic Blood Pressure Lowering according to a Standardized Postoperative Management Protocol to Prevent Symptomatic Cerebral Hyperperfusion after Direct Revascularization Surgery for Moyamoya Disease

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Key Words
Blood pressure lowering · Cerebral hyperperfusion · Extracranial-intracranial bypass · Moyamoya disease · Postoperative management

Abstract
Background: Cerebral hyperperfusion is a potential complication of superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis for moyamoya disease, but the optimal postoperative management has not been determined. Aggressive blood pressure lowering is controversial because of the risk of ischemic complications. ***Objective:*** To establish the optimal postoperative management protocol to prevent symptomatic cerebral hyperperfusion in moyamoya disease. ***Methods:*** N-isopropyl-*p*-[^{123}I]-iodoamphetamine single-photon emission computed tomography was performed 1 and 7 days after STA-MCA anastomosis on 152 hemispheres from 108 consecutive patients with moyamoya disease (2–69, mean 33.3 years). Between 2004 and 2007 (period 1), 65 patients were maintained under normotensive conditions after 93 operations, and only patients with cerebral hyperperfusion underwent blood pressure lowering. Between 2008 and 2010 (period 2), all 43 patients were prospectively subjected to intensive blood pressure lowering (<130 mm Hg of systolic blood pressure) immediately after 59 operations. Then the incidence of symptomatic cerebral hyperperfusion was compared between the two groups. ***Results:*** Systolic blood pressure the day after surgery was significantly lower in period 2 (mean, 120.9 mm Hg) than in period 1 (133.9 mm Hg) ($p < 0.0001$). Symptomatic cerebral hyperperfusion was seen in 22 patients during period 1 (23 hemispheres, 24.7%), but only in 4 patients during period 2 (6.7%, $p = 0.0047$). Multivariate analysis revealed that prophylactic blood pressure lowering was significantly associated with the prevention of symptomatic cerebral hyperperfusion ($p = 0.015$). Symptomatic cerebral hyperperfusion was relieved in all patients without developing a permanent neurological deficit due to cerebral hyperperfusion. ***Conclusion:*** Prophylactic blood pressure lowering prevents symptomatic cerebral hyperperfusion after STA-MCA anastomosis in patients with moyamoya disease. Accurate diagnosis of cerebral hyperperfusion and blood pressure lowering, and considering the severity of hemodynamic compromise in the contralateral and/or remote areas are essential for postoperative management of moyamoya disease.

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