5) Abrams CS, Ellison N, Budzynski AZ, et al : Direct detection of activated platelets and platelet dereived microparticles in humans. Blood **75** : 128-138, 1990
6) Ginsberg MH, Frelinger AL, Lam SCT, et al : Analysis of platelet aggregation disorders based on flow cytometric analysis of membrane glycoprotein IIb-IIIa with conformation-specific monoclonal antibodies. Blood **76** : 2017-2023, 1990
7) Jackson CW, Jennings LK : Heterogeneity of fibrinogen receptor expression on platelets activated in normal plasma with ADP : analysis by flow cytometry. Br J Haematol **72** : 407-414, 1989
8) 山崎昌子，内山真一郎，岩田誠：フローサイトメトリーによる活性化血小板フィブリノゲン結合能の測定条件と薬剤による影響の検討．血栓止血誌 **8** : 103-111, 1997
9) Sternberg PE, McEver RP, Shuman MA, et al : A platelet alpha-granule membrane protein (GMP-140) is expressed on the plasma membrane after activation. J Cell Biol **101** : 880-886, 1985
10) Nieuwenhuis HK, van Oosterhout JJ, Rozemuller E, et al : Studies with a monoclonal antibody against activated platelets ; Evidence that a secreted 53,000-molecular weight lysosome-like granule protein is exposed on the surface of activated platelets in the circulation. Blood **70** : 838-845, 1987
11) Sims PJ, Wiedmer T, Esmon CT, et al : Assembly of the platelet prothrombinase complex is linked to vesiculation of the platelet plasma membrane. Studies in Scott syndrome : an isolated defect in procoagulant activity. J. Biol Chem **264** : 17049-17057, 1989
12) Dachary-Pringent J, Freyssinet JM, Pasquet JM, et al : Annexin V as a prbe of aminophospholipid exposure and platelet membrane vesiculation : A flow cytometry study showing a role for free sulfhydryl groups. Blood **81** : 2554-2565, 1993
13) Davies TA, Drotts D, Weil GJ, et al : Flow cytometric measurements of cytosolic calcium changes in human platelets. Cytometry **9** : 138-142, 1988
14) Kienast J, Schmitz G : Flow cytometric analysis of thiazole orange uptake by platelets : A diagnostic aid in the evaluation of thrombocytopenic disorders. Blood **75** : 116-121, 1990
15) Nakamura T, Uchiyama S, Yamazaki M, et al : Flow cytometric analysis of reticulated platelets in patients with ischemic stroke. Thromb Res **106** : 171-177, 2002
16) Yamazaki M, Uchiyama S, Iwata M : Measurement of platelet fibrinogen binding and p-selectin expression by flow cytometry in patients with cerebral infarction. Thromb Res **104** : 197-205, 2001
17) Marquardt L, Ruf A, Mansmann U, et al : Course of platelet activation markers after ischemic stroke. Stroke **33** : 2570-2574, 2002
18) Grau AJ, Reiners S, Lichy C, et al : Platelet function under aspirin, clopidogrel, and both after ischemic stroke. A case-crossover study. Stroke **34** : 849-855, 2003
19) Yamazaki M, Uchiyama S : Platelet function under aspirin, clopidogrel, and both after ischemic stroke. A case-crossover study. Stroke **34**, 2003 (in press)

脳血栓症診療の最近の動向

Current trend in the management of cerebral thrombosis

内山 真一郎 Shinichiro Uchiyama

東京女子医科大学医学部附属脳神経センター神経内科教授

Summary

脳梗塞急性期には抗血小板薬としてアスピリンの適応があり，本邦では発症後5日以内の脳血栓症にオザグレルが用いられており，抗凝固薬としてはヘパリンの有効性は証明されておらず，推奨できないが，本邦ではアルガトロバンが発症後48時間以内のアテローム血栓性脳梗塞に用いられており，血栓溶解薬としてアルテプラーゼの静注療法が未承認ながら発症後3時間以内の脳梗塞に経験豊富な施設に限定して推奨される。心房細動，左室血栓，急性心筋梗塞，人工弁置換を伴わない脳梗塞の再発予防にはアテローム血栓性脳梗塞，ラクナ梗塞と原因不明の脳梗塞のいずれにも抗血小板療法の適応があり，アスピリンが第1選択薬となり，チクロピジン，少量アスピリンとジピリダモールの併用，シロスタゾールもアスピリンに代用しうる。

Key words

●アテローム血栓性脳梗塞
●ラクナ梗塞
●抗血小板療法
●抗凝固療法
●血栓溶解療法

はじめに

脳梗塞はかつては発生機序により脳血栓症と脳塞栓症に分類されていたが，最近では臨床概念によりアテローム血栓性，心原性，ラクナ，その他の4病型に分類されるようになった。このうち，アテローム血栓性とラクナ梗塞が，血栓性機序で生じると考えられることから脳血栓症に該当することになる。塞栓性機序（動脈源性脳塞栓症または動脈・動脈塞栓症）によるアテローム血栓性脳梗塞は，かつての分類では脳塞栓症に含まれることになるが，実際には血栓性機序によるアテローム血栓性脳梗塞と臨床的な鑑別は困難であり，治療方針も変わらないことから，本稿では脳血栓症に含めることとする。

脳血栓症は血栓による脳動脈の閉塞により生じるので，抗血栓療法は最も本質的な治療法であるといえる。抗血栓療法には抗血小板療法，抗凝固療法，血栓溶解療法がある。脳卒中合同ガイドライン委員会や日本循環器学会の抗血小板・抗凝固療法に関するガイドライン委員会では脳梗塞における抗血栓療法のガイドラインを作成中であり，前者はすでに発表され，後者もまもなく発表される予定であるが，著者は両方のガイド

ライン委員会の委員の1人として関与している。本稿では，このような背景を踏まえ，脳血栓症における抗血栓療法について，ガイドラインの根拠となったエビデンスと最近の動向を述べてみたい。

1 脳血栓症急性期

1．抗血小板療法

発症後48時間以内の脳梗塞患者を対象としたInternational Stroke Trial(IST)[1]とChinese Acute Stroke Trial(CAST)[2]という2件の大規模臨床試験と，著者も共同研究者として関与しているCochrane Stroke Group(CSG)のメタアナリシス[3]により，アスピリンはわずかではあるが有意な長期の転帰改善効果のあることが示されている。これを受け，欧米のガイドラインや脳卒中合同ガイドライン委員会による日本の脳卒中治療ガイドラインでは脳梗塞を発症したら直ちにアスピリンの投与を開始することを推奨している(表1)[3]。アスピリンの用量はISTとCASTで用いられた用量に基づいて160～300(または325)mgが推奨されている。この用量は後述する慢性期の長期予防のための用量より多いが，動脈血栓症急性期には直ちにトロンボキサン(TX)A_2の合成を阻害するloading doseを投与すべきであるというコンセプトにも合致しているともいえる。

本邦ではTXA_2合成酵素阻害薬であるオザグレルが，発症後5日以内の脳血栓症患者に第Ⅲ相臨床試験で運動障害を改善する効果のあることが示されたことから用いられており，脳卒中治療ガイドラインでもこのような適応が記載されることとなったが，海外ではランダム化比較試験(RCT)が行われていないためメタアナリシスによる解析を行うことができず，アスピリンとの比較試験も行われていないので，アスピリンとの優劣も不明である(表1)[4]。

最近，発症後6時間以内の脳梗塞300例を対象として血小板膜糖蛋白(GP)Ⅱb/Ⅲaのモノクローナル抗体であるabciximabのRCTが行われ，その成績が本年2月に米国心臓協会(AHA)主催の国際脳卒中会議で発表された。National Institute of Health Stroke Scale(NIHSS)が4～7の軽症例と8～14の中等症例では3ヵ月後のmodified Rankin scoreが軽症で0～1，中等症で0～2へと改善した症例の比率は，軽症例では実薬群40.2%，対照群25.3%，中等症例では実薬群44.9%，対照群32.9%であり，いずれも実薬群で対照群より有意に多かった。出血合併症も，症候性頭蓋内出血が実薬群3.6%，対照群1.0%，頭蓋外大出血が実薬群1.5%，対照群1.0%であり，いずれも実薬群で対照群より多かったものの，その頻度は血栓溶解薬[5]や抗凝固薬[6]に比べれば低く，きわめて有望な治療法であると考えられた。

2．抗凝固療法

CSGのメタアナリシスによれば，いかなる剤型のヘパリン(未分画ヘパリン，低分子ヘパリン，ヘパリノイド)も脳梗塞急性期患者の転帰改善効果は示されていない(表2)[6]。ヘパリンは治療期間中の脳梗塞の再発を減らすが，脳出血の発症を増やしてしまうので，全脳卒中を減らすことができない[6]。したがって，海外のガイドラインでは脳梗塞急性期の治療法としてヘパリンは推奨されなくなっており，本邦の脳卒中治療ガイドラインでもエビデンスがないので推奨できないと記載されることとなった。

本邦ではトロンビン阻害薬であるアルガトロバンが脳梗塞急性期患者を対象とした第Ⅲ相臨床試験のサブ

表1
脳梗塞急性期の抗血小板療法が追跡最終時(＞1ヵ月)の死亡または要介助に及ぼす効果[4]

薬剤	抗血小板薬群	対照群	オッズ比(95%CI)
アスピリン	9247/20207	9497/20190	0.95(0.91～0.98)
トロンボキサン合成酵素阻害薬	67/140	77/143	0.79(0.49～1.25)
合計	9314/20347	9574/20333	0.94(0.91～0.98)

表2
脳梗塞急性期の抗凝固療法が追跡最終時(＞1ヵ月)の死亡または要介助に及ぼす効果[6]
＊：ヘパリノイド(皮下注も含む)

薬剤	抗凝固薬群	対照群	オッズ比(95%CI)
未分画ヘパリン(皮下注)	6063/9717	6062/9718	1.00(0.94～1.06)
低分子ヘパリン	400/723	210/355	0.85(0.66～1.10)
ヘパリノイド(静注)	159/641	167/635	0.92(0.72～1.19)
合計*	6635/11109	6454/10737	0.99(0.94～1.05)

表3
脳梗塞急性期の血栓溶解療法が追跡最終時の死亡または要介助に及ぼす効果[5]
UK：urokinase，SK：streptokinase，t-PA：tissue plasminogen activator
＊：アスピリンとの併用対アスピリン単独
＊＊：ヘパリン静注との併用対ヘパリン静注単独

薬剤	血栓溶解薬群	対照群	オッズ比(95%CI)
SK静注	311/497	311/486	0.94(0.72～1.24)
t-PA静注	715/1401	773/1363	0.79(0.68～0.92)
SK静注＋ASA*	99/156	94/153	1.09(0.69～1.73)
Pro-UK動注**	91/147	55/73	0.55(0.31～1.00)
合計	1216/2201	1233/2075	0.83(0.73～0.94)

解析で発症後48時間以内のラクナ梗塞を除く脳血栓症(すなわちアテローム血栓性脳梗塞)に転帰改善効果が示されたことから，このような適応が承認されており，脳卒中治療ガイドラインでも同様な記載がなされることとなったが，海外では用いられておらず，メタアナリシスのエビデンスはない[6]。最近，本邦では発症後48時間以内のラクナ梗塞を除く脳血栓症を対象としてオザグレルとの比較試験が行われ，同等であるとの結果が示された[7]。アメリカでは発症後12時間以内の脳梗塞患者を対象として活性化部分トロンボプラスチン時間で用量を調節したアルガトロバンの5日間持続静注療法の安全性を検討するRCTが行われ，安全性が確認された。

3．血栓溶解療法

脳梗塞急性期に行われた血栓溶解療法のRCTを薬剤別にサブ解析したCSGのメタアナリシスによると，ストレプトキナーゼの静注は頭蓋内出血を著しく増加させ，転帰改善効果を認めなかったため，脳卒中治療ガイドラインでも行うべきでない治療とされた(表3)[5]。これに対して組織プラスミノーゲンアクチベーター(アルテプラーゼ)は頭蓋内出血を明らかに増加させるものの，長期の転帰を有意に改善することから，治療ガイドラインでは，経験の豊富な実績のある施設に限定して，発症後3時間以内の脳梗塞には静注療法が推奨されると記載されることとなった[6]。現在，本邦では発症後3時間以内の脳梗塞100症例に対してアルテプラーゼの安全性試験が行われている。

また，米国では発症後6時間以内の脳梗塞にプロウロキナーゼの局所動注療法の有効性が報告された[8]が，1件のポジティブなRCTの結果しかないためFDAはまだ承認していない(表3)[5]。本邦ではこのRCTと同様なプロトコールで塞栓性の中大脳動脈のM1またはM2の閉塞例を対象としてウロキナーゼの全国的なRCT(MELT-Japan)が進行中である。

2 脳血栓症慢性期の抗血小板療法

1．単独療法

著者も共同研究者として関与しているAntithrombotic Trialists' Collaboration(ATT)は閉塞性血管障害の高リスク患者(血管イベントの年間発症率3％以上)を対象として行われた287件のRCTで無作為化された約20万症例をメタアナリシスにより解析した結果を発表した[9]。疾患別のサブ解析では脳梗塞・TIA患者における抗血小板療法の有効性が再確認された。抗血小板薬

別の解析では，アスピリンが23%，チクロピジンが32%，アスピリンとジピリダモールの併用が30%の有意な血管イベント(脳卒中，心筋梗塞，血管死)の相対リスク減少効果を認めた(図1)[9]。

アスピリンの用量別解析では，アスピリンの血管イベント低減効果には Jカーブ現象がみられ，75～150mgが最も効果が大きく，75mg未満の効果は有意ではなかったという結果が示された(図1)[9]。したがって，著者を含むATTの共同研究者間の新しい統一見解として脳梗塞の再発予防には75～150mgを推奨することとなった。本邦の脳卒中治療ガイドラインでも，最もエビデンスが豊富で，安全かつ安価な第1選択の抗血小板薬としてアスピリンが推奨されている。

アスピリンと他の抗血小板薬を直接比較したRCTをメタアナリシスにより解析したATTの成績によれば，血管イベント低減効果はチクロピジンがアスピリンよ

Category of trial	No. of trials with data	No. (%) of vascular events: Allocaled antiplatelet	Adjusted control	Observed-expected	Variance	%Odds reduction (SE)
Aspirin alone (mg daily)*:						
500～1500	34	1621/11215 (14.5)	1930/11236 (17.2)	−147.1	707.8	19 (3)
160～325	19	1526/13240 (11.5)	1963/13273 (14.8)	−219.9	742.6	26 (3)
75～150	12	366/3370 (10.9)	517/3406 (15.2)	−72.0	183.8	32 (6)
<75	3	316/1827 (17.3)	354/1828 (19.4)	−18.9	136.5	13 (8)
Any aspirin	65	3829/29652 (12.9)	4764/29743 (16.0)	−452.3	1717.0	23 (2)
Other antiplatelet drugs:						
Dipyridamole	15	392/2696 (14.5)	458/2734 (16.8)	−30.9	173.0	16 (7)
Sulfinpyrazone	19	315/2411 (13.1)	361/2416 (14.9)	−23.8	140.7	16 (8)
Ticlopidine	42	278/3435 (8.1)	385/3475 (11.1)	−50.5	132.3	32 (7)
Suloctidil	6	47/364 (12.9)	59/367 (16.1)	−5.6	20.5	24 (19)
Picotamide	4	41/1583 (2.6)	66/1602 (4.1)	−12.2	25.8	38 (16)
Sulotroban	4	8/400 (2.0)	14/409 (3.4)	−3.2	5.3	45 (33)
Triflusal	2	10/314 (3.2)	19/309 (6.1)	−4.7	6.7	50 (28)
Other	9	41/647 (6.3)	73/641 (11.4)	−16.1	25.6	47 (15)
Any other single agent**	101	1132/11856 (9.5)	1435/11953 (12.0)	−147.0	529.9	24 (4)
Aspirin+another antiplatelet drug:						
Aspirin+Dipyridamole	46	1036/9703 (10.7)	1393/9738 (14.3)	−172.6	488.7	30 (4)
Aspirin+Sulfinpyrazone	2	38/283 (13.4)	50/278 (18.0)	−6.5	18.5	30 (20)
Any combination	48	1074/9986 (10.8)	1443/10016 (14.4)	−179.1	507.2	30 (4)
All trials	188	6035/51494 (11.7)	7644/51736 (14.8)	−715.7	2499.8	25 (2)

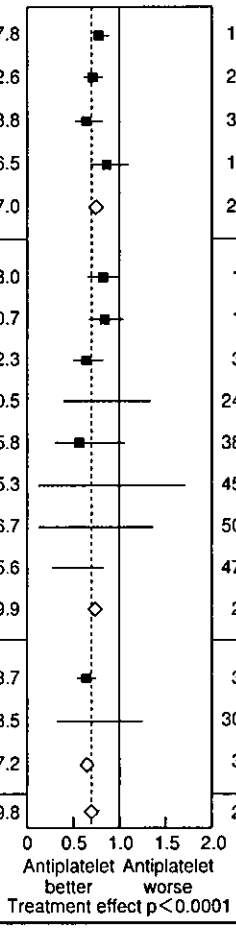

図1 Antithrombotic Trialists' Collaborationによるメタアナリシス[9]
高リスク患者(急性期脳卒中患者を除く)における血管イベントに及ぼす各種抗血小板薬の効果の間接比較。500例以上の高リスク患者を含むメタアナリシスのみを示す。
*：いくつかの試験は1つ以上の比較に貢献している。
**：インドプフェン，フルルビプロフェン，GR32191B，ダゾキシペン，トラピジールを含む。
各試験群の対照群に対する治療群におけるイベントの層別化オッズ比(黒い正方形)と99%信頼区間(水平線)を示す。各比較に対する結果のメタアナリシスと95%信頼区間をオープンダイアモンドで示す。

り12%高く，チクロピジンと同じチエノピリジン誘導体であるクロピドグレルもアスピリンより10%高かったが，これらの差は有意ではなかった(図2)[9]。しかし，チクロピジンとクロピドグレルを同じチエノピリジンとして一括してメタアナリシスにより解析しなおすとアスピリンとの差は有意となる[10]。したがって，チエノピリジンはアスピリンより血管イベント低減効果に有意に優れているといえる。

クロピドグレルはチクロピジンと同じチエノピリジン誘導体であり，脳梗塞・心筋梗塞・末梢動脈閉塞症

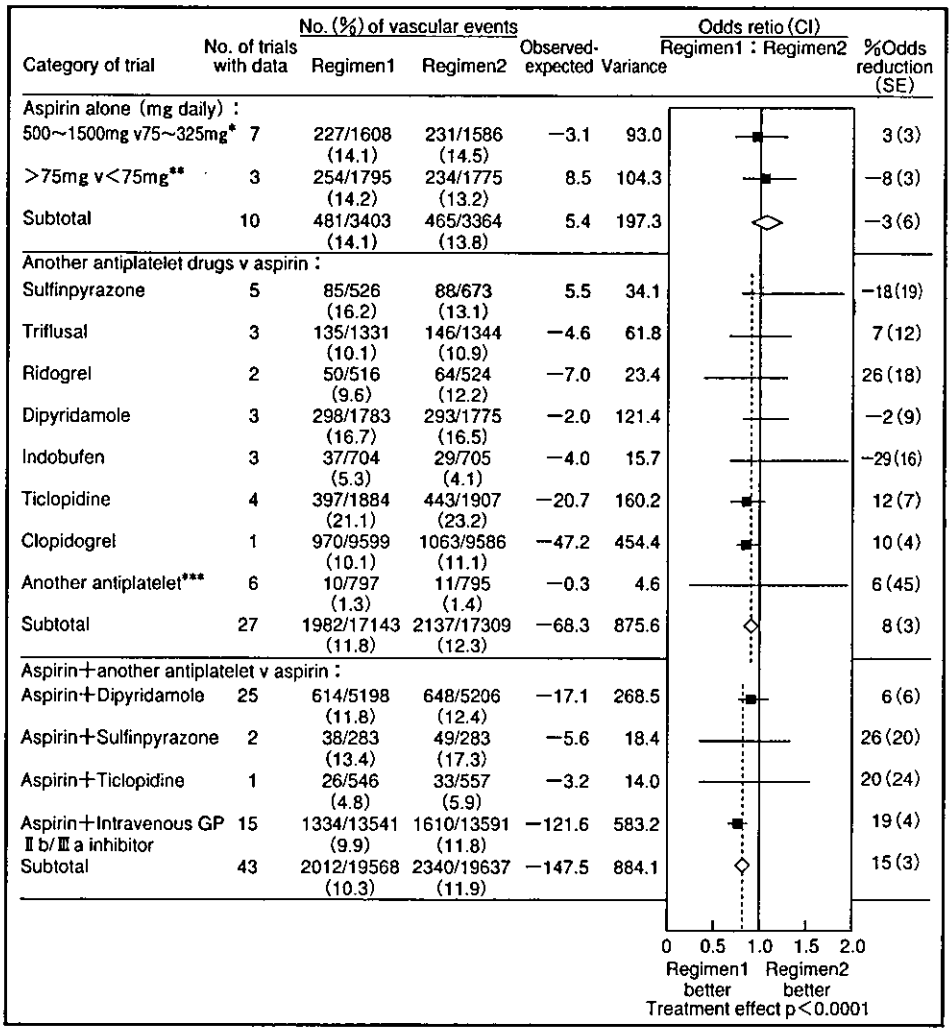

図2　Antithrombotic Trialists' Collaborationによるメタアナリシス[9]

高リスク患者における血管イベントに及ぼす各種抗血小板薬の効果の直接比較。500例以上の高リスク患者を含むメタアナリシスのみを示す。

＊：1400mg/日と350mg/日を比較した試験とジピリダモールも投与された患者間で1000mg/日と300mg/日を比較したもう1件の試験(急性期脳卒中を除外)を含む。

＊＊：75～325mg/日と<75mg/日を比較した2件の試験と500～2500mg/日と<75mg/日を比較した1件の試験を含む。

＊＊＊：シロスタゾール，スロトロバン，トラピジール，E5510，エプチフィバチド，GR32191Bを含む。

各試験群の処方1群と処方2群におけるイベントの層別化オッズ比(黒い正方形)と99%信頼区間(水平線)を示す。特定の比較に対する全試験のメタアナリシスと95%信頼区間をオープンダイアモンドで示す。

においてアスピリンを上回る血管イベント(脳梗塞，心筋梗塞，血管死)低減効果を示し，チクロピジンより副作用が少ないことから海外では高い評価を得ているが，残念ながらまだ日本では承認されていない[11]。現在のところ，本邦ではチクロピジンしか用いることができず，チクロピジンは顆粒球減少や血栓性血小板減少性紫斑病や高度の肝障害などの重篤な副作用が起こりうることから，脳卒中治療ガイドラインでは第2選択の抗血小板薬として位置づけられている。

著者らの検討によれば，生体内での血栓形成に重要な役割を果たしていると考えられる，ずり応力惹起血小板凝集(SIPA)はチクロピジンやクロピドグレルにより強力に抑制されるが，アスピリンによっては抑制されず，このようなチエノピリジンとアスピリンのSIPA抑制効果の差が血管イベント低減効果の差の一因であると考えられる[12]。

シロスタゾールはジピリダモールと同じホスホジエステラーゼ(PDE)阻害薬であるが，ジピリダモールがサイクリックGMPに特異的なPDE5を主に抑制するのに対して，シロスタゾールはサイクリックAMPに特異的なPDE3を抑制する。最近，本邦で1000例以上の脳梗塞患者を対象とし，プラセボを対照薬として用いたCilostazol Stroke Prevention Study(CSPS)によりシロスタゾールの脳梗塞再発予防効果が示された[13]。このRCTの対象となった患者の75%はMRI上，皮質下小梗塞であったが，病型別のサブ解析によりラクナ梗塞で有意な再発予防効果が示された。シロスタゾールはこれまで末梢動脈疾患にのみ適応があったが，本年4月に脳梗塞にも適応が承認され，脳卒中治療ガイドラインにも第2選択の抗血小板薬の1つとしてラクナ梗塞の再発予防効果を証明した，はじめての抗血小板薬であることが明記されている。

2. 併用療法

ジピリダモールの血小板凝集抑制作用にはアデノシンの再取込み抑制作用も関与していると考えられ，アスピリンと併用した場合，これらの抗血小板作用とアスピリンのシクロオキシゲナーゼ(COX)阻害作用が同時に発揮されるため再発予防効果が高まると考えられる。ESPS-2[14]ではアスピリンとジピリダモールの併用療法は相加的に脳梗塞再発予防効果を高めるという結果が示された。この併用効果を支持する根拠として，最近われわれの行った*in vitro*の実験によれば，全血中のSIPAはアスピリンによっては抑制されず，高濃度のジピリダモールにより抑制され，この抑制効果はアスピリンとの併用により増強された[15]。ただし，今回のATTの成績によれば，ESPS-1を含めたメタアナリシスではアスピリン単独療法との血管イベント低減効果の差は証明されなかった(図2)[9]。脳卒中治療ガイドラインではESPS-2の成績に基づき，ジピリダモールは保険適用外ではあるが，少量アスピリンとジピリダモール徐放錠の併用が第2選択の抗血小板療法の1つとして推奨されている。

アスピリンとチクロピジンの併用療法はアスピリンによるCOX阻害作用とチクロピジンによるADP受容体阻害作用が同時に発揮されるので，おのおのの単独療法よりも強力な抗血小板療法であることを著者らは報告してきた[16][17]。しかし，アスピリンとチクロピジンの併用療法をアスピリン単独療法と直接比較したRCTをメタアナリシスにより解析したATTの成績では，血管イベント低減効果の差は証明されていない(図2)[9]。ただし，その後行われた急性冠症候群のステント留置例を対象とした1件のRCTでは併用療法で単独療法より血管イベントが有意に少なかったことから，このような症例ではアスピリンとチクロピジンの併用療法が世界的なコンセンサスとなっている[18]。

海外ではチエノピリジンの中では主にクロピドグレルが用いられているが，最近はアスピリンかクロピドグレルかという選択よりもアスピリンとクロピドグレルの併用療法に関心が向けられており，多くの大規模臨床試験が行われている。たとえば，何らかの危険因子を有する軽症脳梗塞またはTIA7600例を対象にクロピドグレル(75mg)単独療法とクロピドグレル(75mg)・アスピリン(75mg)併用療法の血管イベント低減効果を比較するManagement of Atherothrombosis with Clopidogrel in High-Risk Patients(MATCH)，血管障害の危険因子を有する心房細動患者14000例を対象としてアスピリンとクロピドグレルの併用療法をワルファリン療法またはアスピリン単独療法と比較し，さらにアンジオテンシン受容体阻害薬の併用効果を検討す

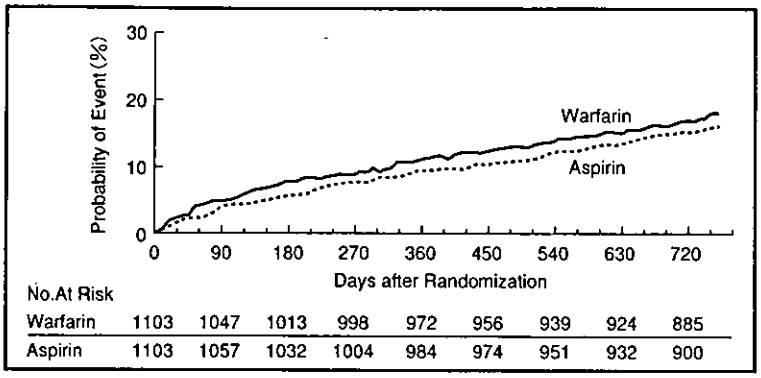

図3
Warfarin-Aspirin Recurrent Stroke Studyの成績[21]
虚血性脳卒中の再発または死亡のKaplan-Meier解析。

るAtrial Fibrillation Clopidogrel Trial with Irbesaltan for Prevention of Vascular Events (ACTIVE)，虚血性脳血管障害，冠動脈疾患，末梢動脈疾患，頸動脈病変，アテローム血栓症の危険因子のいずれかを有する15200例を対象としてアスピリンの単独療法とクロピドグレルとの併用療法を比較するClopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance(CHARISMA)などが進行中である。

GPⅡb/Ⅲa阻害薬はあらゆる血小板受容体アゴニストによる血小板凝集の最終共通経路であるGPⅡb/Ⅲaへのフィブリノーゲンの結合を阻害する強力な抗血小板薬である[19]。ATTの解析ではアスピリンとGPⅡb/Ⅲa阻害薬の併用療法はアスピリン単独療法より有意に血管イベント低減効果が大きかった(図2)[9]。しかし，これまでに行われたRCTはいずれも急性冠症候群を対象としており，まだ虚血性脳卒中を対象としたRCTは行われておらず，本併用療法はアスピリン単独療法より出血合併症が多かったことも今後の課題である[19]。

3. 米国における再発予防のための抗血栓療法のガイドライン

米国心臓協会脳卒中評議会によるガイドラインによれば，アテローム血栓性脳梗塞では頸動脈狭窄の有無や程度の如何にかかわらず，全例に抗血小板療法の適応があり，ラクナ梗塞と原因不明の脳梗塞を含む他の脳梗塞にも抗血小板療法の適応があるとされていた[20]。Warfarin-Aspirin Recurrent Stroke Study(WARSS)[21]によると，明らかな心内塞栓源として心房細動，左室血栓，急性心筋梗塞，人工弁置換を伴う脳梗塞を除いた非心原性脳梗塞2000例においてワルファリン(INR1.4～2.8)投与群ではアスピリン(325mg/日)投与群より再発率が有意ではないものの11%高く，大出血も多い傾向があったという成績が示され，ガイドラインを支持する結果となった(図3)。

文　献

1) International Stroke Trial Collaborative Group : The International Stroke Trial(IST) ; a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19,435 patients with acute ischaemic stroke. Lancet **349** : 1569-1581, 1997
2) CAST(Chinese Acute Stroke Trial)Collaborative Group : Randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. Lancet **349** : 1641-1649, 1997
3) 脳卒中合同ガイドライン委員会：脳卒中治療ガイドライン2003, 2003
4) Cochrane Stroke Group(Gubits G, Counsell C, Sandercock P) : Antiplatelet therapy for acute ischaemic stroke(review). The Cochrane database of systematic reviews. *in* The Cochrane Library, The Cochrane Collaboration, Issue 4, 2002
5) Wardlow JM, del Zoppo G, Yamaguchi T, et al : Thrombolysis for acute ischaemic stroke. *in* The Cochrane Library, Issue 4, Update Software, Oxford, 2002
6) Cochrane Stroke Group(Gubits G, Counsell C, Sandercock P, et al) : Anticoagulants for acute ischaemic stroke(review). The Cochrane database of

systematic reviews. *in* The Cochrane Library, The Cochrane Collaboration, Issue 4, 2002
7) 福内靖男，東儀英夫，篠原幸人，他：脳血栓症急性期におけるアルガトロバンの効果—sodium ozagrelとの比較臨床試験—．神経治療 **18**：273-282, 2000
8) Furlan AJ, Higashida R, Wechsler L, et al : Intra-arterial prourokinase for acute ischemic stroke. The PROACT Ⅱ Study : A randomized controlled trial. JAMA **282** : 2003-2011, 1999
9) Antithrombotic Trialists' Collaboration : Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocaridialinfarction, and stroke in high risk patients. Br Med J **324** : 71-86, 2002
10) Hankey GJ, Sudlow CLM, Danbabin DW, et al : Thienopyridines or aspirin to prevent stroke and other serious vascular events in patients at risk of vascular disease? A systematic review of the evidence from randomized trials. Stroke **31** : 1779-1784, 2000
11) CAPRIE Steering Committee : A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events(CAPRIE). Lancet **348** : 1329-1339, 1996
12) Uchiyama S, Yamazaki M, Maruyama S, et al : Shear-induced platelet aggregation in cerebral ischemia. Stroke **25** : 1547-1551, 1994
13) Gotoh F, Tohgi H, Hirai S, et al : Cilostazol Stroke Prevention Study ; a placebo-controlled double-blind trial for secondary prevention of cerebral infarction. J Stroke Cerebrovasc Dis **9** : 147-157, 2000
14) Diener HC, Cunha L, Forbes C, et al : European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci **143** : 1-13, 1996
15) Nakamura T, Uchiyama S, Yamazaki M, et al : Effects of dipyridamole and aspirin on shear-induced platelet aggregation in whole blood and platelet-rich plasma. Cerebrovasc Dis **14** : 264-282, 2002
16) Uchiyama S, Nagayama T, Sone R, et al : Combination therapy with low-dose aspirin and ticlopidine in cerebral ischemia. Stroke **20** : 1643-1647, 1989
17) Yamazaki M, Uchiyama S, Iwata M, et al : Measurement of platelet fibrinogen binding and P-selectin expression in patients with ischemic cerebrovascular disease. Thromb Res **104** : 197-205, 2001
18) Leon MB, Baim DS, Popma JJ, et al : A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. N Engl J Med **339** : 1665-1671, 1998
19) 内山真一郎，山崎昌子：新しい抗血小板療法—GPⅡb/Ⅲa阻害薬—．杉田秀夫，福内靖男，柴崎 浩 監，脳血管障害とその治療．神経・筋疾患の最新医療，先端医療シリーズ14 神経・筋疾患．東京，先端医療技術研究所，78-82, 2001
20) Wolf PA, Clagett P, Easton JD, et al : Preventing ischemic stroke in patients with prior stroke and transient ischemic attack ; a statement for healthcare professionals from the Stroke Council of the American Heart Association. Stroke **30** : 1991-1994, 1999
21) Mohr JP, Thompson JLP, Lazar RM, et al(for the Warfarin-Aspirin Recurrent Stroke Study Group) : A comparison of warfarin and aspirin for prevention of recurrent ischemic stroke. N Engl J Med **345** : 1444-1451, 2001

□ ORIGINAL ARTICLE □

Clinical Characteristics in Transient Ischemic Attack Patients with Atrial Fibrillation

Kazumi KIMURA, Kazuo MINEMATSU, Kuniyasu WADA, Kiminobu YONEMURA and Makoto NAKAJIMA

Abstract

Objective **The aim of this study was to clarify the characteristics of transient ischemic attack (TIA) patients with atrial fibrillation (AF) compared to those without.**

Methods **We divided 67 TIA patients with left hemispheric involvement into two groups; patients with AF (AF group) and without AF (Non-AF group) and compared the clinical characteristics between the two groups.**

Patients **AF group included 12 patients (73.0±9.7 years old) and the Non-AF group 55 patients (64.1±9.8 years old).**

Results **Clinically, arterial disease was less frequently seen in the AF group than in the Non-AF group (17% vs 53%, p=0.028). No significant differences were observed between the two groups in the duration (<1 hour; AF vs Non AF group: 50% vs 32%) or number of TIAs (more than 1; 17% vs 37%), use of anticoagulation or antiplatelet at time of symptom onset (34% vs 14%), past history of stroke and TIA (58% vs 38%) and ischemic heart diseases (8% vs 13%), and risk factors for atherosclerosis including hypertension (42% vs 71%), diabetes mellitus (17% vs 31%), hyperlipidemia (17% vs 47%) , smoking (50% vs 51%) and other emboligenic cardiac diseases except for AF (0% vs 4%). Aphasia was observed more frequently in the AF group than in the Non-AF group (67% vs 20%, p=0.003), whereas, hemiparesis without aphasia was seen less frequently in the AF group than in the Non-AF group (17% vs 55%, p=0.025).**

Conclusion **TIA patients with AF are more likely than those without AF to exhibit a major hemispheric syndrome, such as aphasia.**

(Internal Medicine 42: 255–258, 2003)

Key words: transient ischemic attack, atrial fibrillation, aphasia, clinical symptoms, hemiparesis

Introduction

The two typical embolic sources of transient ischemic attacks (TIAs) are microemboli from a plaque in the extracranial carotid artery, and cardiogenic embolism (1, 2). Carotid disease is the source of emboli in 20–52% of TIA patients, whereas in 23–32% of TIA patients a potential cardiac source of emboli has been reported (1, 2). In stroke and TIA patients, atrial fibrillation (AF) is the most common potential cardioembolic source. Among stroke patients, neurological events are more severe and the outcome is significantly poorer in those with AF (3).

To the best of our knowledge, no detailed analysis of the clinical characteristics of TIA patients with AF has been done. It is thought that the heart can be the source of large emboli, which can impact on large cerebral arteries and lead to severe neurological deficits. On the other hand, since microemboli from carotid disease can travel easily through the large cerebral arteries, they become lodged only in the small vessels, resulting in mild neurological deficits. Therefore, we hypothesized that TIA patients with AF were more likely to have more severe initial neurological deficits compared to TIA patients without AF. We conducted this study in order to examine this hypothesis.

Subjects and Methods

We retrospectively analyzed the clinical record review of 114 consecutive patients with carotid TIAs admitted to our hospital within two weeks of TIA onset between June 1990 and March 1999. We excluded 47 patients with right hemispheric involvement from this study. These patients were excluded because in TIA patients with right hemispheric (non-dominant) involvement, transient cortical signs, such as left unilateral spatial neglect and agnosia during a TIA attack are often undetected. Thus, it may be difficult to establish the presence of cortical signs during a TIA when a patient or his

From the Cerebrovascular Division, Department of Medicine, National Cardiovascular Center, Osaka
Received for publication October 16, 2002; Accepted for publication December 11, 2002
Reprint requests should be addressed to Dr. Kazumi Kimura, the Cerebrovascular Division, Department of Medicine, National Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565

family is interviewed after the TIA attack. A total of 67 patients with left hemispheric involvement were finally enrolled. These patients consisted of 47 men and 20 women aged 65.7±10.3 years. A diagnosis of carotid TIA was made by neurologists based on the National Institute of Neurological Disorders and Stroke classification III (4). Patients with amaurosis fugax were also excluded from this study.

Computed tomography (CT) was performed on all patients within two weeks of onset of the TIA in order to exclude nonischemic brain lesions such as brain hemorrhage, chronic subdural hematoma, and brain tumors.

Information on symptoms during the TIAs was obtained from the patients or their families. If a patient had a speech disturbance, a careful history was taken so as to distinguish aphasia from dysarthria. Two of the authors (K. W. and K. Y.), who were blinded to the patients' clinical and laboratory data, independently assessed the TIA symptoms documented in the admission records and classified the patients into three subgroups according to TIA symptoms: 1) the aphasia group, patients having an aphasia with or without paresis; 2) the monoparesis group, those presenting with an isolated motor or sensory disturbance restricted to either the face, arm or leg; and 3) the hemiparesis group, those presenting with hemiparesis or hemisensory deficits without aphasia. When the two investigators disagreed on a patient's classification, they discussed the case and reached an agreement on the final classification.

The following baseline and clinical characteristics were evaluated: 1) age and gender: 2) duration of TIA (<1 hour, and 1–24 hours): 3) number of TIAs: 4) use of antiplatelet agents or anticoagulants: 5) past history of brain infarction, TIA, myocardial infarction, or definite angina pectoris: 6) risk factors for stroke, including hypertension, diabetes mellitus, hyperlipidemia, and current smoking: 7) significant arterial pathologies in the left carotid system: and 8) potential cardiac sources of emboli.

The criteria for stroke risk factors were as follows: 1) use of antihypertensive agents, systolic blood pressure (SBP) >160 mmHg or diastolic blood pressure (DBP) >95 mmHg: 2) use of oral hypoglycemic agents, insulin, or glycosylated hemoglobin (HbA1C) >6.4%: 3) use of antihyperlipidemic agents, or serum cholesterol level >220 mg/dl: and 4) current smoking defined as a history of smoking in the preceding three months.

To detect potential cardiac sources of emboli (emboligenic cardiac diseases), all patients underwent 12-lead electrocardiography (ECG), 24-hour ECG monitoring, and transthoracic echocardiography. AF included both paroxysmal and persistent AF and was identified during hospitalization. Emboligenic cardiac diseases included non-valvular AF: acute myocardial infarction, old myocardial infarction with intraventricular thrombus: mitral valve disease: prosthetic cardiac valve: implantation of a pacemaker: and dilated cardiomyopathy.

We performed color-flow duplex carotid ultrasonography, conventional angiography, and MR angiography (MRA) in order to evaluate significant arterial pathologies in the ipsilateral carotid system. Color-flow duplex carotid ultrasonography (Toshiba SSA 270A or 260A, Toshiba Inc, Tokyo) was performed to assess the extracranial carotid stenotic lesions in all patients. The carotid arteries were examined in longitudinal and transverse planes from anterior, lateral, and posterior approaches using B-mode and color flow imaging. This allowed direct measurement of the residual lumen diameter of the stenotic lesions.

We performed conventional cerebral angiography in 39 patients (58%), MRA in 30 (45%), and both assessments were done in 7 patients (10%). Therefore, in 62 patients (93%) the intra-cranial carotid artery, anterior cerebral artery and middle cerebral artery were assessed by either conventional cerebral angiography or MRA. The grade of stenosis of the internal carotid artery (ICA) was determined by the method used in the North American Symptomatic Carotid Endarterectomy Trial (5). Stenosis in the middle cerebral artery (MCA) was calculated in a similar manner by measuring the diameter of the stenotic lesion and that of an adjacent intact portion of the artery.

The lesions were considered significant if the horizontal portion of the MCA had a >50% stenosis, and the ICA was a >70% stenosis or if an ulceration was evident in the carotid bifurcation.

The risk factors, past history, arterial or cardiac diseases, number of TIAs, and TIA duration were compared between the two groups using the χ^2 test. Patient age was analyzed using the Mann-Whitney U test. Statistical analysis was performed using a commercially available software package (Stat-View, version 5, SAS Institute Inc. USA). Data were expressed as mean±SD. P values <.05 were considered statistically significant.

Results

Twelve patients had AF (the AF group) and 55 did not have AF (non-AF group). Table 1 shows the clinical characteristics of these two groups. The mean of age in the AF group was higher than in the non-AF group (p=0.014). No significant differences between the two groups were observed in: the duration or number of TIAs: use of medication: past history: or risk factors. Arterial diseases were seen more frequently in the non-AF group than in the AF group (53% vs 17%, p=0.028)

Among the 62 patients evaluated with color-flow duplex carotid ultrasonography and conventional angiography or MRA, significant arterial disease was detected in the carotid axis ipsilateral to the affected side in 30 (45%) patients. The following arterial lesions were observed: MCA occlusion in 4 patients, anterior cerebral artery occlusion in 1 patient, more than 50% stenosis of the horizontal portion of the MCA in 9 patients, ICA occlusion in 2 patients, more than 70% ICA stenosis in 10 patients, and less than 70% ICA stenosis but with ulceration in 4 patients. In 1 of the 4 patients who did not have conventional angiography or MRA

Table 1. Demographic Features of TIAs in the 2 Groups

	AF Group n=12	Non-AF Group n=55	p
Age, years	73.0±9.7	64.1±9.8	0.014
TIA duration, n			N.S
<1 hour	6 (50%)	32 (58%)	
1 hour–24 hours	6 (50%)	23 (42%)	
Number of TIAs, n			N.S
1	10 (83%)	35 (64%)	
2–3	2 (17%)	12 (22%)	
4–9	0	8 (15%)	
Medication at TIA, n (%)			
Anticoagulation	2 (17%)	1 (2%)	N.S
Antiplatelet	2 (17%)	13 (24%)	N.S
Past history, n (%)			
TIA	3 (25%)	10 (18%)	N.S
Brain infarction	4 (33%)	11 (20%)	N.S
Angina pectoris	0 (0)	4 (7%)	N.S
Myocardial infarction	1 (8%)	3 (5%)	N.S
Risk factor, n (%)			
Hypertension	5 (42%)	39 (71%)	N.S
Diabetes mellitus	2 (17%)	17 (31%)	N.S
Hyperlipidemia	2 (17%)	26 (47%)	N.S
Smoking	6 (50%)	28 (51%)	N.S
Arterial disease	2 (17%)	29 (53%)	0.028
Emboligenic cardiac diseases			
Others except for AF	0	4 (7%)	N.S

N.S: not significant.

Table 2. Clinical TIA Symptoms of the 2 Groups

	AF Group n=12	Non-AF Group n=55	p
Hemiparesis without aphasia	2 (17%)	30 (55%)	0.025
Monoparesis without aphasia	2 (17%)	14 (25%)	0.517
Aphasia	8 (67%)	11 (20%)	0.003

examinations, color-flow duplex carotid ultrasonography demonstrated a 75% stenosis in the internal carotid artery in one patient. Thus a total of 31 patients had significant arterial diseases (Table 1).

Emboligenic cardiac diseases were observed in 16 (24%) patients: 12 patients had non-valvular AF: 2 had a prosthetic mitral valve: 1 had a pacemaker: and 1 had an acute myocardial infarction. Other than AF, there were no significant differences observed in emboligenic cardiac diseases between the two groups (Table 1).

Overall, 19 patients (28%) had transient aphasia with either hemiparesis or monoparesis, 16 (24%) had monoparesis without aphasia, and 32 (48%) had hemiparesis without aphasia (Table 2). Aphasia was observed more frequently in the AF group than in the non-AF group (67% vs 20%, p=0.003). Hemiparesis without aphasia was seen less frequently in the AF group than in the non-AF group (17% vs 55%, p=0.025).

Discussion

The present study showed that TIA patients with AF had aphasia more frequently than TIA patients without AF. Mohr et al (6, 7) reported that some patients with cardiogenic embolism showed an abrupt onset of a major hemispheric symptom, such as aphasia, hemianopia, or unilateral spatial neglect, which was followed within hours to days by a disappearance of most of the clinical manifestations. This phenomenon of rapid recovery was termed "a spectacular shrinking deficit (SSD)". Minematsu et al (8) reported that the SSD was closely related to cardiogenic brain embolism. TIAs with a major hemispheric symptom partly overlap with SSD, and therefore may be related to cardiogenic brain embolism. A cardiogenic embolus may be larger than an embolus from arterial disease. Therefore, patients with AF might have a transient embolic occlusion in the larger vessels, which leads to major hemispheric symptoms such as aphasia.

In the present study, hemiparesis without aphasia was more frequently found in the non-AF group than in the AF group. The etiology of the TIAs in the AF group is likely be cardioembolic. In TIA patients without emboligenic cardiac diseases, Hankey and Warlow (9) have proposed that the TIAs could be classified into lacunar and cortical TIA syndromes according to the clinical symptoms during the attack. Cortical TIA syndromes are associated with atheromatous disease in the ipsilateral extracranial ICA. On the other hand, lacunar TIA syndromes are caused by the involvement of the penetrating lenticulostriate arteries from the MCA. In our study, the etiology of the TIAs in the non-AF group included not only artery to artery embolism from carotid disease but also the involvement of lenticulostriate branches from the MCA, which often results in hemiparesis without major hemispheric symptoms. This would explain why the non-AF group had hemiparesis without aphasia more frequently than the AF group.

Harrison and Marshall reported that the duration of symptoms in TIA patients with AF tended to be longer than 60 minutes (10). In this study, 50% of the patients with AF had a TIA duration of more than 60 minutes. In 5 of 6 aphasic patients with AF, the TIAs lasted for over 60 minutes. Therefore, patients in AF with a TIA, who present with aphasia are likely to have a TIA of long duration.

Although internal carotid artery dissection is recognized as a cause of TIA (11), our study did not have any patients with internal carotid artery dissection. This is likely because in Japan TIAs and strokes due to internal carotid artery dissection are very rare (12).

Recently, the importance of other emboligenic factors that cause cerebral embolism has been recognized (13). Of particular interest these include: aortic arch atheromatous plaques, patent foramen ovale (PFO), and atrial septal aneurysms. Pop et al studied 72 consecutive TIA patients using

both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE). They concluded that TEE significantly increased the yield in visualizing potential intracardiac sources of emboli compared with TTE (14). In the present study, patients were not routinely evaluated by TEE, and thus these intracardiac lesions may have been overlooked. However, it was our intention to study the differences between patients with AF and without AF.

Thus, in conclusion, TIA patients with AF appear to be more likely than those without AF to have a major hemispheric syndrome such as aphasia.

Acknowledgments: This study was supported in part by Research Grants for Cardiovascular Disease (12A-4, 14C-1) from the Ministry of Health, Labor and Welfare of Japan.

References

1) Bogousslavsky J, Hachinski VC, Boughner DR, Fox AJ, Vinuela F, Barnett HJM. Cardiac and arterial lesions in carotid transient ischemic attacks. Arch Neurol **43**: 223–228, 1986.
2) de Bono DP, Warlow CP. Potential sources of emboli in patients with presumed transient cerebral or retinal ischemia. Lancet **1** (8216): 343–346, 1981.
3) Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham study. Stroke **27**: 1760–1764, 1996.
4) Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III Stroke **21**: 637–676, 1990.
5) Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med **325**: 445–453, 1991.
6) Mohr JP, Barnett HJM. Classification of ischemic strokes. in: Stroke: Pathophysiology, Diagnosis, and Management, vol; 1, Barnett HJM, Stein BM, Mohr JP, Yatsu FM, Eds. Churchill Livingstone, New York, 1986: 281–291.
7) Mohr JP, Gautier JC, Heir DB, Stein RW. Middle cerebral artery. in: Stroke: Pathophysiology, Diagnosis, and Management, vol.; 1, Barnett HJM, Stein BM, Mohr JP, Yatsu FM, Eds. Churchill Livingstone, New York, 1986: 377–450.
8) Minematsu K, Yamaguchi T, Omae T. "Spectacular shrinking deficit": Rapid recovery from a major hemispheric syndrome by migration of an embolus. Neurology **42**: 157–162, 1992.
9) Hankey GJ, Warlow CP. Lacunar transient ischaemic attacks: A clinically useful concept? Lancet **337**: 335–338, 1991.
10) Harrison MJ, Marshall J. Atrial fibrillation, TIAs, and completed strokes. Stroke **15**: 441–442, 1984.
11) Treiman GS, Treiman RL, Foran RF, et al. Spontaneous dissection of internal carotid artery: a nineteen-year clinical experience. J Vasc Surg **24**: 597–607, 1996.
12) Ichikawa H, Katoh T, Fukui T, Kawamura M, Sugita K. A case of cerebral infarction with dissection of the internal carotid and superior mesenteric arteries. Jpn J Stroke **18**: 409–414, 1996.
13) Feinberg WM, Albers GW, Barnett HJ, et al. Guidelines for the management of transient ischemic attacks. From the Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks of the Stroke council of the American Heart Association. Circulation **89**: 2950–2965, 1994.
14) Pop G, Sutherland GR, Koudstaal PJ, Sit TW, de Jong G, Roelandt JR. Transesophageal echocardiography in the detection of intracardiac embolic sources in patients with transient ischemic attacks. Stroke **21**: 560–565, 1990.

AJNR Am J Neuroradiol 24:427–435, March 2003

Topographic Distribution of Misery Perfusion in Relation to Internal and Superficial Borderzones

Shuji Arakawa, Kazuo Minematsu, Teruyuki Hirano, Yutaka Tanaka, Yasuhiro Hasegawa, Kohei Hayashida, and Takenori Yamaguchi

BACKGROUND AND PURPOSE: **Whether misery perfusion (MP) commonly accompanies brain borderzones (BZs) in patients with major cerebral artery occlusion remains unclear. We elucidated topographic patterns of chronic hemodynamic failure in such patients.**

METHODS: **Twenty-four patients with unilateral occlusion or severe stenosis (>75% in diameter) of the internal carotid artery (ICA) or middle cerebral arterial (MCA) trunk with minimal or no infarct underwent PET with ^{15}O-labeled gas inhalation. Mean cerebral blood flow (CBF), cerebral blood volume (CBV), cerebral metabolic rate of oxygen, oxygen extraction fraction (OEF), and CBV/CBF ratio were determined in the superficial BZs, internal BZ, and MCA territory excluding BZs. Values in BZs were standardized and compared with those in controls. Topographic distributions of regions with OEF greater than that in controls were determined.**

RESULTS: **Values in patients and controls were not significantly different. Topographic distributions included matched perfusion in 10 patients, MP in only the ipsilateral internal BZ in four, MP in both ipsilateral internal and superficial BZs in two, MP in the ipsilateral MCA territory including BZs in one, MP in the ipsilateral MCA territory including BZs and contralateral BZs in two, and MP in the ipsilateral MCA territories including BZs in five.**

CONCLUSION: **Only 25% of the patients had MP localized in affected BZs Although localized MP more frequently accompanied the internal BZ than other regions, no patient had elevated OEF in the superficial BZ alone. These results are inconsistent with clinical observations that 80% of BZ infarctions develop superficially. Thus, hemodynamic mechanisms may not cause most superficial BZ infarctions.**

Borderzone (BZ) infarcts or watershed infarcts are ischemic lesions that occur in the junction between two main arterial territories. These account for approximately 10% of all brain infarcts (1). Supratentorial BZs consist of three regions: 1) the anterior BZ, the superficial area between the territories of the middle cerebral artery (MCA) and anterior cerebral artery (ACA); 2) the posterior BZ, the superficial area between the territories of the MCA and the posterior cerebral artery (PCA); and 3) the internal BZ, the deep area between the territories of the cortical branches and the penetrators of the MCA. Hemodynamic theory has been emphasized as the most predominant mechanism of BZ infarction; it states that mild-to-moderate hypotension selectively diminishes perfusion in the BZs in patients with major cerebral artery occlusive disease, (2–4). Recently, several investigators have reported that many BZ infarcts cannot be explained by the hemodynamic theory, or they are supposed to be embolic; that is, emboli of a certain small size occlude terminal portions of the cortical branches and cause superficial watershed infarction (5–14). These conflicting observations indicate the need to reexamine the pathogenesis of BZ infarcts.

By using positron emission tomography (PET), cerebral perfusion and metabolism have been studied in patients with occlusive diseases of the internal carotid artery (ICA), but whether hemodynamic impairments

Received July 12, 2002; accepted after revision September 11.

From the Cerebrovascular Division, Department of Medicine (S.A., K.M., T.H., Y.T., Y.H., T.Y.) and Department of Diagnostic Radiology (K.H.), National Cardiovascular Center, Osaka, Japan.

Supported in part by Special Coordination Funds for Promoting Science and Technology (Encouragement of COE and Strategic Promotion System for Brain Science) from the Ministry of Education, Culture, Sports, Science and Technology of Japan; research grants for cardiovascular diseases 5A-5, 6A-1, 12A-2, and 12C-10 from the Ministry of Health, Labour and Welfare of Japan; and a research grant from the Japan Cardiovascular Research Foundation.

Presented at the 3rd World Stroke Congress, September 1–4, 1996, Munich, Germany.

Address reprint requests to: Kazuo Minematsu, MD, Cerebrovascular Division, Department of Medicine, National Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan.

localized to the BZ areas actually exist remains controversial. Leblanc et al (15) reported that, in seven patients with severe ICA stenosis, cerebral blood flow (CBF) and the CBF–cerebral blood volume (CBV) ratio was significantly decreased in the anterior BZ. Yamauchi et al (16) reported that, in nine patients with ICA occlusion and good collateral circulation through the anterior communicating (Acom) artery, CBF was significantly decreased, whereas the oxygen extraction fraction (OEF) was significantly increased in the territory of MCA and the surrounding BZs, especially in the posterior BZ. Both groups concluded that BZs might be selectively vulnerable to ICA occlusive diseases. On the other hand, Carpenter et al reported that, in 32 patients with either severe ICA stenosis or occlusion, CBV/CBF ratios and OEF in the BZ did not significantly differ from those in control subjects; these results indicated no evidence for selective hemodynamic impairments in BZs (17). Carpenter et al used BZ/MCA ratios to study whether patients with abnormal hemodynamics in the MCA territory have further selective abnormalities localized to the BZs. Again, their results are conflicting, although the patterns of collateral supply of the patients might be different among the studies, and variability in the arterial distributions of the brain might have influenced their results (18). Furthermore, the hemodynamics in the internal BZ was not examined in the previous PET studies.

The purpose of this study was to evaluate the topographic patterns of chronic hemodynamic failure in patients with occlusive disease of the major cerebral arteries, with special interest in the internal and superficial BZs. We also sought to elucidate the mechanisms and hemodynamic implications of BZ infarction.

Methods

Subjects

In the patients who were admitted to our hospital between January 1, 1992, and May 31, 1994, we performed PET studies in 24 patients. These patients had either unilateral occlusion or severe stenosis (>75% in diameter) of the ICA or the trunk of the MCA, with minimal or no infarction according to the CT and MR imaging findings. (Minimal infarction was defined as lacunar infarction or cortical/subcortical infarction smaller than 15 mm in diameter.) Excluded were patients with a cardiac source of emboli and those who had ischemic lesions in the BZ areas, as shown on CT and MR images. The study group included 19 men and five women, with a mean age of 66.0 years (range, 52–81 years). They comprised three patients with no ischemic episodes, four with transient ischemic attacks (TIAs) and 17 with minor completed strokes. In the patients with completed stroke or TIA, the potential mechanism of stroke or TIA was clinically judged and classified into the following categories: artery-to-artery (A-to-A) embolic, hemodynamic, and unclassified; these categories were modified from the NINDS classification of cerebrovascular disease III (19). The diagnostic criteria of each category have been described previously (20). A-to-A embolism was diagnosed in patients without a cardiac source of emboli when 1) intraluminal filling defects suggesting emboli or recanalization of the previously occluded arteries distal to the proximal arterial lesions (occlusion, severe stenosis, or ulceration) were confirmed angiographically or when 2) a hemorrhagic infarction was detected with CT or MR imaging. Hemodynamic TIA or stroke was diagnosed when 1) hemodynamic episodes such as orthostatic hypotension and excessive antihypertensive medication were evident immediately before stroke onset or when 2) fluctuation of neurologic signs and symptoms was accompanied by orthostatic hypotension or decrease in blood pressure. Patients whose conditions did not fit these criteria were grouped as unclassified.

Both CT and MR imaging were performed in all patients. In patients with TIA or minor completed stroke, the examinations were performed after their neurologic status became stable. MR imaging evaluation was performed by using a 1.5-T unit (MAGNETOM; Siemens, Erlangen, Germany). T1-weighted and T2-weighted images were obtained.

In 19 patients, arterial lesions of the neck and brain vessels were evaluated by means of conventional angiography or intra-arterial digital subtraction angiography. For the remaining five patients, intravenous digital subtraction angiography was performed in two patients with ICA stenosis. Both MR angiography and carotid sonography was performed in two patients with ICA occlusion and in one with MCA trunk occlusion. For the symptomatic patients, the evaluation of the cerebral artery was performed within 1 week of their admission to the hospital, and the results were confirmed in a repeat evaluation before the PET study to ensure that the proximal arterial lesion did not change. The extent of stenosis was obtained as the ratio of the diameter at the narrowest portion to the diameter at the distal portion that seemed normal. For the 19 patients who underwent conventional angiography or intra-arterial digital subtraction angiography, the most predominant route of blood flow to the affected MCA territory was evaluated and classified as blood flow through the stenotic lesion, the Acom artery, the posterior communicating (Pcom) artery, the ophthalmic artery, or the leptomeningeal anastomosis.

The cerebrovascular risk factors were hypertension in 21 patients, diabetes mellitus in eight, and hyperlipidemia in nine. Severe stenosis of the ICA were present in 10 patients; occlusion of ICA, in six; and severe stenosis or occlusion of MCA trunk, in eight. Infarction in the MCA territory was not evident on CT and MR images in two patients. Twelve patients had lacunes, whereas the other 10 patients had small cortical/subcortical infarcts in the MCA territory. In 21 symptomatic patients, neurologic deficits at onset were hemiparesis in 19, hemisensory disturbance in three, aphasia in five, and anosognosia or unilateral spatial neglect in two. The stroke or TIA mechanism was A-to-A embolic in five, hemodynamic in six, and unclassified in 10. Clinical and neuroradiologic data for the patients are summarized in Table 1.

PET studies

Regional CBF, OEF, cerebral metabolic rate of oxygen ($CMRO_2$), and CBV were measured by using a Headtome IV PET scanner (Shimadzu, Kyoto, Japan) with a spatial resolution of 4.5 mm at full width half maximum and the ^{15}O-labeled gas-inhalation technique (21, 22). An emission scan with an external ^{68}Ge-^{68}Ga ring source was corrected for the effects of tissue attenuation by using corresponding transmission scans. Transmission scanning was performing when a patient was in a supine position with his or her eyes closed. Two separate scans were performed during the continuous inhalation of ^{15}O-labeled carbon dioxide ($C^{15}O_2$) and molecular oxygen ($^{15}O_2$) for measurement of CBF and OEF, respectively. The third scan was obtained after a 2-minute inhalation of ^{15}O-labeled carbon monoxide ($C^{15}O$) for the measurement of CBV. During the scans, serial blood samples were obtained through a fine-gauge radial (or brachial) arterial catheter for measuring the arterial isotope activity, arterial oxygen content (O_2C), and arterial pCO_2. A value of $CMRO_2$ was calculated with the following equation: $CMRO_2 = CBF \times OEF \times O_2C$.

In the patients with stroke or TIA, PET was performed at least 3 weeks after the latest ischemic event, when their neu-

TABLE 1: Patient characteristics

Case No.	Age (y)/ Sex	Associated Conditions	Type of Ischemia	Mechanism	Neurologic Deficits*	CT/MRI Findings	Angiographic Findings	Main Flow to Affected MCA†	Other Collateral‡	PET Findings, Distribution of MP‡
1	66/M	HT, HLP	Completed stroke	Hemodynamic	L sensory deficit	Bil lacunar infarcts	R ICS	Antegrade flow	None	Matched perfusion (G1)
2	71/M	HT	Completed stroke	A-to-A embolism	L hemiparesis, L hemianopsia	R small cortical infact	R ICS	Antegrade flow	None	Matched perfusion (G1)
3	62/M	DM, HT, HLP, MI, ASO	Completed stroke	Unclassified	R hemiparesis, motor aphasia	L lacunar infarcts	L ICS	None	None	Affected IBZ and SBZ (G3)
4	66/M	DM, HT, AP, ASO	Completed stroke	Unclassified	R hemiparesis	L lacunar infarct	L ICS	Antegrade flow	Acom→L ACA	Matched perfusion (G1)
5	78/M	HT	Completed stroke	Unclassified	L hemiparesis, L sensory deficit	R small cortical infact	R ICS	Antegrade flow	None	Matched perfusion (G1)
6	81/F	HT, ASO, af	Completed stroke	Hemodynamic	R hemiparesis, R sensory deficit	L lacunar infarct	L ICS	None	None	Bil MCAt including BZ (G6)
7	66/F	HT	Asymptomatic			None	R ICS	None	None	Affected IBZ alone (G2)
8	63/F	HT, HLP	TIA	A-to-A embolism	R hemiparesis, motor aphasia	Bil lacunar infarcts	L ICS	Antegrade flow	Acom→L ACA	Matched perfusion (G1)
9	68/M	HT, HLP	TIA	Hemodynamic	L hemiparesis	Bil lacunar infarcts + R small cortical infact	R ICS	R opthalmic A→	Acom→R ACA	Affected MCAt including BZ + non-affected BZ (G5)
10	68/M	DM, HT, HLP	Completed stroke	A-to-A embolism	R hemiparesis	Bil lacunar infarcts + L small cortical infact	L ICS	Antegrade flow	None	Matched perfusion (G1)
11	62/M	DM, HT, HLP	Completed stroke	Unclassified	R hemiparesis	L lacunar infarct	L ICO	Acom→	None	Affected IBZ alone (G2)
12	52/F	DM, HT	Completed stroke	Unclassified	R hemiparesis, motor aphasia	L lacunar infarct	L ICO	Acom→	L PCA→LM	Affected IBZ and SBZ (G3)
13	70/M	HT	Completed stroke	A-to-A embolism	L hemiplegia, USN, anosgnosia	R small cortical infact	R ICO	R ACA→LM	A com→R ACA	Affected MCAt including BZ + non-affected BZ (G5)
14	69/M	HT	TIA	Hemodynamic	L hemiparesis	R small cortical infact	R ICO	R opthalmic A→	A com→R ACA	Bil MCAt including BZ (G6)
15	75/M	HT, AP	Completed stroke	A-to-A embolism	L hemiparesis	R small cortical infact	R ICO	None	None	Affected IBZ alone (G2)
16	69/M	DM	Completed stroke	Unclassified	Global aphasia	L small cortical infact	L ICO	Pcom→	None	Bil MCAt including BZ (G6)
17	58/M	DM, ASO	TIA	Hemodynamic	R hemiparesis, motor aphasia	L lacunar infarct	L MCS	L ACA, PCA→LM	A com→L ACA	Bil MCAt including BZ (G6)
18	60/M	DM, HT	Completed stroke	Unclassified	R hemiparesis	L lacunar infarct	L MCO	L ACA, PCA→LM	None	Affected MCAt including BZ (G4)
19	64/M	HT	Completed stroke	Hemodynamic	R hemiparesis	L lacunar infarct	L MCO	None	None	Matched perfusion (G1)
20	56/F	HT, HLP	Completed stroke	Unclassified	L hemiparesis	R lacunar infarcts	R MCO	R ACA→LM	None	Affected MCAt including BZ + non-affected BZ (G5)
21	67/M	HT, HLP	Completed stroke	Unclassified	R hemiparesis, R hemianopsia, anosognosia	L small cortical infacts	L MCO	L ACA, PCA→LM	None	Matched perfusion (G1)
22	71/F	HT, HLP	Completed stroke	Unclassified	R hemiparesis	None	L MCO	L ACA→LM	A com→L ACA	Affected IBZ alone (G2)
23	54/M	DM, HT	Asymptomatic			Bil lacunar infarcts	R MCO	R ACA, PCA→LM	None	Matched perfusion (G1)
24	69/M		Asymptomatic			L small cortical infacts	L MCO	L ACA→LM	None	Matched perfusion (G1)

Note.—Abbreviations are as follows: af indicates atrial fibrillation; AP, angina pectoris; ASO, arteriosclerosis obliterans; DM, diabetes mellitus; HLP, hyperlipidemia; IBZ, internal BZ; ICO, occlusion of the ICA; ICS, severe stenosis of the ICA; MCAt, MCA territory; MCO, occlusion of the M1 portion; MCS, severe stenosis of the M1 portion; HT, hypertension; MI, old myocardial infarction; SBZ, superficial BZ; USN, unilateral spatial neglect; Bil, bilateral.

* Defects at the onset in patients with TIA and at the time of hemodynamic studies in other patients.

† In patients who underwent conventional angiography or intra-arterial digital subtraction angiography.

‡ Number shows the type of the MP distribution.

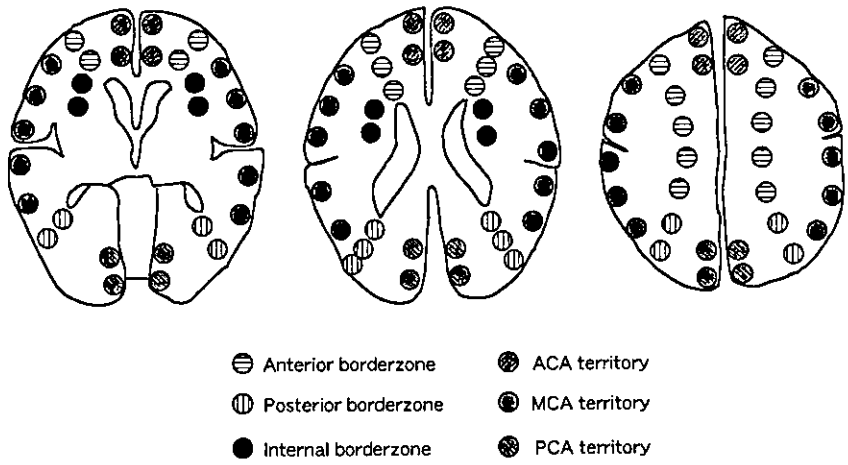

FIG 1. Location of regions of interest. These are divided into six areas on the basis of the idealized standard concept of arterial distributions of the brain, as follows: territories of the ACA, MCA, PCA, anterior BZ (between the territories of the ACA and MCA), posterior BZ (between the territories of the MCA and PCA), and internal BZ (between the territories of the cortical branches and penetrators of the MCA).

rologic conditions became stable. In asymptomatic patients, PET was performed at least 4 weeks after the first CT examination. Four healthy volunteers with a mean age of 47.5 years (range, 30–63 years) underwent PET studies to determine the normal values. These patients consisted of three men and one woman who were free of any cerebrovascular risk factors and neurologic deficits. No focal brain lesions were detected with CT and MR imaging in these subjects.

As shown in Figure 1, we analyzed the PET images in three tomographic planes parallel to the orbitomeatal line: 1) the levels of the basal ganglia and thalamus, 2) the body of the lateral ventricle, and 3) the centrum semiovale. Each image was examined by placing 18–20 circular regions of interest (ROIs) that were 9 mm in diameter. According to the atlas of Damasio (23), ROIs were placed at the territories of the ACA, MCA, PCA, anterior BZ, posterior BZ, and internal BZ. The mean values of each PET parameter in these vascular territories were obtained. To detect a selective BZ hemodynamic impairment, we calculated the ratios of the PET parameter in each BZ to that in the ipsilateral MCA territory and used them as standardized values. According to their arterial lesions, the patients were classified into the following three groups: 1) patients with severe stenosis of the ICA (ICA stenosis group), 2) those with occlusion of the ICA (ICA occlusion group), and 3) those with severe stenosis or occlusion of MCA trunk (MCA group). The averages of absolute and standardized PET values obtained in each group were compared with those in the healthy volunteers. We also calculated the 95% confidence interval of OEF in each vascular territory of the control group and defined misery perfusion (MP) as the legions with OEF above this interval. We determined the topographic distribution of the MP in the patient groups.

Statistical Analysis

Statistical analyses were performed by using an analysis of variance (ANOVA) with Scheffé F correction. A P value of $< .05$ was considered to indicate a significant difference.

Results

Comparison of the Absolute and Standardized Values

Table 2 shows the mean and SD values for regional CBF, CBV, $CMRO_2$, OEF, and CBF/CBV ratio for the patient and control groups. In the hemisphere ipsilateral to the vascular lesion, all of the patient groups had a significantly decreased regional CBF and $CMRO_2$, both in the BZs and MCA territory. All patient groups tended to have an elevated OEF and a prolonged CBF/CBV ratio, both in the BZs and MCA territory. The ICA occlusion group alone had a significantly increased OEF in all vascular territories, except for anterior BZ. This group also had a significantly prolonged CBF/CBV ratio in those areas, except for the posterior BZ, as compared with values in the control group. In the hemisphere contralateral to the vascular lesion, the CBF tended to decrease, while the OEF tended to increase both in the BZs and the MCA territory. There were no significant differences in each PET parameter in either hemisphere among the patient groups.

Table 3 shows the standardized values for each PET parameter in the three patient groups and control subjects. There were no significant differences among the groups.

Topographic Distribution of the MP

Topographic distributions of the areas with elevated OEF were classified into six patterns as shown in Fig 2. Matched perfusion throughout the brain was found in 10 patients (group 1), MP was found in only the ipsilateral internal BZ in four (group 2), MP was found in both the ipsilateral internal and superficial BZs in two (group 3), MP was found in the ipsilateral MCA territory including BZs in one (group 4), MP was found in the ipsilateral MCA territory including BZs and the contralateral BZs in two (group 5), and MP was found in the bilateral MCA territories including BZs in five (group 6). MP localized in the ipsilateral BZs (groups 2 and 3) was demonstrated in six of 24 patients. Although the internal BZ was most frequently accompanied with localized MP, as compared with the other regions, no patients had elevated OEF in the superficial BZs alone.

Table 4 shows the topographic pattern of MP by patient group. MP in only the ipsilateral BZs was seen in all groups, 20% of the patients in the ICA stenosis group, 50% in the ICA occlusion group, and 12.5% in the MCA group. There was no significant difference regarding the distribution of the areas with elevated OEF among the groups (contingency table analysis, $P = .42$).

TABLE 2: Values for regional CBF, CBV, CMRO2, OEF, and CBF/CBV ratio of patients and control subjects

Value	Ipsilateral Side to the Vascular Lesion					Contralateral Side to the Vascular Lesion				
	Hemisphere	Anterior BZ	Posterior BZ	Internal BZ	MCA Territory	Hemisphere	Anterior BZ	Posterior BZ	Internal BZ	Non-BZ
CBF (mL/100 g/min)										
Control	47.5 ± 9.4	44.0 ± 8.1	45.9 ± 9.2	43.1 ± 12.9	53.6 ± 11.9	47.5 ± 9.4	44.0 ± 8.1	45.9 ± 9.2	43.1 ± 12.9	53.6 ± 11.9
ICA stenosis	35.1 ± 6.1*	29.7 ± 5.0*	32.5 ± 6.1*	28.6 ± 5.8*	38.4 ± 8.0*	37.8 ± 5.2*	32.3 ± 4.6*	34.9 ± 5.5*	30.4 ± 3.4*	43.2 ± 7.2
ICA occlusion	30.7 ± 5.5*	26.5 ± 6.3*	30.7 ± 4.5*	26.9 ± 5.7*	31.8 ± 7.0*	34.3 ± 4.4*	30.7 ± 4.7*	32.6 ± 7.0*	29.2 ± 3.1*	37.7 ± 5.9*
MCA lesion	35.4 ± 3.4*	31.2 ± 4.0*	33.1 ± 3.3*	29.9 ± 4.8*	36.6 ± 4.6*	38.6 ± 4.6	33.5 ± 4.3*	36.5 ± 5.9	33.2 ± 7.0	41.7 ± 4.9
CBV (mL/100 g)										
Control	3.64 ± 0.41	3.06 ± 0.60	3.47 ± 0.40	2.45 ± 0.51	4.08 ± 0.53	3.64 ± 0.41	3.06 ± 0.60	3.47 ± 0.40	2.45 ± 0.51	4.08 ± 0.53
ICA stenosis	3.41 ± 0.46	2.67 ± 0.60	2.94 ± 0.76	2.51 ± 0.76	3.72 ± 0.62	3.35 ± 0.40	2.55 ± 0.42	3.16 ± 0.61	2.42 ± 0.55	3.79 ± 0.34
ICA occlusion	4.04 ± 0.91	3.24 ± 1.10	3.37 ± 0.70	3.34 ± 0.98	3.99 ± 0.88	3.37 ± 0.34	2.58 ± 0.71	3.31 ± 0.66	2.64 ± 0.66	3.32 ± 0.35*
MCA lesion	3.65 ± 0.39	2.94 ± 0.52	3.33 ± 0.56	2.87 ± 1.28	3.93 ± 0.52	3.55 ± 0.65	3.00 ± 0.35	2.83 ± 0.95	2.78 ± 0.47	3.67 ± 0.39
$CMRO_2$ (mL/100 g/min)										
Control	34.0 ± 0.46	31.5 ± 5.1	35.8 ± 4.9	29.8 ± 5.5	37.7 ± 4.3	34.0 ± 0.46	31.5 ± 5.1	35.8 ± 4.9	29.8 ± 5.5	37.7 ± 4.3
ICA stenosis	25.9 ± 2.6*	22.2 ± 2.9*	25.6 ± 4.4*	21.3 ± 3.3*	28.2 ± 3.0*	27.9 ± 3.3*	24.1 ± 3.0*	27.0 ± 4.4*	23.4 ± 3.3*	31.7 ± 4.6
ICA occlusion	27.3 ± 2.7*	22.8 ± 3.2*	29.0 ± 2.7*	23.3 ± 4.3	28.9 ± 3.4*	29.2 ± 1.8	26.3 ± 3.3	28.6 ± 3.4*	24.8 ± 1.4	32.2 ± 3.2
MCA lesion	27.2 ± 2.2*	23.5 ± 1.7*	26.7 ± 3.3*	22.4 ± 3.9*	28.9 ± 4.2*	29.2 ± 1.7*	24.3 ± 2.5*	28.8 ± 2.2*	24.2 ± 2.7*	33.4 ± 5.5
OEF										
Control	41.9 ± 6.4	42.0 ± 7.5	45.2 ± 5.8	41.0 ± 6.3	41.4 ± 6.7	41.9 ± 6.4	42.0 ± 7.5	45.2 ± 5.8	41.0 ± 6.3	41.4 ± 6.7
ICA stenosis	47.1 ± 6.5	48.6 ± 8.0	49.8 ± 7.9	48.5 ± 8.1	46.2 ± 6.1	46.4 ± 5.7	47.5 ± 7.0	48.0 ± 7.1	47.6 ± 5.4	45.7 ± 5.4
ICA occlusion	53.7 ± 5.4*	52.2 ± 4.8	56.5 ± 4.9*	52.6 ± 5.7*	54.4 ± 6.9*	51.1 ± 2.8*	51.1 ± 3.1	52.9 ± 4.7	50.3 ± 3.0	50.9 ± 2.9*
MCA lesion	48.8 ± 5.1	49.0 ± 5.4	50.7 ± 5.7	48.7 ± 5.1	49.4 ± 5.4	47.3 ± 5.8	46.0 ± 6.3	50.8 ± 5.8	48.5 ± 7.4	46.8 ± 6.1
CBF/CBV ratio (/min)										
Control	0.078 ± 0.016	0.071 ± 0.016	0.078 ± 0.013	0.060 ± 0.014	0.078 ± 0.013	0.078 ± 0.016	0.071 ± 0.016	0.078 ± 0.013	0.060 ± 0.014	0.078 ± 0.013
ICA stenosis	0.101 ± 0.019	0.093 ± 0.019	0.098 ± 0.036	0.090 ± 0.026	0.101 ± 0.024	0.093 ± 0.022	0.084 ± 0.018	0.096 ± 0.026	0.080 ± 0.024	0.093 ± 0.025
ICA occlusion	0.135 ± 0.039*	0.130 ± 0.049*	0.111 ± 0.037	0.121 ± 0.036*	0.130 ± 0.032*	0.101 ± 0.018	0.088 ± 0.028	0.108 ± 0.025	0.088 ± 0.023	0.090 ± 0.015
MCA lesion	0.106 ± 0.016	0.099 ± 0.023	0.102 ± 0.021	0.100 ± 0.039	0.111 ± 0.020	0.095 ± 0.014	0.092 ± 0.014	0.080 ± 0.031	0.090 ± 0.020	0.091 ± 0.013

Note.—Values are the mean ± SD.

* $P < .05$, different from control as determined by means of ANOVA with the Scheffé F test.

TABLE 3: Standardized values for regional CBF, CBV, CMRO2, OEF, and CBF/CBV ratio of patients and control subjects

Value	Ipsilateral Side to the Vascular Lesion			Contralateral Side to the Vascular Lesion		
	ABZ/MCA	PBZ/MCA	IBZ/MCA	ABZ/MCA	PBZ/MCA	IBZ/MCA
CBF						
Control	0.83 ± 0.06	0.86 ± 0.09	0.80 ± 0.07	0.83 ± 0.06	0.86 ± 0.09	0.80 ± 0.07
ICA stenosis	0.78 ± 0.10	0.86 ± 0.11	0.75 ± 0.10	0.76 ± 0.07	0.82 ± 0.13	0.71 ± 0.08
ICA occlusion	0.83 ± 0.09	0.98 ± 0.09	0.83 ± 0.08	0.82 ± 0.05	0.86 ± 0.08	0.79 ± 0.12
MCA lesion	0.86 ± 0.11	0.91 ± 0.09	0.83 ± 0.15	0.80 ± 0.06	0.87 ± 0.08	0.79 ± 0.11
CBV						
Control	0.75 ± 0.10	0.86 ± 0.12	0.60 ± 0.09	0.75 ± 0.10	0.86 ± 0.12	0.60 ± 0.09
ICA stenosis	0.73 ± 0.19	0.81 ± 0.22	0.70 ± 0.24	0.68 ± 0.12	0.84 ± 0.17	0.64 ± 0.15
ICA occlusion	0.81 ± 0.13	0.86 ± 0.19	0.81 ± 0.30	0.78 ± 0.22	1.04 ± 0.27	0.79 ± 0.18
MCA lesion	0.75 ± 0.13	0.85 ± 0.14	0.72 ± 0.30	0.82 ± 0.11	0.77 ± 0.25	0.76 ± 0.13
$CMRO_2$						
Control	0.83 ± 0.06	0.95 ± 0.07	0.79 ± 0.10	0.83 ± 0.06	0.95 ± 0.07	0.79 ± 0.10
ICA stenosis	0.79 ± 0.09	0.91 ± 0.11	0.76 ± 0.09	0.77 ± 0.09	0.86 ± 0.13	0.74 ± 0.06
ICA occlusion	0.79 ± 0.07	1.01 ± 0.05	0.78 ± 0.09	0.82 ± 0.05	0.90 ± 0.09	0.78 ± 0.10
MCA lesion	0.83 ± 0.14	0.93 ± 0.08	0.78 ± 0.10	0.74 ± 0.11	0.88 ± 0.15	0.74 ± 0.13
OEF						
Control	1.01 ± 0.03	1.10 ± 0.08	0.99 ± 0.07	1.01 ± 0.03	1.10 ± 0.08	0.99 ± 0.07
ICA stenosis	1.05 ± 0.09	1.08 ± 0.04	1.05 ± 0.09	1.04 ± 0.07	1.05 ± 0.06	1.04 ± 0.06
ICA occlusion	0.97 ± 0.05	1.05 ± 0.09	1.00 ± 0.13	1.00 ± 0.03	1.04 ± 0.06	0.99 ± 0.05
MCA lesion	0.99 ± 0.06	1.03 ± 0.04	0.99 ± 0.12	0.98 ± 0.03	1.09 ± 0.03	1.04 ± 0.06
CBF/CBV ratio						
Control	0.91 ± 0.09	1.00 ± 0.07	0.76 ± 0.11	0.91 ± 0.09	1.00 ± 0.07	0.76 ± 0.11
ICA stenosis	0.96 ± 0.30	0.98 ± 0.33	0.94 ± 0.36	0.93 ± 0.19	1.08 ± 0.34	0.90 ± 0.36
ICA occlusion	0.98 ± 0.22	0.86 ± 0.15	0.95 ± 0.38	0.97 ± 0.28	1.20 ± 0.26	1.00 ± 0.37
MCA lesion	0.91 ± 0.21	0.92 ± 0.10	0.88 ± 0.26	1.02 ± 0.21	0.88 ± 0.35	0.99 ± 0.14

Note.—ABZ indicates the anterior BZ; IBZ, internal BZ; PBZ, posterior BZ. No significant differences were observed between the four groups (Kruskal-Wallis test).

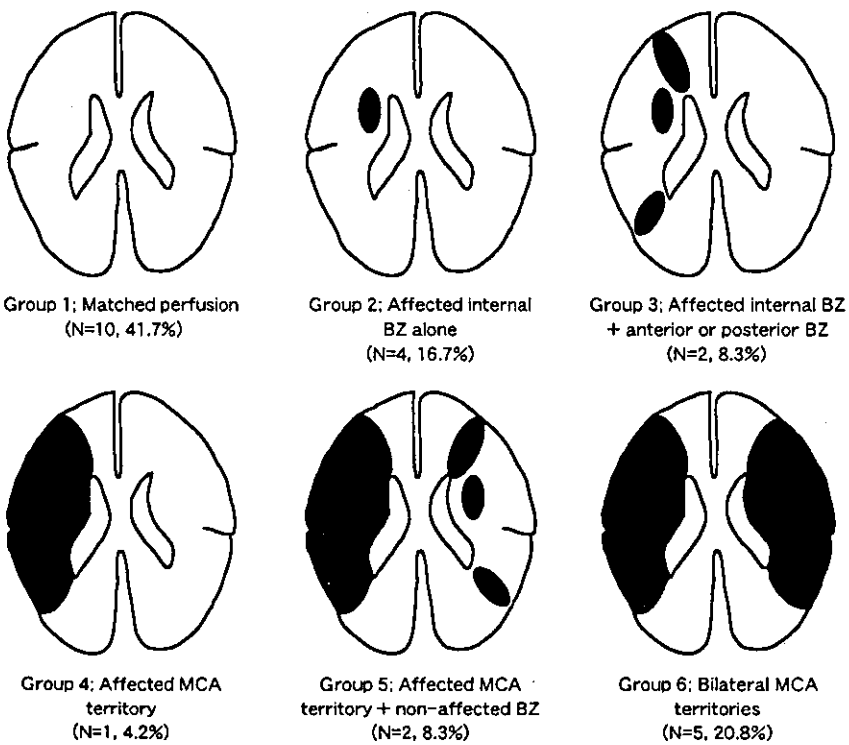

FIG 2. Distribution of MP in unilateral occlusive disease of the major cerebral arteries.

Table 5 shows the relationship of the topography of MP to the most predominant routes of blood flow to the affected MCA territory. Patients with antegrade flow through the ICA had matched perfusion. Patients with collateral flow crossing through the Acom artery to the MCA had MP in only the BZ of the affected hemisphere. Patients whose affected MCA territory was perfused through only the leptomenin-

TABLE 4: Distribution of MP in each patient group

Group	ICA Stenosis	ICA Occlusion	MCA Lesion*	Total
1	6	0	4	10
2	1	2	1	4
3	1	1	0	2
4	0	0	1	1
5	0	1	1	2
6	2	2	1	5
Total	10	6	8	24

* MCA lesions include severe stenosis or occlusion of the trunk of the MCA.

TABLE 5: Distribution of MP according to the collateral flow patterns

Group	Main Route of Blood Flow to the Affected MCA Territory				Total
	Antegrade	Acom	Lept	OA/Pcom	
1	5	0	4	0	9
2	0	1	1	0	2
3	0	1	0	0	1
4	0	0	1	0	1
5	0	0	2	0	2
6	0	0	1	3	4
Total	5	2	9	3	19

Note.—Lept indicates leptomeningeal anastomosis; OA, ophthalmic artery.

geal collateral channels had various topographies of the MP. Patients whose affected MCA territory was perfused through the ophthalmic or Pcom artery had the MP in both MCA territories. There was a significant difference in the topography of the area with an elevated OEF among the collateral flow patterns (contingency table analysis, $P < .05$).

Discussion

When we analyzed the standardized values of the PET parameters, we found no evidence that selective hemodynamic failure consistently occurs in the internal and superficial BZ areas. A small number of patients with ICA/MCA occlusive disease, 25% in the present series, had elevated OEF localized in the BZ areas, which always included the internal one. The internal BZ area was more frequently accompanied by localized MP than were the other regions. On the other hand, no patients had elevated OEF in only superficial BZ areas. These results were inconsistent with the clinical observation that approximately 80% of BZ infarctions develop superficially (4). Superficial BZ infarction may not be caused by a hemodynamic mechanism.

A selection bias of the patients may possibly have influenced the present results. Our classification of stroke mechanisms was derived without knowledge of the distribution of infarcts on CT and MR images, and therefore, they not affected by the neuroimaging results. A potential stroke mechanism in the present patients was sometimes an A-to-A embolic one (five of 24 patients). Only six of the 24 patients had a clinical diagnosis of a condition caused by the hemodynamic mechanism. However, none of these six (patients 1, 6, 9, 14, 17, 19) had the localized MP in the BZ areas. On the other hand, of five patients whose stroke mechanism was A-to-A embolic, only one (patient 15) had elevated OEF in the internal BZ alone. These results suggest that patient selection, or the potential mechanism diagnosed before the PET studies, did not directly influence the PET results.

van der Zwan et al (18) reported anatomic variations in vascular territories on the basis of findings from an autopsy series. This raised the possibility that the location of ROIs might be sometimes inaccurate because individual arterial territories cannot be identified in vivo. This is an unavoidable problem in PET studies that focused on the regional hemodynamic status in watershed areas. Another problem was the inadequate matching of ages between our patients and control subjects. We examined four healthy controls to determine the normal values of the PET parameters. The control data obtained from the present series were fairly comparable with those determined with similar PET equipment (24). In the PET studies, our control subjects were younger than the patients (47.5 years ± 13.8 and 66.0 years ± 7.0, respectively). This difference could imply that the control values were not appropriate for comparisons with the patient data. However, we did not detect any age-related change in the PET parameters. Previous PET studies have demonstrated that gray matter CBF, CBV, and/or $CMRO_2$ decrease with advancing age, but gray matter OEF and CBV/CBF (or CBF/CBV) and all PET parameters in the white matter remain fairly stable (21, 25–27). Therefore, at least for OEF and CBV/CBF, the values in control subjects can be used as the standard in evaluating the hemodynamic state in patients.

As shown in Table 5, the main route of blood flow to the affected MCA territory had a significant relationship to topographic pattern of the MP. All five patients who had an antegrade flow through the stenotic ICA also had matched perfusion throughout the brain. The two patients with collateral flow through the Acom artery to the affected MCA territory also had MP in only the affected BZ areas, which always included the internal one. Nine patients whose affected MCA territory was perfused through the leptomeningeal anastomosis alone have a variety of topographic patterns of the MP. The remaining three patients with an ophthalmic artery or a Pcom artery as a collateral channel to the affected MCA territory had MP of the bilateral MCA territory. In Table 5, six patients had MP in the contralateral MCA territory (group 5 or 6). In four of these patients, the Acom artery was also functioning as a collateral channel, but in the remaining two (patients 16 and 20), the affected hemisphere was not perfused from the contralateral ICA. Therefore, it was difficult to explain the MP of the contralateral MCA territory on the basis of the collateral circulation in these two cases. After all, in 17 of 19 patients in Table 5, the relation-