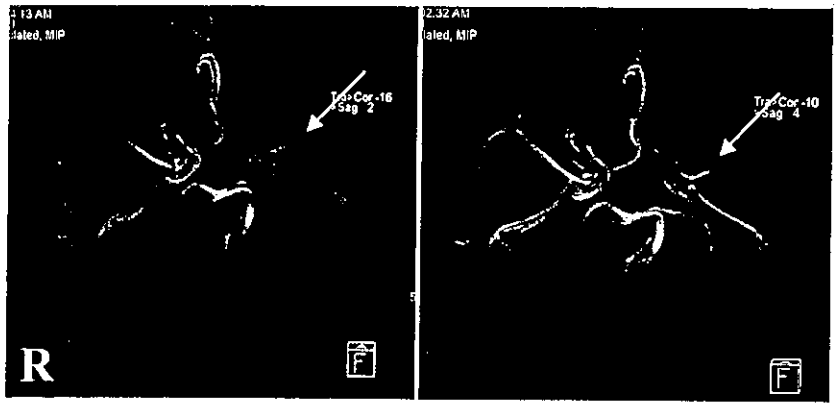

図 1　発症から 2 時間後（左）および 5 時間 30 分後（右）の MRA 所見
左中大脳動脈は起始部より閉塞し(矢印), 5 時間 30 分後も閉塞したまま(矢印）であった。

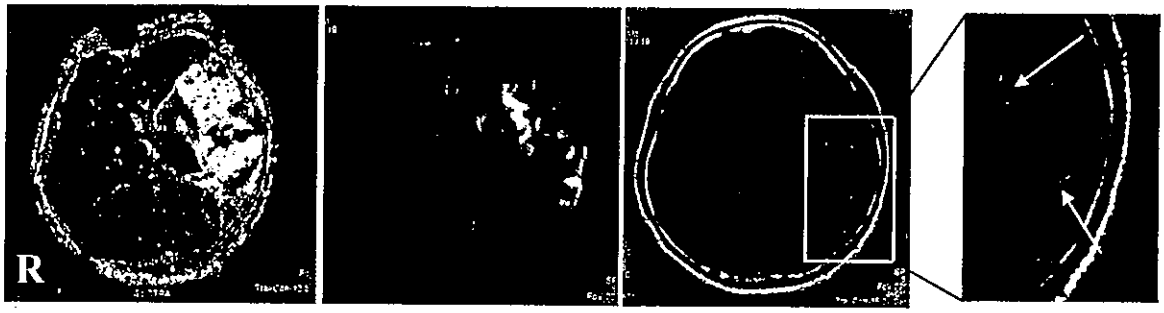

図 2　発症 2 時間後の MRI 所見
perfusion 画像（左）で中大脳動脈の支配領域で広範囲に灌流時間が遅延していた。diffusion 画像（中）では尾状核や島，大脳皮質および白質の一部が高信号を呈していた。FLAIR 画像（右）では閉塞血管は高信号に描出されていたが（拡大図の矢印）脳実質に明らかな異常所見を認めなかった。

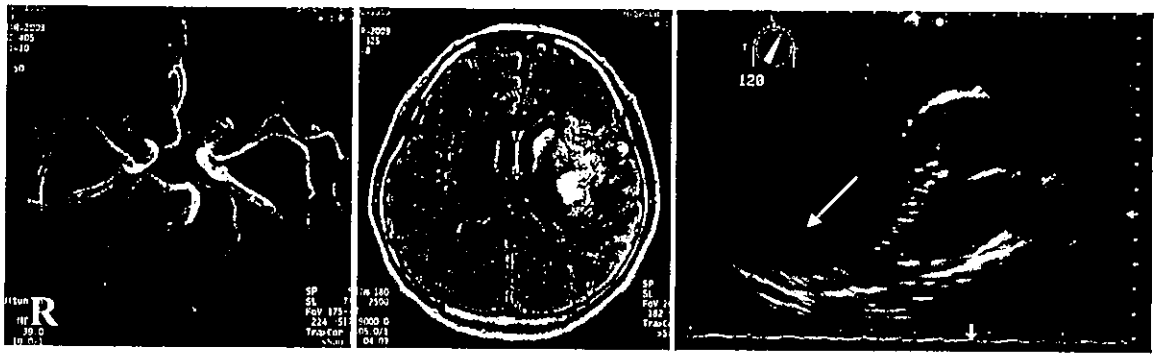

図 3　発症 6 日後の MRA，MRI および経食道心エコー所見
閉塞部位は再開通し（左），入院時の diffusion 画像にほぼ一致する部位に，FLAIR 画像（中）で高信号の病変を認めた。経食道心エコー（右）では心尖部の左心室内腔に血栓を認めた。

え，施行しないこととなり，エダラボンの点滴静注とアスピリン 330 mg の投与により治療を開始した。発症 5 時間 30 分後も再開通は認められず，11 時間 30 分後には，右上肢の筋力が 1/5 まで低下した。ただちに低分子デキストランの投与を行い，4 時間後には 4/5 に回復した。発症翌日の朝から意識レベルが低下し（JCS 3 から 10 で変動），48 時間程度持続した後，徐々に清明となった。第 6 病日の MRA では，中大脳動脈は再開通しており（図 3, 左），不均一な信号強度の虚血病巣と点状の出血性梗塞を認めた（図 3，中）。その後筋力はほぼ正常に復し，高次脳機能も SLTA(Standard Language Test of Apha-

sia）はほぼ正答率100%，WAIS-R（Wechsler Adult Intelligence Scale-Revised）でもIQは117で，「算数でやや難がある」のみのレベルとなった。また，入院中の経食道心エコーで，心筋梗塞のため壁運動の悪い心尖部に血栓と考えられる病変があり（図3，右），これによる心原性脳塞栓症と考えた。再発予防のためワルファリンの投与を開始した後，自宅へ退院した。

考　　察

今回われわれは，エダラボンとアスピリンの併用療法が奏効した左心室内血栓による心原性脳塞栓症の1例を経験した。本症例のような，主要血管の閉塞による脳梗塞の急性期には血栓溶解薬であるt-PAの経静脈的投与[1]あるいはプロウロキナーゼの経動脈的投与[2]の有効性が示されているが，わが国ではその使用が認可されていない。それ以外には，脳梗塞の急性期治療として抗血小板薬のアスピリンの有効性が示されているが，臨床病型別にその効果が詳しく検討されているとはいえず，その作用は強力なものではないとされる[3,4]。特に心房細動の合併例では無効であると報告されており，心原性脳塞栓症に対する効果は今後慎重に検討する必要がある[5]。また，ヘパリンについては，急性の再発を減らす効果はあっても，出血合併症がその効果を打ち消してしまう可能性が高いと考えられ，現時点においては積極的な使用は推奨されていない[6]。一方，現在わが国のみで使用可能な脳保護薬のエダラボンは，急性期からの使用により単独でも効果があることが実証されているが，抗凝固・血小板作用を有さないので，心原性脳塞栓症において急性期の再発を抑制できるか否かについて疑問が残る。以上より，現時点において，心原性脳塞栓症の急性期治療はエダラボンを基本としてアスピリンあるいは症例に応じてヘパリンの併用を行うのが適切と考えた。

本症例においては，少なくとも発症から約5時間30分以降に閉塞血管が再開通したと考えられるが，点状の出血性梗塞像を示したのみであること，経胸壁からのアプローチでは検出できなかった心室内血栓が経食道心エコーで明らかとなったことが特徴的であった。エダラボンは神経および血管内皮細胞に対して保護作用を有するとされ，血栓溶解療法のtherapeutic time windowを延長する効果が期待されている。今後，特に発症6時間以降に閉塞血管が自然再開通した症例について症例を蓄積し，出血性脳梗塞の発症頻度などにエダラボンの使用が影響を与えるか否か検討していく必要があると考えた。心室内血栓については，一般的に経胸壁からのエコー検査で観察可能と考えられているが，本症例では経食道からのアプローチでのみ観察可能であり，心筋梗塞後の脳梗塞の塞栓源検索にも必須の検査の1つであることが再確認された。

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脳卒中患者におけるT2* 強調画像を用いた微小出血の検討

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I. 緒　言

脳卒中の診断や病態把握には脳MRIが広く用いられているが，最近脳MRI診断法の一つの撮像法としてGradient Echo (GE) 法により撮像されるT2* (T-two-star) 強調画像が用いられるようになった。T2* 強調画像は出血性病変の検出力が極めて高く，特に無症候性微小出血の検出力が他のMRI画像に比べて各段に優れている。これまでに脳卒中患者において微小出血の頻度が高いことが報告され，微小出血を早期に発見することの持つ臨床的意義が注目を集めている。今回，当院に入院した急性期脳卒中患者においてT2* 強調画像を撮像し，微小出血の頻度および微小出血を認める症例の臨床的特徴を検討した。

II. 対象と方法

当院に平成14年10月～12月に入院し頭部MRI T2* 強調画像を撮像し得た急性期脳卒中連続45例（68.9±11.2歳）を対象とした。脳卒中臨床病型はラクナ梗塞（17例），アテローム血栓性脳梗塞（7例），心原塞栓性脳梗塞（3例），脳出血（18例）に分類した。脳卒中初発例が31例，再発例が14例であった。初発例のうちラクナ梗塞の1例は心房細動のためワルファリンを内服していた。再発例のうち4例は初発の脳梗塞後に抗血小板薬を内服していた。これらの症例について1.0 Tesla MRI (SIEMENS社，MAGNETON Harmony) を用いてT2* 強調画像軸位断にて無症候性微小出血の有無を評価した。またFLAIR画像軸位断で大脳白質病変の程度を評価し，Fazekas分類を用いgrade 0 (absent)，1 (punctate)，2 (early confluent)，3 (confluent) に分類した[1]。またMRアンギオグラフィー (MRA) にて頭蓋内主要血管の狭窄度を評価し，軽度（狭窄度50%未満），中等度（50%以上70%未満，信号途絶なし），高度（70%以上，信号途絶あり），閉塞（信号完全途絶）に分類した。臨床病型別の微小出血の頻度，脳卒中初発・再発例の微小出血の頻度，微小出血の有無と大脳白質病変の程度や頭蓋内主要血管の狭窄の程度との関連を検討した。

III. 結　果

MRI T2* 強調画像において微小出血を認めた症例は15例であった（33.3%）（図1）。臨床病型別では，ラクナ梗塞17例中3例（17.6%），アテローム血栓性脳梗塞7例中1例（14.3%），心原塞栓性脳梗塞3例中0例（0%），脳出血18例中11例（61.1%）に微小出血を認めた（表1）。微小出血を認める群は認めない群と比較し，有意に大脳白質病変が高度であった（Fazekas分類，1.92±0.95 vs 0.53±0.70，Mann-WhitneyのU検定，P=0.0002）が，MRAで評価した頭蓋内血管の狭窄の程度には差がなかった（Mann-WhitneyのU検定）。微小出血は脳卒中初発例（6/31例，19.4%）よりも再発例（9/14例，64.3%）において有意に高頻度に認められた（χ^2 独立性の検討，P=0.0009）（表2）。微小出血を認めた再発例は脳出血再発（5例）が最も多く，ついでラクナ梗塞後ラクナ梗塞3例，ラクナ梗塞後脳出血1例であった（表3）。

一方，微小出血を認めた初発例も脳出血（5例）が最も多く，ついでアテローム血栓性脳梗塞1例であった（表3）。発症前よりワルファリンを内服していた初発例では微小出血を認めなかった。また，初回の脳梗塞後に抗血小板薬を内服していた4例の再発例のうち微小出血を認めたのは2例であった。

IV. 考　察

近年，脳卒中患者においてT2* 強調画像で微小出血を高頻度に認めることが報告されるようになっており，特に脳出血やラクナ梗塞との関連が指摘されている[2)-7)]。脳出血およびラクナ梗塞はともに脳細動脈の障害を基盤とする病態であることから微小出血の存在は脳細動脈病変との関連が指摘されている。症例数が

Tatsunari Sasada, Hiromitsu Naka, Masaya Oda, Eiichi Nomura, Yoshimasa Sueda, Naokado Ikeda, Shinichi Wakabayashi, Chieko Wakabayashi, Hiroshi Kajikawa: Evaluation of microbleeds on T2*-weighted images in patients with stroke. Department of Neurosurgery, Neurology, and Radiology, Suiseikai Kajikawa Hospital.
翠清会梶川病院脳神経外科／脳神経内科／放射線科

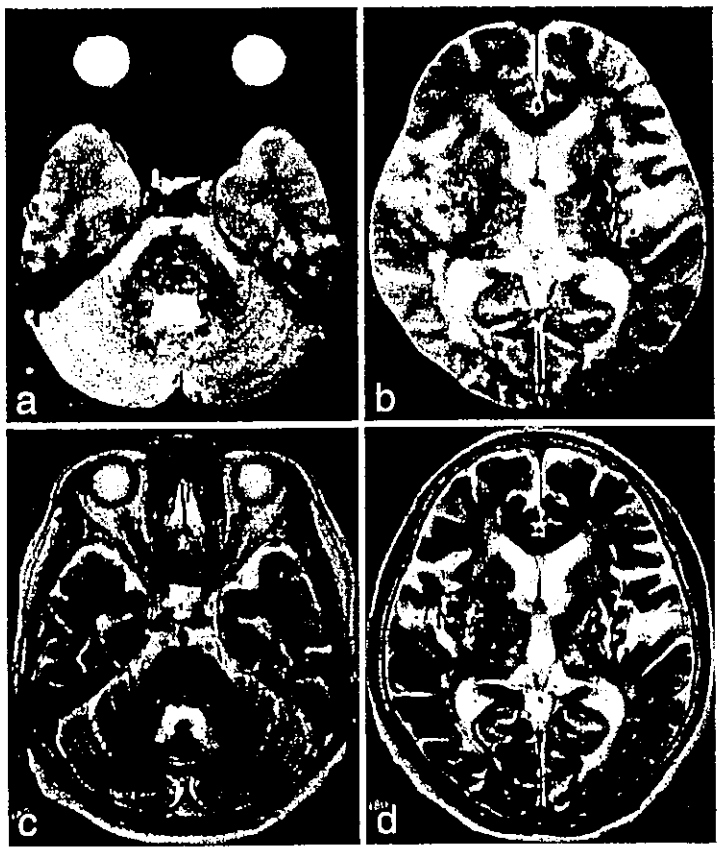

図1　75歳女性，左皮殻出血（8年前）後に右頭頂葉出血を来たした症例
右頭頂葉出血発症後10日目に撮像したT2*強調画像（a，b）では脳幹，小脳，基底核，大脳半球に多発性の無信号域（微小出血）を認める。左被殻には陳旧性出血の所見として無信号域を認める。同時に撮像したT2強調画像（c，d）では微小出血は明らかではない。

表1　臨床病型別の微小出血の頻度

ラクナ梗塞	3/17　(17.6%)
アテローム血栓性脳梗塞	1/7　(14.3%)
心原性脳塞栓	0/3　(　0%)
脳出血	11/18　(61.1%)

表2　初発例と再発例における微小出血の頻度

	微小出血	
	あり	なし
初発例	6/31 (19.4%)	25/31 (80.6%)
再発例	9/14 (64.3%)	5/14 (35.7%)

表3　微小出血を認めた例の臨床病型別分布

初発例（計6例）		再発例（計9例）	
脳出血	5例	脳出血再発	5例
アテローム血栓性脳梗塞	1例	ラクナ梗塞後ラクナ梗塞	3例
		ラクナ梗塞後脳出血	1例

いまだ十分多くはないが，今回の検討では，微小出血は脳出血例で最も頻度が高く，その一方ラクナ梗塞，アテローム血栓性脳梗塞では頻度が低く，心原塞栓性脳梗塞では微小出血を認めず，微小出血と脳出血との関連が強いことが示された。これまでの報告でも，脳卒中の臨床病型の中でも特に脳出血において微小出血の頻度がとりわけ高いことが報告されている。Tsushimaらは微小出血を脳出血の52.2%，脳梗塞の20.7%に認め，微小出血が脳出血に多く認められることを報告している[5]。また，Kimらは白質病変が軽度の例では微小出血の存在は脳梗塞よりも脳出血と関連していると報告している[7]。

さらに今回の研究では，大脳白質病変の程度およびMRAで評価した頭蓋内主要血管の狭窄性病変の程度と微小出血との関連を検討した。その結果，微小出血を認める群では認めない群より大脳白質病変が高度であったが，頭蓋内主要血管の狭窄性病変の程度には有意な差を認めなかった。微小出血の数と白質病変の程度は相関し大脳白質病変は脳細動脈の障害に起因するとされており[6]，われわれの結果もその微小出血と脳細

動脈との関連を支持するものであった。

今回の結果で興味深い点は，微小出血が脳卒中再発例で高頻度に認められたことである。脳卒中再発は様々な神経症状が新たに出現する結果ADL低下や高次脳機能低下などをきたし，予後に影響を与える極めて重要な病態である。微小出血は初発例よりも再発例において高頻度であり，さらに臨床病型の中でも微小出血は脳出血再発例において高頻度に認め，微小出血と脳卒中再発とくに脳出血再発との関連が示唆された。微小出血を認める例が再発性脳出血を来たしやすいのか，または細動脈障害が進展した結果症候性脳出血や微小出血を来たしているのかは不明であるが，脳梗塞後に急性脳出血を来たした例では微小出血を認める率が高いとの報告もあり[8),9)]，微小出血の存在が症候性脳出血再発の予測因子となる可能性もある。今後，初発時微小出血の有無と，脳卒中再発とくに脳出血再発との関連を経時的に評価していく必要があると思われる。しかし，今回微小出血を認めた脳卒中再発例の中には初発の脳梗塞後に抗血小板薬を内服していた例も2例含まれており，抗血小板薬内服により細動脈の脆弱性・易出血性が進展した結果，微小出血が出現している可能性も否定できない。現在，T2* 強調画像で認める微小出血の存在が虚血性脳血管障害の治療方針決定においても重要な情報となること，すなわち微小出血の存在が症候性脳出血の危険因子である可能性も示唆されており，抗血小板薬・抗凝固薬使用により微小出血が出現するか，また微小出血存在下でのこれらの薬剤の使用が症候性出血を起こすかについて今後の検討が必要と思われる。

V. 結　　語

T2* 強調画像で確認される微小出血は脳細動脈病変と関連し，とくに脳出血において高頻度に認めた。さらに再発性脳卒中，とくに脳出血において高頻度に認め，T2* 強調画像で微小出血の存在を知ることは，症候性脳出血再発の危険性を予測する重要な情報源となる可能性が示された。

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（受付　2002－12－24）

新たな展開をみせる薬物療法

虚血性脳血管障害の急性期治療

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はじめに

EBMの重要性が強調される昨今、世界ではAmerican Heart AssociationやRoyal College of Physicians等が中心となり、エビデンスに基づいた脳卒中の治療ガイドラインがそれぞれ作成されてきた。わが国でも数年前から複数の脳卒中に関連した学会（日本脳卒中学会、日本脳神経外科学会、日本神経学会、日本神経治療学会、日本リハビリテーション医学会）が共同してガイドラインの作成に着手し、2003年にその内容が公開された。本稿ではこのガイドラインの内容を中心に虚血性脳血管障害の急性期治療の現状について紹介する。そこで、脳卒中ガイドラインにおいて使用されているevidence levelに関する分類を［表1］に、recommendation grade（推奨グレード）に関する分類を［表2］に示す。

超急性期の治療

脳梗塞の治療としては、発症から極めて短時間のうちに閉塞した血管を再開通させる血栓溶解療法を行うことができれば理想的である。実際に発症から3時間以内の超急性期にt-PAの静脈内投与を行うことの有効性が証明され（Ib；表1に示した脳卒中ガイドライン委員会によるevidence level、以下同様）、米国を中心にいくつかの国で使用が認可されている。また、発症から6時間以内の中大脳動脈閉塞に対するプロウロキナーゼの経動脈的な投与による選択的局所血栓溶解療法の有効性も報告されている（Ib-III）。ガイドラインではt-PAの静脈内投与はグレードA（表2に示した脳卒中ガイドライン委員会による推奨グレード、以下同様）、経動脈的な選択的局所血栓溶解療法はグレードBの推奨となっているが、現時点ではどちらの治療法もわが国において保険適応はなく、現在臨床試験が実施中である。

急性期の治療

現時点においてわが国では血栓溶解療法には保険適応がないことと、発症6時間以降に来院する症例も少なくはないため、わが国の脳梗塞患者の大部分には脳保護薬あるいは抗血小板・抗凝固薬の投与を中心とした治療が行われている。

脳保護療法

脳保護薬では、フリーラジカルスカベンジャーであるエダラボンが、わが国で行われた臨床試験においてその有効性が確認され（Ib）、臨床病型を問わず広く用いられている（推奨グレードB）。ただし、エダラボンは抗血小板・凝固作用を有さず、単独での使用は脳梗塞発症後の急性期における再発、症状進行を抑制できない可能性があるため、抗血小板・抗凝固薬が併用されることも多い。エダラボンの単独療法は血腫を伴うような出血性脳梗塞を生じる可能性がある重症の心原性脳梗塞に対して用いられていることが多い。

一方、アルガトロバンとの併用はアテローム血栓性梗塞に、オザグレルとの併用はラクナ梗塞に対して行われることが多い。ただし、エダラボンの脳梗塞における有効性が確認された国内第Ⅲ相試験で対象となった症例のうち、重症の心原性脳塞栓症の割合は低く、併用療法についての検討も行われていないため、今後は、これらの有効性の検証を進めていく必要があると考える。また、血栓溶解療法との併用も理論的には有効な手段であるので血栓溶解療法の保険適応が得られた後、早急に有効性の検証を進める必要がある。

抗血小板療法

抗血小板薬では、臨床病型を問わず脳梗塞の発症から48時間以内のアスピリン投与の有効性が証明され（Ia）、その使用が強く推奨されている（推奨グレードA）。ただし、転帰改善効果に対するnumber needed to treatは80であり、その効果は必ずしも十分とはいえない。また、わが国においては発症5日以内の脳血栓症に対するオザグレルナトリウムの点滴静注の有効性が確認されており（Ib）、ラクナ梗塞を中心に広く用いられている（推奨グレードB）。血小板がその病態に強く関与するアテローム血栓性梗塞に対してはさらに強力な抗血小板療法が有効である可能性があるが、最近、血小板のGPIIb/IIIa拮抗薬のabciximabの虚血性脳血管障害に対する有効性が発表され注目されている。

抗凝固療法

抗凝固薬では、抗トロンビン薬であるアルガトロバンの点滴静注が、発症48時間以内の病変最大径が1.5cmを超すような脳梗塞（心原性脳梗塞を除く）に対して有効であることが確認されており（Ib）、アテローム血栓性脳梗塞を中心に使用されている（推奨グレードB）。急性期からの未分画ヘパリンの使用は、脳梗塞の再発は有意に減少するが、出血性合併症がその有効性を相殺してしまうとして、現時点ではその使用は積極的には推奨されていない（推奨グレードC1）。低分子ヘパリンやヘパリノイドについてもヘパリノイドがアテローム血栓性脳梗塞で有効であるとの報告がみられるものの（Ib）やはり積極的な使用は推奨されていない（推奨グレードC1）。しかし、現実にはヘパリンは心原性脳塞栓症や進行性の脳梗塞を中心に広く用いられている。ヘパリンは出血性脳梗塞のリスクが低い症例を選択して使用できれば有効である可能性が高いので、入院時に重症度（Japan Stroke Scaleや NIH Stroke Scale等で評価）や画像診断（Diffusion MRI、Perfusion MRI等で評価）を組み合わせて出血性脳梗塞のリスクを評価し、リスクの少ない症例を選んで使用するといった工夫が必要になってくると思われる。また、前述のエダラボンとヘパリンの併用、アルガトロバンの心原性脳塞栓に対する有効性、あるいはトロンボモジュリン製剤など新しい抗凝固薬の有効性等についても今後検討していく必要がある。

その他の治療

脳浮腫管理ではグリセロールの静脈内投与は脳浮腫を改善し、さらに脳血流量の増加、脳代謝の改善効果もあり大梗塞での救命に有効であることが証明され（Ia-Ib）、その使用が推奨されている（推奨グレードB）。一方、マンニトールの効果は科学的根拠に乏しく推奨グレードはC1となっている。開頭による外減圧療法については70歳未満で、保存的治療を施行しても進行性の意識障害を有し、CT所見で明らかな脳幹部への圧迫所見を認める症例では、発症24時間以内の硬膜形成を伴う外減圧術の有効性が証明され（Ⅱa, Ⅲ）、グレードBで推奨されている。それ以外の減圧開頭術、脳室ドレナージの推奨レベルはグレードC1となっている。その他、デキストラン、アルブミンによる血液希釈療法、高圧酸素療法は推奨グレードC1となっている。低体温療法、平温療法、急性期の緊急頸動脈内膜剥離術（CEA）、経皮的血管形成術（PTA）、ステント留置術もいずれも推奨グレードC1となっており、今後のエビデンスの集積が待たれる。

まとめ

以上、ガイドラインの内容を中心に虚血性脳血管障害の急性期治療について紹介した。今後、新たな治療薬の開発はもちろんのこと、臨床病型別の治療ガイドラインの整備、各種薬剤の併用療法の有効性の検証等が行われることが望まれる。

参考文献
篠原幸人ら編：脳卒中ガイドライン2003.

表1 脳卒中のevidence levelに関する分類

エビデンスのレベル	内容
Ia	RCTのメタアナリシス（RCTの結果がほぼ一致）
Ib	RCT
IIa	良くデザインされた比較研究（非ランダム化）
IIb	良くデザインされた準実験的研究
III	良くデザインされた非実験的記述研究（比較・相関・症例研究）
IV	専門家の報告・意見・経験

表2 脳卒中のrecommendation gradeに関する分類

推奨のグレード	内容
A	行うよう強く勧められる（少なくとも1つのレベルIの結果）
B	行うよう勧められる（少なくとも1つのレベルIIの結果）
C1	行うことを考慮してもよいが、十分な科学的根拠がない
C2	科学的根拠がないので、勧められない
D	行わないよう勧められる

厚生労働科学研究費補助金

循環器疾患等総合研究事業

脳血管疾患の再発に対する高脂血症治療薬のHMGCoA阻害剤の予防効果に関する研究

（H14－効　果（生活）－023）
（H15－効　果（生活）－020）
（H16－循環器（生習）－003）

平成14年度～16年度　総合研究報告書

6/7

雑 誌 (Ⅳ)

主任研究者　松 本 昌 泰
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平成17年（2005年）3月

Ⅲ．研究成果の刊行物・別刷

雑　　誌　(Ⅳ)

（平成16年度）

Higher Levels of Interleukin-6 Are Associated With Lower Echogenicity of Carotid Artery Plaques

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Background and Purpose—Echo-lucent carotid plaques can be fragile and vulnerable to rupture, representing a risk factor for ischemic stroke. Given the studies showing that elevated levels of circulating inflammatory markers are predictive of cardiovascular events, we sought to determine whether higher levels of serum interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hsCRP) are associated with lower echogenicity of carotid plaques.

Methods—The study comprised 246 patients who had carotid atherosclerotic plaques as evidenced by ultrasound. Using acoustic densitometry, we quantified the echogenicity of the largest plaque in each patient by integrated backscatter analysis. Serum IL-6 and hsCRP levels were determined in all patients.

Results—Both log-transformed IL-6 and hsCRP concentrations were negatively correlated with carotid plaque echogenicity ($r=-0.28$, $P<0.001$, and $r=-0.14$, $P<0.05$, respectively). When traditional atherosclerotic risk factors, plaque thickness, and medication use were controlled for, IL-6 levels were inversely associated with plaque echogenicity ($\beta=-0.21$, $P<0.01$), whereas such an association was of borderline significance for hsCRP ($\beta=-0.12$, $P=0.06$).

Conclusions—Higher IL-6 levels, in addition to hsCRP levels, appear to be associated with lower echogenicity of carotid plaques, suggesting a link between inflammation and potential risk of plaques. **(*Stroke*. 2004;35:677-681.)**

Key Words: atherosclerosis ■ carotid arteries ■ inflammation ■ interleukins ■ ultrasonography

Carotid plaque echogenicity, as assessed by B-mode ultrasound, is associated with its histological content. Particularly, echo-lucent plaques are thought to be lipid rich with increased density of macrophages, often containing a large lipid pool or hemorrhage.[1-3] These properties are consistent with the features of rupture-prone plaques, which are commonly characterized by a large necrotic/lipid core with a thin fibrous cap infiltrated by inflammatory cells.[4] Also, studies have shown that echo-lucent carotid plaques are associated with the risk for ischemic stroke.[5,6] From these findings, we can assume that echo-lucent carotid plaques are fragile and susceptible to rupture, representing a risk factor for stroke.

From studies to date, inflammatory processes are thought to be involved in the pathogenesis of atherosclerotic plaques and their thrombotic complications.[7] In particular, elevated levels of C-reactive protein (CRP) and interleukin-6 (IL-6) have been associated with the risk for cardiovascular disease (CVD).[8-10] Nevertheless, the mechanism that links such inflammatory markers and CVD risk remains to be determined. If higher levels of high-sensitivity CRP (hsCRP) and IL-6 are associated with echo-lucent carotid plaques, they may help us understand the link between inflammation and the risk of atherosclerotic plaques.

Integrated backscatter (IBS) analysis is a quantitative method to evaluate echogenicity of atherosclerotic plaques. This analysis defines acoustic propagation properties through the estimation of native radiofrequency signals from the tissue, allowing objective evaluation of plaque echogenicity.[11] Using IBS analysis, we examined the relationships of serum IL-6 and hsCRP levels with carotid plaque echogenicity.

Methods

Subjects

The subjects of this investigation were patients at the Department of Internal Medicine and Therapeutics at Osaka University Hospital who had undergone standard carotid ultrasound examination between October 2000 and September 2002. Because of the high prevalence of CVD and its risk factors, carotid ultrasound examinations were performed to screen for carotid atherosclerosis and stenosis or, in some cases, to assess vertebral artery circulation. Of note, under the current healthcare system in Japan, carotid ultrasound examination can be performed not only for patients with carotid stenosis but also for those with cardiovascular risk factors.

Because we focused on the echogenicity of plaques, the inclusion criterion for this study was the existence of carotid plaques (≥1.3 mm in thickness). Patients with smaller plaques were not included because such plaques could not be clearly separated from diffusely thickened intima-media complex. When carotid plaques

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were identified, the purpose and procedures for IBS analysis and inflammatory marker evaluation were explained to patients. After written informed consent was obtained, patients underwent IBS and blood sample testing.

During the study period, IBS examinations were performed on 332 patients. However, patients with the following criteria were excluded: (1) calcified plaques with acoustic shadow (n=45) or occluded carotid artery (n=8) because it was technically impossible to determine their echogenicity reliably; (2) carotid endarterectomy (n=6); and (3) acute inflammatory diseases (n=3), vasculitis/collagen diseases (n=5), malignant neoplasm (n=12), or recent (< 3 months) CVD events (n=7) because levels of inflammatory markers could be modified in such patients.

After exclusion of patients with any of the above criteria, the study sample comprised 246 patients (mean±SD age, 65.7±7.8 years), including 80 patients with a history of stroke/transient ischemic attack (TIA) (25 atherothrombotic infarctions, 26 lacunar infarctions, 5 cardioembolic infarctions, 4 cerebral hemorrhages, 9 other or unclassified strokes, and 11 TIAs based on our criteria[12]). In stroke/TIA patients, the average interval between the events and IBS/blood testing was 60 months. Although the prevalence of atherosclerotic risk factors was relatively high in the study sample, they were generally well controlled by medication (Table 1).

Carotid Ultrasonography

All ultrasound examinations and subsequent analyses were performed with a Phillips SONOS 5500 equipped with a 7.5-MHz linear-array transducer.

Initially, the common and internal carotid arteries were scanned cross-sectionally and longitudinally by B-mode and color Doppler methods, through which the largest plaque was identified for evaluation of plaque echogenicity. Also, plaque thickness was measured on the longitudinal B-mode or color Doppler images perpendicular to the vascular wall.

TABLE 1. Patient Characteristics

Age, y	65.7±7.8
Men, %	65
Body mass index, kg/m^2	23.3±2.5
Hypertension/medical treatment/ACEI or ARB use, %	79/68/30
Systolic blood pressure, mm Hg	136±16
Diastolic blood pressure, mm Hg	78±11
Diabetes mellitus/medical treatment, %	22/13
Fasting blood glucose, mmol/L (mg/dL)	5.8±1.5 (104±27)
Hyperlipidemia/medical treatment/statin use, %	76/40/33
Total cholesterol, mmol/L (mg/dL)	5.7±0.8 (211±31)
Triglycerides, mmol/L (mg/dL)	1.6±0.8 (138±72)
HDL cholesterol, mmol/L (mg/dL)	1.5±0.4 (56±16)
Smokers, %	23
History of CVD, %	46
Stroke/transient ischemic attack, %	28/4
Ischemic heart disease, %	19
ASO, %	4
Aspirin use, %	23
Inflammatory markers	
hsCRP, mg/dL	0.15±0.23 (0.07)*
IL-6, pg/mL	2.75±2.60 (2.07)*
Ultrasound parameters	
IBS index	48±17
Plaque thickness, mm	2.48±1.03

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker; and ASO, arteriosclerosis obliterans.
*Median.

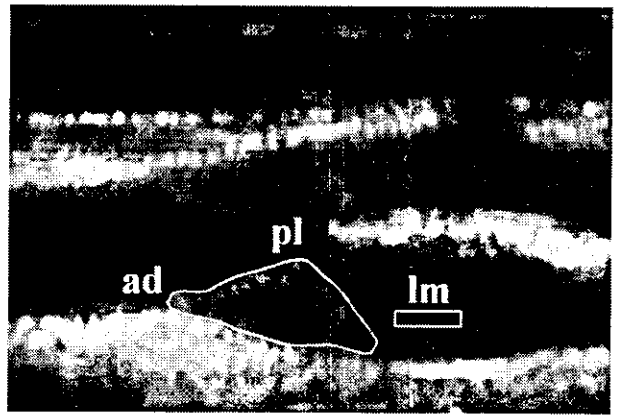

Figure 1. IBS analysis of carotid plaques. Through acoustic densitometry, IBS values are obtained from the plaque (pl), vessel lumen (lm), and adventitia (ad) at same depth, where IBS index is defined as (pl−lm)/(ad−lm)×100.

Subsequently, with the use of acoustic densitometry, longitudinal IBS images of the largest plaque were recorded onto optical disks and used for the echogenicity evaluation. The acoustic densitometry system is capable of providing 2-dimensional IBS images in which the gray level is displayed proportionally to the integrated backscattered power. The IBS value is internally calibrated in decibels, having a dynamic range of 0 to 64 dB in the SONOS 5500 system.[11] For all patients, IBS images were acquired with the same time gain compensation setting and gain control values. IBS values were obtained from outline of the plaque (pl), vessel lumen (lm), and adventitia (ad) at the same depth of the plaque (Figure 1). Because reproducibility of carotid plaque echogenicity was better when 2 reference structures (vessel lumen and adventitia) were used than when 1 reference was used,[13] we defined IBS index as (pl−lm)/(ad−lm)×100. Accordingly, a lower IBS index corresponds to lower echogenicity. In case of echo-lucent plaques, color Doppler images were used to help identify the blood-plaque boundaries.

All examinations were done by 1 sonographer (H.Y.) who was blinded to patients' clinical details. Before this study, we examined the reproducibility of the IBS index for 43 randomly selected plaques without severe calcification; IBS analyses were performed twice by the same examiner (H.Y.) and subsequently by 2 examiners (H.Y.

TABLE 2. Associations of IBS Index With Atherosclerotic Risk Factors and Plaque Thickness

	r or Mean±SD	*P*
Age, y	0.07	0.31
Sex, men/women	46±18/53±15	0.002
Body mass index, kg/m^2	−0.05	0.43
Hypertension, Y/N	49±18/47±16	0.51
Diabetes mellitus, Y/N	45±16/49±18	0.09
Total cholesterol, mg/dL	0.01	0.89
Triglycerides, mg/dL	−0.11	0.08
HDL cholesterol, mg/dL	0.19	0.003
HLP medication, Y/N	50±18/47±17	0.22
Smoking, Y/N	48±18/48±17	0.96
History of CVD, Y/N	47±19/49±16	0.31
Plaque thickness, mm	−0.37	<0.001

HLP indicates hyperlipidemia.

and M.S). Intraobserver and interobserver coefficients of variation for IBS index measurements were 8.9% and 9.2%, respectively.

Measurement of Serum Inflammatory Markers

After IBS examinations, blood was drawn with minimally traumatic venipuncture for measurement of serum inflammatory markers. Then, blood was centrifuged at 3000 rpm at 4°C for 15 minutes, and aliquots were stored at −70°C. Serum IL-6 was measured by enzyme-linked immunosorbent assay (High Sensitivity Quantikine kit, R&D System). The detectable limit for IL-6 was 0.10 pg/mL. Circulating levels of hsCRP were measured by latex turbidimetric immunoassay with a sensitivity of 0.01 mg/dL (Shionogi Biomedical Laboratory Inc).

Evaluation of Atherosclerotic Risk Factors

Supine blood pressure was evaluated before the IBS examination. Levels of fasting blood glucose, serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were determined from the blood sample taken for inflammatory marker evaluation. Information on patients' medical histories and medication use was obtained from the clinical records with the IBS data masked. Hypertension was defined by casual blood pressure ≥140/90 mm Hg or current use of antihypertensive agents. Diabetes mellitus was defined by fasting blood glucose ≥7.0 mmol/L or use of glucose-lowering agents. Hyperlipidemia was defined by fasting serum total cholesterol >5.7 mmol/L, triglycerides >1.7 mmol/L, or use of cholesterol-lowering agents. Smoking status was categorically evaluated from self-reports, with a smoker defined as currently smoking ≥10 cigarettes per day for >1 year.

Statistical Analyses

All analyses were performed with SPSS 9.0J (SPSS Japan Inc). Because distributions of hsCRP and IL-6 levels appeared to be left skewed, they were normalized by log transformation. Thereafter, relationships between IBS index and continuous variables were examined by Pearson's correlation analysis. For categorical variables, differences in IBS index were examined by unpaired *t* test. Subsequently, multiple linear regression analyses were performed to examine associations between IBS index and inflammatory markers by controlling for traditional atherosclerotic risk factors, plaque thickness, and medication use. Additionally, IBS index was compared across the IL-6 tertiles by the general linear model, followed by Bonferroni's post hoc test. Probability values were 2-tailed, and values of $P<0.05$ were considered significant.

Results

The associations of IBS index with atherosclerotic risk factors, lipid measures, and plaque thickness are shown in Table 2. As a measure of plaque echogenicity, IBS index was positively correlated with HDL cholesterol and negatively associated with plaque thickness. Also, IBS index was lower in men than in women and had a trend for negative correlation with triglycerides. Additionally, although IBS index was similar by history of CVD, it was lower in patients with than in those without ischemic stroke/TIA (44.9±17.6 versus 49.6±17.0, $P=0.046$).

Table 3 shows the associations between IBS index and log-transformed concentration of IL-6 or hsCRP. By univariate analysis, IBS index was found to be negatively correlated with IL-6. When traditional atherosclerotic risk factors and CVD history were controlled for, IBS index remained negatively associated with IL-6. Moreover, the association was only slightly attenuated when plaque thickness and medication use were also controlled for. In addition to IL-6, IBS index had a negative weak association with hsCRP. However, the association was only of borderline significance when traditional atherosclerotic risk factors, as well as plaque thickness and medication use, were controlled for.

TABLE 3. Associations of IBS Index With Inflammatory Markers

	IL-6*		hsCRP*	
	r or β	*P*	*r* or β	*P*
Univariate	−0.28	<0.001	−0.14	0.03
Multivariate†	−0.29	<0.001	−0.11	0.09
Multivariate‡	−0.21	0.002	−0.12	0.06
Multivariate§	−0.21	0.003	−0.12	0.06

*hsCRP and IL-6 were analyzed as log-transformed values.

†When controlling for age, sex, body mass index, hypertension, diabetes mellitus, smoking status, history of CVD, total cholesterol, triglycerides, HDL cholesterol, and hyperlipidemia medication.

‡When additionally controlling for plaque thickness.

§When additionally controlling for use of statin, aspirin, and angiotensin-converting enzyme inhibitors/angiotensin II type I receptor blockers.

Given the association between IBS index and IL-6, the magnitude of the IBS index was compared across the tertiles of IL-6 (Figure 2 and Table 4). IBS index was lower in patients in the highest tertile than in those in the middle or lowest tertile. Moreover, the differences persisted after adjustment for traditional atherosclerotic risk factors, plaque thickness, medication use, and log-transformed hsCRP.

Discussion

In the present study, we have found that elevated serum IL-6 levels are associated with lower echogenicity of carotid plaques as quantified by IBS analysis. Also, plaque echogenicity was lower in patients with higher IL-6 levels than in those with lower levels after adjustment for other putative factors, including hsCRP. To the best of our knowledge, this is the first study to demonstrate associations between IL-6 levels and echogenicity of carotid plaques.

For evaluation of carotid plaque echogenicity, we have defined the IBS index, which is derived from the IBS value of plaques in reference to vessel lumen and adventitia (Figure 1). Namely, a lower IBS index implies lower echogenicity of plaques. Studies using B-mode methods have shown associations between echo-lucent carotid plaques and lower HDL cholesterol, advanced stenoses, male sex, and increased levels of triglyceride-rich lipoprotein.[2,14,15] In the present study, lower IBS index was associated with lower HDL cholesterol

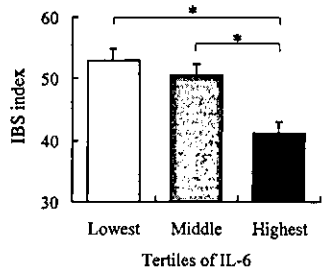

Figure 2. IBS index stratified by IL-6 tertiles. Error bars are SEM. IBS index in highest tertile was lower than that in middle or lowest tertile. *$P<0.05$.

TABLE 4. IBS Index Stratified by IL-6 Tertiles

	IL-6 Tertile			
	Lowest (<1.67 pg/mL)	Middle (1.67–2.66 pg/mL)	Highest (>2.66 pg/mL)	ANOVA *P*
Observed IBS index	52.9±1.8	50.5±1.8	41.1±1.8§‖	<0.001
Adjusted IBS index*	53.5±2.4	51.3±2.2	41.4±2.3§‖	<0.001
Adjusted IBS index†	51.9±2.5	50.6±2.3	42.2±2.4§‖	<0.001
Adjusted IBS index‡	51.4±2.6	50.4±2.3	42.4±2.4§‖	0.002

ANOVA indicates analysis of variance. Values shown are mean±SEM.

*IBS index after adjustments for age, sex, body mass index, hypertension, diabetes mellitus, smoking status, history of CVD, total cholesterol, triglycerides, and HDL cholesterol.

†IBS index after additional adjustments for plaque thickness and use of stain, aspirin, and angiotensin-converting enzyme inhibitors/angiotensin II type I receptor blockers.

‡IBS index after additional adjustments for log-transformed hs-CRP.

§$P<0.05$ vs lowest tertile; ‖$P<0.05$ vs middle tertile.

and greater plaque thickness (Table 2). Also, the IBS index was lower in men and had a trend toward negative correlation with triglycerides. Thus, carotid plaque echogenicity as assessed by IBS analysis appears to have associations with atherosclerotic risk factors and plaque size similar to those found by B-mode methods. Particularly, IBS index was lower in patients with than in those without ischemic stroke/TIA, which is consistent with the risk of echo-lucent plaques for ischemic cerebrovascular diseases.[5]

In addition to commonly known atherosclerotic risk factors, circulating inflammatory markers such as hsCRP and IL-6 represent novel predictors of CVD.[8,9] In the present study, IBS index was negatively associated with IL-6, and the association remained significant when traditional atherosclerotic risk factors, plaque thickness, and medication use were controlled for (Table 3). These findings suggest an association between lower echogenicity of carotid plaques and enhanced levels of inflammation. In contrast, despite a negative weak association between IBS index and hsCRP, the association was only of borderline significance when other factors were controlled for. This finding is not surprising because circulating levels of IL-6 and hsCRP do not always move in parallel. Additionally, the finding is slightly different from that of Gronholdt et al,[16] who reported the lack of association between hsCRP and carotid plaque echogenicity as assessed by B-mode method. We are unaware of other studies linking hsCRP and plaque echogenicity; further studies are required to disclose their linkages.

To further demonstrate the associations between carotid plaque echogenicity and IL-6, IBS index was compared across the tertiles of IL-6 levels. IBS index was found to be lower in patients belonging to the highest tertile than in those belonging to the middle or lowest tertile (Figure 2 and Table 4). Moreover, the differences persisted after adjustment for traditional atherosclerotic risk factors, plaque thickness, medication use, and hsCRP. On the basis of these results, IL-6 appears to have an association with plaque echogenicity that is independent of hsCRP.

Rus et al[17] have shown 200-fold-higher levels of IL-6 in atherosclerotic arterial walls than in blood. Also, increased expression of IL-6 was found in atherosclerotic plaques, predominantly colocalized with macrophages.[18] Thus, increased IL-6 production from inflammatory cells in plaques could contribute to higher IL-6 as found in this study. However, whether it is derived from carotid echo-lucent plaques or from diffuse systemic atherosclerosis cannot be determined by the data presented. Additionally, IL-6 could facilitate the formation of unstable plaques through the stimulation of mononuclear cells,[19] proinflammatory cytokines,[20] and matrix metalloproteinases.[21,22] Thus, the link between higher IL-6 and lower IBS index may offer a clue to the understanding of the risk of atherosclerotic plaques.

This study has some limitations. First, because this study is cross-sectionally designed, we cannot determine the causal relationships between higher IL-6 levels and lower plaque echogenicity. Second, patient selection bias can exist because we excluded a relatively large portion of the original patients (86 of 332), predominantly because of the technological limitations of ultrasound. Third, although associations between IBS index and inflammatory markers were virtually unmodified by medication use (Table 3 and 4), IL-6 and hsCRP levels have been shown to be modified by statins, aspirin, angiotensin-converting enzyme inhibitors, and angiotensin II type 1 receptor blockade.[23–26] Future studies are needed to examine the effect of such medications on carotid plaque echogenicity. Larger prospective studies, probably using other methods combined with ultrasound, are necessary to establish the associations between IL-6, hsCRP, and carotid plaque echogenicity.

In conclusion, we have demonstrated an association between higher IL-6 levels and lower echogenicity of carotid plaques. The finding can broaden our understanding of the link between inflammation and the risk of atherosclerotic plaques.

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Frequency of Asymptomatic Microbleeds on T2*-Weighted MR Images of Patients with Recurrent Stroke: Association with Combination of Stroke Subtypes and Leukoaraiosis

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BACKGROUND AND PURPOSE: **Asymptomatic microbleeds shown by T2*-weighted MR imaging are associated with small-artery diseases, especially with intracerebral hemorrhage. Few studies have focused on the prevalence of microbleeds in patients with recurrent stroke. We investigated frequency of microbleeds in patients with recurrent stroke and association of presence of microbleeds with a combination of stroke subtypes and severity of leukoaraiosis.**

METHODS: **The study population consisted of 102 patients with primary stroke and 54 patients with recurrent stroke. Microbleeds were counted and classified by using T2*-weighted MR imaging with a 1.0-T system.**

RESULTS: **Patients with recurrent stroke showed a significantly higher prevalence of microbleeds (68.5%) than did patients with primary stroke (28.4%) ($P < .0001$). Among patients with recurrent stroke, the highest frequency of microbleeds occurred in those with intracerebral hemorrhage alone (92.3%), with the next highest frequency occurring in those with a combination of intracerebral hemorrhage and ischemic stroke (76.5%) and then those with ischemic stroke alone (50.0%) ($P < .05$). Leukoaraiosis was more severe in patients with recurrent stroke than in patients with primary stroke, and correlations between grade of microbleeds and severity of leukoaraiosis were found in patients with primary stroke ($r = 0.367$, $P < .001$) and in patients with recurrent stroke ($r = 0.553$, $P < .0001$). Logistic regression analysis identified recurrent stroke (odds ratio, 4.487; 95% confidence interval, 1.989–10.120) and leukoaraiosis (odds ratio, 5.079; 95% confidence interval, 2.125–12.143) as being significantly and independently associated with microbleeds.**

CONCLUSION: **Asymptomatic microbleeds are observed to occur frequently in patients with recurrent stroke, either hemorrhagic or ischemic stroke, and are closely associated with the severity of leukoaraiosis.**

Gradient-echo T2*-weighted MR imaging is extremely sensitive for detecting silent microbleeds, which are shown as signal intensity loss, representing hemosiderin deposit (1, 2). Recent studies using T2*-weighted MR imaging have shown a high frequency of microbleeds in patients with severe leukoaraiosis, lacunar infarction, and cerebral hemorrhage, indicating that an association exists between microbleeds and small-artery disease (3–10).

Recurrent stroke potentially affects the prognosis and physical and psychologic disability of the patient, and it is extremely important not only to prevent recurrence of stroke by antiplatelet or anticoagulation therapy or by control of risk factors but also to assess which patients are prone to recurrence by using neuroradiologic tools. Previous stroke trials have revealed considerable recurrence of stroke despite treatment with antiplatelet or anticoagulation therapy for the prevention of recurrence (11–16), but characteristic neuroradiologic findings of patients who are prone to recurrent stroke have not been elucidated. T2*-weighted MR imaging is expected to have the potential to identify those patients who are prone to

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recurrence. However, few studies have focused on the prevalence of microbleeds in patients with recurrent stroke. Recognition of microangiopathy that causes a patient to be prone to bleeding is extremely important, and T2*-weighted MR imaging could be useful if the presence of microbleeds on T2*-weighted MR images enables prediction of the recurrence of specific stroke subtypes. Therefore, the aim of the present study was to evaluate frequency of microbleeds in patients with recurrent stroke and association between presence of microbleeds with combination of stroke subtypes and findings on conventional MR images and MR angiograms.

Methods

We prospectively evaluated inpatient and outpatient subjects with acute primary or recurrent stroke who underwent MR imaging studies at our hospital from September 2002 to March 2003. Histories of neurologic episodes were carefully obtained from the patients and/or their families. Diagnosis of acute stroke was made on the basis of neurologic signs and symptoms and on the basis of results of neuroradiologic examinations. Stroke was classified into ischemic stroke and intracerebral hemorrhage, and ischemic stroke was further classified according to the criteria of the National Institute of Neurologic Disorders and Stroke as atherothrombotic infarction, cardioembolic infarction, and lacunar infarction (17). Cases of undetermined classification were excluded from this study. Acute ischemic stroke was confirmed based on diffusion-weighted images and apparent diffusion coefficient maps, and intracerebral hemorrhage was diagnosed on the basis of CT findings. Cases in which hematoma was not caused by spontaneous intracerebral hemorrhage (eg, caused by vascular malformation, trauma, cavernous hemangioma, or brain tumor) were excluded from this study. The requirement for diagnosis of previous stroke was symptomatic episodes that had been diagnosed as stroke and had been treated; cases with lesions suggestive of stroke on MR images alone without neurologic symptoms were not diagnosed as recurrent stroke. In patients who had suffered recurrent stroke, the subtype of the previous stroke and whether they had undergone antiplatelet or anticoagulation therapy after the previous ischemic stroke were evaluated. Subsequent worsening of the same neurologic dysfunction after continuous disturbance of focal neurologic function after the acute stroke was not recognized as recurrent stroke.

All patients in the study were examined with the use of a 1.0-T clinical MR imaging unit (Siemens, Magneton Harmony), and the whole brain was imaged with a section thickness of 5 mm and intersection gap of 1.5 mm. The imaging protocol consisted of axial view T2-weighted spin-echo sequences (4500/112 [TR/TE]; field of view, 201 × 230; matrix, 225 × 512), axial view T2*-weighted gradient-echo sequences (800/26; flip angle, 20 degrees; field of view, 230 × 230; matrix, 192 × 256), diffusion-weighted imaging with single shot echo-planar spin-echo sequences (5300/135; field of view, 196 × 261; matrix, 80 × 128; b values, 0 and 1000 mm^2/s), and intracranial MR angiography (3D time-of-flight sequence; 39/10; field of view, 150 × 200; matrix, 192 × 512). Patients were excluded if their MR images could not be evaluated because of artifacts.

Microbleeds were defined as homogeneous, round hypointense lesions on T2*-weighted MR images, excluding lesions in the globus pallidum and in the subarachnoid space, which are likely to represent calcification and adjacent pial blood vessels, respectively. Intracerebral lesions with a hemorrhagic component were also excluded. Microbleeds were classified as absent (grade 0), mild (grade 1; total number of microbleeds, one to two), moderate (grade 2; total number of microbleeds, three to 10), and severe (grade 3; total number of microbleeds, >10) according to the grading scale presented by Lee et al (18). MR angiography was used to examine intracranial large arteries, including the intracranial internal carotid, anterior cerebral, middle cerebral, posterior cerebral, basilar, and intracranial vertebral arteries, for the presence of intracranial large-artery diseases, defined as >50% luminal narrowing. Arterial occlusion suspected to be due to embolism by thrombus in patients with cardioembolic infarction was not considered to be large-artery disease. Leukoaraiosis shown by T2-weighted imaging was graded by using the scoring system presented by Fazekas et al (19): grade 0, absent; grade 1, punctate; grade 2, early confluent; and grade 3, confluent. MR images were independently evaluated by two of the authors (H.N., E.N.) without knowledge of the patients' clinical profiles; the number of microbleeds and the grading scores of intracranial large-artery diseases and leukoaraiosis were determined by consensus.

Values were expressed as means ±SD. For the cases of primary and recurrent stroke, the χ^2 test for independence was used for comparison of sex ratio, hypertension, atrial fibrillation, diabetes mellitus, hyperlipidemia, and intracranial large-artery diseases, Student's t test was used for comparison of age, and Mann-Whitney's U test was used for comparison of grade of leukoaraiosis and microbleeds. Prevalences of microbleeds or intracranial large-artery diseases among the groups were compared by conducting the χ^2 test for independence. Prevalences of hypertension and lacunar infarction among the patients with intracranial large-artery diseases with and those without microbleeds were also compared by conducting the χ^2 test for independence. Comparisons of grades of microbleeds in three or four groups were performed by the Kruskal-Wallis rank test with post hoc comparisons (Scheffé). Correlation between degrees of microbleeds and leukoaraiosis was examined by using the Spearman rank correlation test. Logistic regression analysis was used to assess the relationships of microbleeds with the following variables: age, sex, hypertension, atrial fibrillation, diabetes mellitus, hyperlipidemia, intracranial large-artery diseases, leukoaraiosis, and primary or recurrent stroke.

TABLE 1: Background of the patients

	Primary Stroke	Recurrent Stroke	P
Patients, n (M/F)	102 (57/45)	54 (38/16)	.0777
Age, yr (SD)	69.0 (12.7)	68.6 (11.4)	.8377
Hypertension, n (%)	65 (63.7)	38 (70.4)	.4045
Atrial fibrillation, n (%)	14 (13.7)	5 (9.3)	.4171
Diabetes mellitus, n (%)	23 (22.5)	9 (16.7)	.3867
Hyperlipidemia, n (%)	20 (19.6)	10 (18.5)	.8695
Intracranial large-artery disease, n (%)	38 (37.3)	16 (29.6)	.3409
Leukoaraiosis, grade (SD)	1.04 (0.91)	1.74 (0.99)	<.0001

Note.—M indicates male; F, female.

Results

The study population consisted of 156 Japanese patients with acute stroke, including 102 (57 men and 45 women; age, 69.0 ± 12.7 years) with primary stroke and 54 (38 men and 16 women; 68.6 ± 11.4 years) with recurrent stroke. Patient data are summarized in Table 1. No statistical differences were observed in age, sex ratio, or prevalences of hypertension, atrial fibrillation, diabetes mellitus, hyperlipidemia, or intracranial large-artery diseases between the primary and recurrent stroke groups. However, the grade of leukoaraiosis was higher in the recurrent stroke group than in the primary stroke group ($P < .0001$).

TABLE 2: Prevalence and grade of microbleeds in patients with primary stroke

	Microbleeds n (%)	Grade of Microbleeds			
		Absent (grade 0), n	Mild (grade 1), n	Moderate (grade 2), n	Severe (grade 3), n
Stroke subtype					
Atherothrombotic (n = 22)	5 (22.7)	17	3	2	0
Cardioembolic (n = 13)	0 (0)	13	0	0	0
Lacunar (n = 31)	7 (22.6)	24	4	0	3
Intracerebral hemorrhage (n = 36)	17 (47.2)	19	5	10	2
Total (n = 102)	29 (28.4)	73	12	12	5

TABLE 3: Combination of stroke subtypes in patients with recurrent stroke

	Antiplatelet or Anticoagulation Therapy after Previous Stroke	Patients, n	Microbleeds, n
Combination of stroke subtype*			
Intracerebral hemorrhage/intracerebral hemorrhage		9	8
Lacunar/lacunar	+	6	2
Intracerebral hemorrhage/lacunar		9	8
Intracerebral hemorrhage (three times)		4	4
Lacunar/intracerebral hemorrhage	−	3	2
Atherothrombotic/lacunar	+	3	1
Intracerebral hemorrhage/atherothrombotic		2	1
Atherothrombotic/atherothrombotic	−	2	1
Lacunar/atherothrombotic	−	2	2
Lacunar/lacunar	−	2	1
Lacunar/atherothrombotic	+	2	1
Lacunar/intracerebral hemorrhage	+	2	2
Cardioembolic/cardioembolic	+	2	1
Atherothrombotic/atherothrombotic	+	2	2
Intracerebral hemorrhage/cardioembolic		1	0
Lacunar (three times)	+	1	1
Atherothrombotic/lacunar	−	1	0
Cardioembolic/cardioembolic	−	1	0
Total		54	37

* Combination of stroke subtype expressed as previous stroke subtype/latest stroke subtype; Present is indicated by + and absent by −.

Prevalences and grades of microbleeds in the patients in the primary stroke group are summarized in Table 2. Microbleeds were observed more frequently in patients with intracerebral hemorrhage (47.2% of the patients) than in patients with atherothrombotic infarction (22.7%) or lacunar infarction (22.6%). Microbleeds were not observed in patients with cardioembolic infarction. The grade of microbleeds was highest in patients with intracerebral hemorrhage, with statistical significance for patients with cardioembolic infarction ($P < .05$). A significant correlation was shown between grade of microbleeds and severity of leukoaraiosis ($r = 0.367$, $P < .001$). No significant difference was shown in incidences of intracranial large-artery diseases between patients with primary stroke with microbleeds and patients with primary stroke without microbleeds.

Combinations of stroke subtypes in patients with recurrent stroke are summarized in Table 3. Two patients with intracerebral hemorrhage who had undergone antiplatelet therapy after previous ischemic stroke (cases of lacunar/intracerebral hemorrhage) exhibited severe microbleeds. On the other hand, three patients who had not undergone antiplatelet or anticoagulant therapy after previous ischemic stroke exhibited intracerebral hemorrhage (cases of lacunar/intracerebral hemorrhage), and two of the three exhibited microbleeds. Patients with recurrent stroke had a significantly higher prevalence of microbleeds than did patients with primary stroke (68.5% versus 28.4%, $P < .0001$). The grade of microbleeds was also significantly higher in patients with recurrent stroke than in patients with primary stroke ($P < .0001$). Representative T2- and T2*-weighted MR images are shown in Figure 1. The prevalences and grades of microbleeds in patients with ischemic stroke (including atherothrombotic infarction, cardioembolic infarction, and lacunar infarction) alone, in patients with intracerebral hemorrhage alone, and in patients with a combination of ischemic stroke and intracerebral hemorrhage are summarized in Table 4. Frequency of microbleeds was highest in the group of patients with intracerebral hemorrhage alone (92.3%), next highest in the group of patients with intracerebral hemorrhage and ischemic stroke (76.5%), and then in the group of patients with ischemic stroke alone (50.0%) ($P < .05$). The order of grades of microbleeds was the same: highest in the

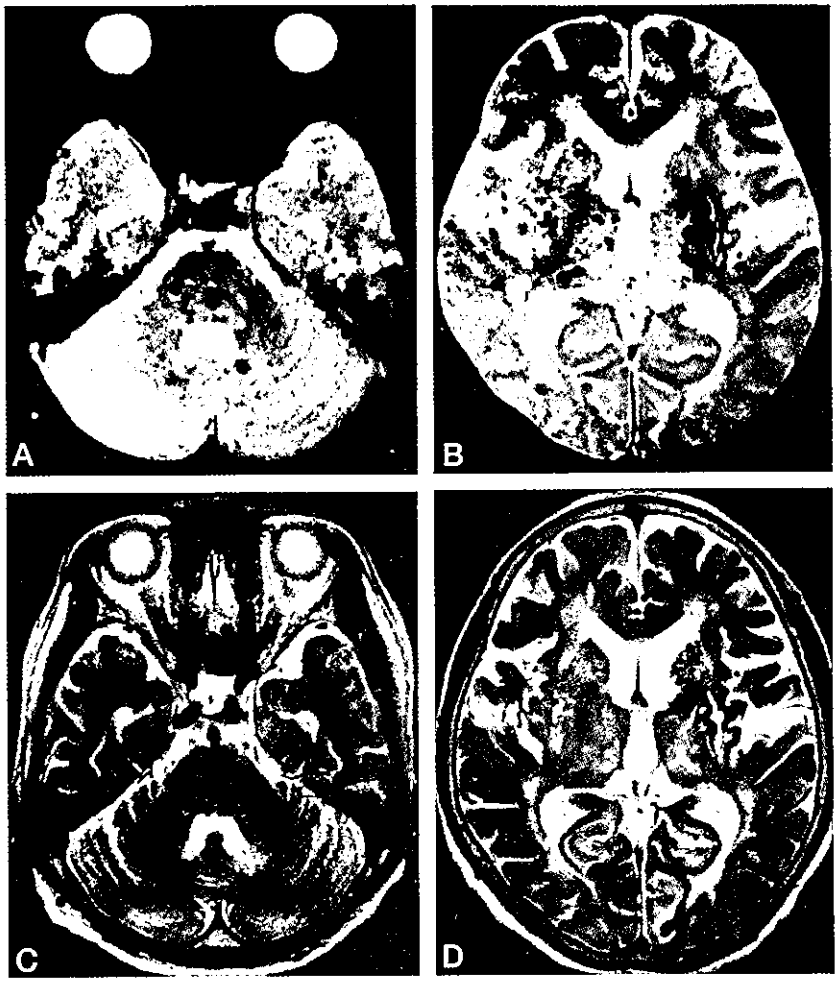

FIG 1. MR images of a 75-year-old patient with intracerebral hemorrhage in the right parietal lobe 8 years after the occurrence of intracerebral hemorrhage in the left putamen.

A and *B*, T2*-weighted gradient-echo images (800/26; flip angle, 20 degrees) reveal multiple foci of signal intensity loss (microbleeds) in the brain stem, cerebellum, basal ganglia, and cerebral hemispheres. In addition, old intracerebral hemorrhage is evident in the left putamen.

C and *D*, T2-weighted spin-echo images (4500/112) show the site of old intracerebral hemorrhage in the left putamen, but microbleeds are not evident.

TABLE 4: Prevalence and grade of microbleeds in patients with each combination of subtypes of recurrent stroke

	Microbleeds n (%)	Grade of Microbleeds			
		Absent (grade 0), n	Mild (grade 1), n	Moderate (grade 2), n	Severe (grade 3), n
Combination of stroke subtype					
Intracerebral hemorrhage alone (n = 13)	12 (92.3)	1	1	4	7
Intracerebral hemorrhage and ischemic stroke (n = 17)	13 (76.5)	4	1	5	7
Ischemic stroke alone (n = 24)	12 (50.0)	12	4	5	3
Total (n = 54)	37 (68.5)	17	6	14	17

group of patients with intracerebral hemorrhage alone, next highest in the group of patients with intracerebral hemorrhage and ischemic stroke, and then in the group of patients with ischemic stroke alone ($P < .01$). Although a significant correlation was found between grade of microbleeds and severity of leukoaraiosis in the patients with recurrent stroke ($r = 0.553, P < .0001$), no significant difference was observed in incidences of intracranial large-artery diseases between patients with recurrent stroke with microbleeds and patients with recurrent stroke without microbleeds.

Among the patients with intracranial large-artery diseases (54 patients), 22 were shown to have microbleeds. Patients with intracranial large-artery diseases and microbleeds showed a significantly higher prevalence of hypertension or lacunar infarction (90.9%) than did those with intracranial large-artery diseases but without microbleeds (59.4%) ($P = .0110$).

Results of logistic regression analysis showed that recurrent stroke (odds ratio, 4.487; 95% confidence interval, 1.989–10.120) and leukoaraiosis (odds ratio, 5.079; 95% confidence interval, 2.125–12.143) were significantly and independently associated with presence of microbleeds, whereas atrial fibrillation had a significant and independent negative association with presence of microbleeds (Table 5).

TABLE 5: Logistic regression analysis

Variable	Odds Ratio	95% CI	P
Age	0.992	0.957–1.029	.6771
Sex	1.764	0.754–4.125	.1905
Hypertension	1.986	0.823–4.794	.1271
Atrial fibrillation	0.209	0.047–0.934	.0404
Diabetes mellitus	1.257	0.495–3.192	.6306
Hyperlipidemia	0.566	0.205–1.564	.2721
Intracranial large-artery diseases	0.981	0.425–2.264	.9642
Leukoaraiosis	5.079	2.125–12.143	.0003
Recurrent stroke	4.487	1.989–10.120	.0003

Note.—CI indicates confidence interval.

Discussion

In the present study, we evaluated frequency of microbleeds in patients with recurrent stroke and association of microbleeds with combination of stroke subtypes and severity of leukoaraiosis. The following results were obtained: 1) prevalence and grade of microbleeds were significantly higher in patients with recurrent stroke than in patients with primary stroke; 2) microbleeds were observed more frequently and were of higher grade in patients with intracerebral hemorrhage than in patients with either primary or recurrent ischemic stroke but were frequently observed even in patients with recurrent ischemic stroke (prevalence of 50%); and 3) leukoaraiosis was more severe in patients with recurrent stroke than in patients with primary stroke, and a correlation was found between grade of microbleeds and severity of leukoaraiosis in both patients with primary stroke and those with recurrent stroke.

Previous studies using T2*-weighted MR imaging have revealed that there is an association between presence of microbleeds and small-artery disease (3–10), as was also indicated by the results of the present study, which showed a high frequency of microbleeds in patients with intracerebral hemorrhage or severe leukoaraiosis but no association between presence of microbleeds and intracranial large-artery diseases. Association of microbleeds with small-artery diseases but not with intracranial large-artery diseases was further indicated by the results; among patients with intracranial large-artery diseases, those with microbleeds showed a significantly higher prevalence of hypertension or lacunar infarction, which is associated with small-artery disease, than did those without microbleeds. However, to the best of our knowledge, few studies have focused on microbleeds in patients with recurrent stroke. Some studies have included cases of recurrent stroke. Roob et al (5) reported that among patients with primary intracerebral hemorrhage, those with microbleeds more frequently have histories of stroke than do those without. Kato et al (7) revealed a correlation between number of microbleeds and number of intracerebral hemorrhages or lacunar infarctions. However, no detailed evaluation of the combination of stroke subtypes was conducted in those studies.

The present study clearly showed that patients with recurrent stroke had a higher prevalence and higher grade of microbleeds than did those with primary stroke. In addition, the prevalences of microbleeds were similar but not exactly the same in patients with primary and recurrent stroke with each subtype of stroke; although microbleeds were associated more with intracerebral hemorrhage than with ischemic stroke in patients with primary and recurrent stroke, their prevalence was high in patients with recurrent stroke with all combinations of subtypes. Association between microbleeds and symptomatic intracerebral hemorrhage has been shown in many studies (8–10, 20–24). Tsushina et al (9) reported that the presence of microbleeds was most significantly correlated with history of hemorrhagic stroke. Microbleeds have been reported to be a risk factor for acute postischemic cerebral hemorrhage (22, 23) and also to be associated with intracerebral hemorrhage in patients with cerebral amyloid angiopathy (20, 21). In addition, some studies have indicated that the presence of microbleeds increases the risk of hemorrhagic transformation in patients receiving thrombolytic therapy for acute ischemic stroke (23) or the risk of aspirin-associated intracerebral hemorrhages (10). In the present study, two antiplatelet-treated cases of intracerebral hemorrhage exhibited severe microbleeds. The presence of microbleeds may identify the patients with bleeding-prone microangiopathy, by which decision of using antiplatelet or anticoagulation therapy after ischemic stroke would be possible. Cohort studies are needed to clarify whether patients with microbleeds are really prone to bleeding or whether both microbleeds and symptomatic intracerebral hemorrhage occur after the progression of microangiopathy.

The notable findings of this study are the high frequency of microbleeds in patients with recurrent stroke and the different microbleed prevalences in patients with each subtype of recurrent stroke than in patients with each subtype of primary stroke. Not only were extremely high prevalences shown in patients with intracerebral hemorrhage alone and in patients with a combination of intracerebral hemorrhage and ischemic stroke, but also, a relatively high prevalence (50%) was shown in patients with ischemic stroke alone. This may be explained by the more severe leukoaraiosis in patients with recurrent stroke than in patients with primary stroke. Previous studies have revealed that microbleeds are associated with leukoaraiosis (3, 5, 7–9) but not with intracranial large-artery diseases (18), indicating that small-artery disease results in the presence of microbleeds. In addition, leukoaraiosis has been shown to be closely linked with both intracerebral hemorrhage and ischemic injury (25–27). Either rupture or occlusion associated with microangiopathy may result in intracerebral hemorrhage or ischemic stroke, depending on the circumstances. Kim et al (8) revealed that microbleeds are a predictor of intracerebral hemorrhage in patients with no or mild leukoaraiosis but they occur similarly in association with both ischemic stroke and hemorrhagic stroke in patients with advanced leukoaraiosis. Progression of leukoaraiosis in the course of

continuous disturbance of a small artery related to long-standing exposure to stroke risk factors after primary stroke might result in the appearance of microbleeds and finally result in recurrence of stroke of any subtype, not restricted to intracerebral hemorrhage.

Conclusion

Asymptomatic microbleeds shown by T2*-weighted MR imaging frequently occur in patients with recurrent stroke, either hemorrhagic or ischemic stroke, and the microbleeds are closely associated with severity of leukoaraiosis. The presence of microbleeds may be an increased risk factor for recurrent stroke, and we might be able to identify those patients who are likely to experience recurrent stroke.

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Clinical significance of cerebrovascular reserve in acetazolamide challenge —Comparison with acetazolamide challenge H_2O-PET and Gas-PET—

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Objective: The response of cerebral blood flow (CBF) to acetazolamide (ACZ) challenge is frequently determined in clinical settings to evaluate cerebrovascular reserve (CVR). A reduced CVR can indicate patients with occlusive cerebrovascular disease and compromised hemodynamics who may be at increased risk of cerebral ischemia. However, how precisely ACZ reflects cerebral hemodynamic impairment remains obscure. The present study aims to clarify the pathological significance of CVR in patients with occluded carotid arteries. ***Methods:*** We recruited seventeen patients with occlusive lesions in the internal carotid artery (ICA) or middle cerebral artery (MCA). We assessed these patients in terms of resting cerebral blood flow (CBF) and the CVR response to ACZ challenge using H_2O positron emission tomography (PET). In addition, we evaluated hemodynamic parameters including oxygen extraction fraction (OEF) using Gas-PET. ***Results:*** We identified a significant negative correlation between the CVR and OEF or the cerebral blood volume (CBV)/CBF ratio, as a potential index of cerebral perfusion pressure. Although the CVR values were reduced in all regions with elevated OEF (Stage II), these values were highly variable regardless of the CBV/CBF ratios. The cut-off value of CVR alone could not detect Stage II, but when combined with resting CBF, misery perfusion accompanied by increased OEF was detected with high sensitivity (6/7) and specificity (61/62). ***Conclusion:*** CVR could be applied as an index reflecting both autoregulatory capacity and OEF. The present study also supported the notion that SPECT with ACZ challenge can be clinically applied to detect misery perfusion.

Key words: acetazolamide, hemodynamics, positron emission tomography

INTRODUCTION

DETERMINING THE DEGREE of hemodynamic compromise in chronic cerebrovascular disease is clinically important to predict subsequent ischemic stroke.[1–3] According to Powers' classification of chronic hemodynamics compromised with occlusive cerebrovascular disease,[4,5] hemodynamic impairment can be categorized into two stages. Stage I (autoregulatory vasodilatation) is defined as an increase in cerebral blood volume (CBV) in the hemisphere distal to the occlusive lesion, with normal cerebral blood flow (CBF), oxygen extraction fraction (OEF), and cerebral metabolism rate for oxygen ($CMRO_2$). Stage II (autoregulatory failure) is characterized by reduced CBF and increased OEF with normal $CMRO_2$ and is termed "misery perfusion."[6] These stages were originally defined using ^{15}O gas steady state positron emission tomography (Gas-PET) and have been widely applied to assess patients with severe atherosclerotic carotid artery stenosis or occlusion. Although PET is a very reliable quantitative tool with which to evaluate cerebral hemodynamic status, the procedure is expensive and is not routinely available.

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