される．

実験小動物の SPECT イメージングではピンホールコリメータを使って高い空間解像度が実現でき，また従来から問題とされた空間解像度の不均一さは撮像軌道の工夫[5]や，複数ホールコリメータの利用によってほぼ解決した．さらに，ヒトなど大きな対象においてもトランケーションによるアーチファクトを回避する理論が開発され，局所を高解像度撮像できることが示された（図 2C）．さらなる技術整備によって実用化が待たれる．

4. 動態解析の進歩

核医学の動態解析における課題のひとつは，動的な機能変化の検出である．従来から一回の検査ではひとつの機能情報が得られるのみで，負荷に対する変化や，状況変化させた際の機能画像の定量化はひとつに限られていた．一方，**図 3A** に示すように複数投与した動態解析において残存薬剤の影響を動態に組み込む理論が提案された[6, 7]．また，PET や SPECT で撮像した画像は，検査中における平均ではなく過渡的な重みを有すること[8, 9]を応用して，検査中の組織血流量やシナプス間隙の内因性神経伝達物質の濃度の時間変化が試みられている．また，脳賦活によるドーパミンリリース変化のタイミングをとらえる試みもなされ，この遅れがある種の疾患の本質であるとしている[10, 11]．図 3B には SPECT 検査中に I-123 標識 iodoamphetamine（IMP）を 2 回投与し，安静時と血管拡張薬（Diamox）投与による血管反応性の検査結果の例を示す．また図 3C には，短時間の間に ^{15}O-標識酸素ガスと ^{15}O-標識水を連続投与し，従来 1 時間以上要していた検査が全体で 6〜9 分間の PET 撮像のみから局所脳血流量（CBF），局所脳酸素代謝量（$CMRO_2$），酸素摂取率（OEF），局所脳血液量（CBV）の画像を計算した例を示す．種々の脳神経イメージングにおいてこのような撮像法の応用が可能であり，これは生体機能の調節機能の解明に貢献すると考えられる．

5. マルチモダリティイメージング

核医学画像と MRI などの形態画像との融合処理は，多くの自動化プログラムが開発され，脳委縮の評価や部分容積効果の補正などに応用されている（**図 4**）．また，CT/PET や CT/SPECT 一体型装置に続いて，MRI/PET 一体化装置の実用化が進んでいる．**図 5A** には，ドイツ国ユーリッヒ研究所で開発中の 9.7 テスラ全身 MRI への高解像度・高感度 PET 組み込みのシェーマを示す．MRI 装置の外に磁気シールドを設置し，さらに外側の RF シールドとの間に血液分析システム一式を設置するなど，極めて大がかりなシステムである．最新の PET 動態解析手法を駆使することで，fMRI や神経連絡イメージングと同時に PET 受容体賦活検査や，MRS，PET 代謝イメージングなど多くの撮像情報から病態研究が試みられる．このような検査においては，特に上で述べたような複数核医学イメージングが望まれる．また，高磁場中ではポジトロン飛程が短くなることが予測され（図 5B）[12]，これは空間解像度というよりも画像コントラストの向上に貢献することが予測されている．実際に，シンチレーション結晶から磁場外の光電子増倍管まで長いライトガイドを装着したり，光

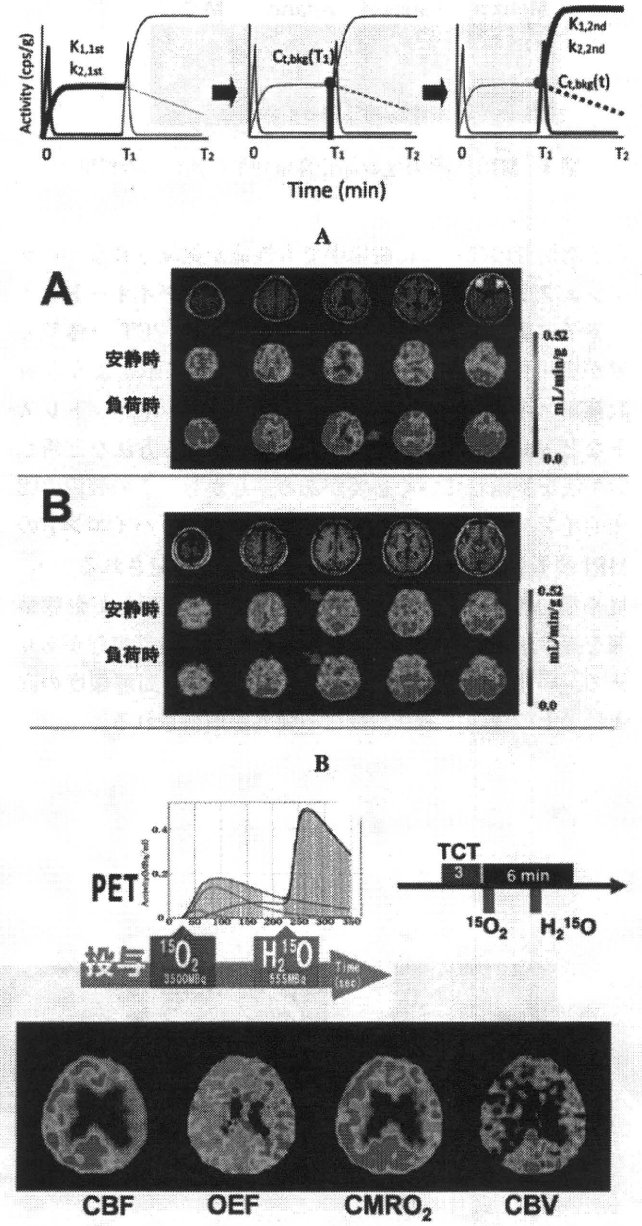


図 3　複数薬剤投与法の効果．（A）複数トレーサ投与時の入力関数と脳内放射能濃度曲線を示す．バックグランド画像を推定し，さらに 2 回目投与後の脳内放射能濃度から機能画像を推定することが可能である．（B）I-123 IMP の 2 回連続投与法に基づく典型的な安静時と Diamox 負荷後の局所脳血流量画像．症例 A では軽度血管狭窄を予測し，症例 B では高リスク血管狭窄を予測した．（C）迅速 ^{15}O-ガス PET 検査への利用．従来 1 時間以上を要していた一連の検査が，10 分間以内のスキャンで可能になった．

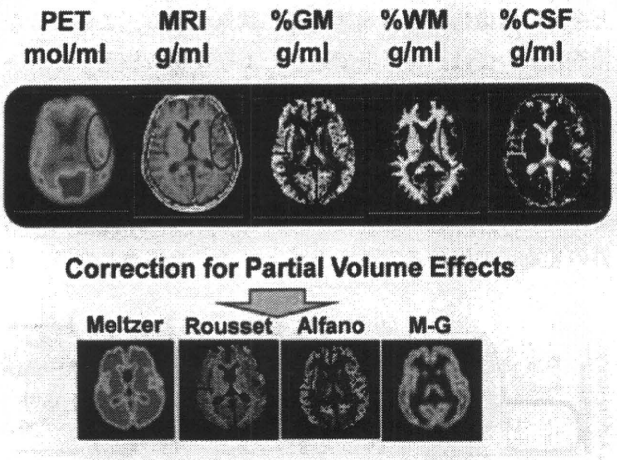


図4　MRI形態画像の部分容積効果の補正への利用.

電子増倍管の代わりに磁場中でも性能が保証されるアバランシェフォトダイオードやシリコンフォトダイオードなどの素子に置き換えることで，具体的なMR-PET一体型装置が実用化されている．現実には，図6に示すような吸収補正スキャンを行うだけでも，RFコイルやヘッドレストなどMRIで撮像できない構造を推定する方法など新しい手法を整備していく必要がある．しかし，この装置の臨床的インパクトは相当大きいと予想される．ハイエンドのMRI装置にPETを装着するシステムが開発される一方，従来型のPETにローコストMRI装置を付加して形態情報を提供するような装置など，いくつかの設計思想がありえる．いずれにせよ，PET計測における時間解像度の向上は至上の課題であり，今後の発展が期待される．

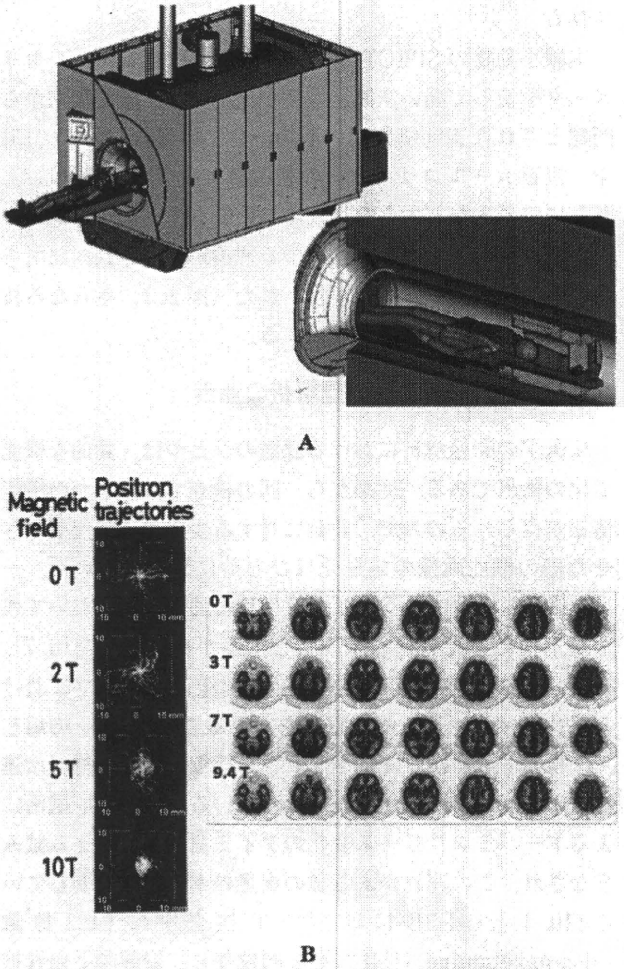


図5　MRIとPETの一体化．(A) ドイツで開発中の9.4 T全身MRI装置と高性能PET装置の一体化のシェーマ．(B) 高磁場中でPET撮像を行うとポジトロン飛程が減少する．これは空間解像度というよりも画像コントラストの向上に貢献するとされる．過去に行われたモンテカルロシミュレーションだけでなく3D脳ファントムを使った検討（I-120を利用）でもその効果が実証されつつある．

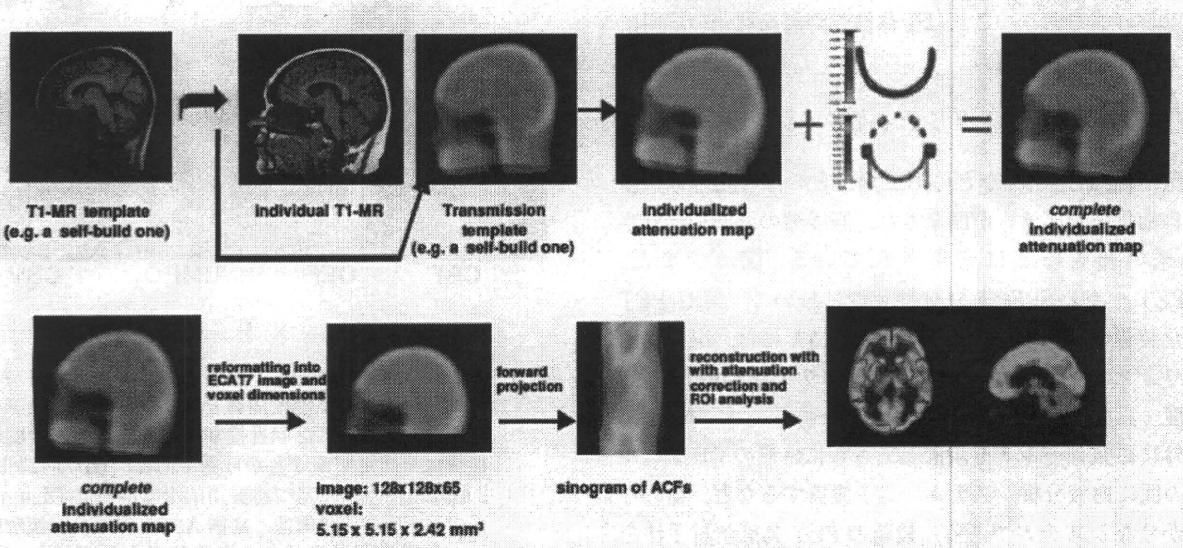


図6　MRI-PET一体型装置におけるMRIデータを使った吸収補正法の一例．予めデータベース化したトランスミッションデータを，MRI撮像データをもとに個々の症例に非線形に一致させる．これにヘッドレストやRFコイルなどの吸収を発生させる構造を付加させる．

6. おわりに

PET，SPECT 機器，動態解析技術の現状と将来への期待について述べた．撮像や画像解析にかかる地道な技術整備が必要であり，この分野における物理工学研究者の活躍を期待したい．

文　献

1. Hapdey S, Soret M, Ferrer L, Koulibaly PM, Henriques J, Bardiès M, Darcourt J, Gardin I, Buvat I: Quantification in SPECT: myth or reality? A multicentric study. IEEE Nuclear Science Symposium Conference Record. **5** (3): 3170-3173, 2004.
2. Fujita M, Ichise M, Zoghbi SS, Liow JS, Ghose S, Vines DC, Sangare J, Lu JQ, Cropley VL, Iida H, Kim KM, Cohen RM, Bara-Jimenez W, Ravina B, Innis RB: Widespread decrease of nicotinic acetylcholine receptors in Parkinson's disease. Ann Neurol. **59** (1): 174-177, 2006.
3. Fujita M, Varrone A, Kim KM, Watabe H, Zoghbi SS, Seneca N, Tipre D, Seibyl JP, Innis RB, Iida H: Effect of scatter correction on the compartmental measurement of striatal and extrastriatal dopamine D2 receptors using [123I]epidepride SPET. Eur J Nucl Med Mol Imaging. **31** (5): 644-654, 2004.
4. Kim KM, Varrone A, Watabe H, Shidahara M, Fujita M, Innis RB, Iida H: Contribution of scatter and attenuation compensation to SPECT images of nonuniformly distributed brain activities. J Nucl Med. **44** (4): 512-519, 2003.
5. Zeniya T, Watabe H, Aoi T, Kim KM, Teramoto N, Hayashi T, Sohlberg A, Kudo H, Iida H: A new reconstruction strategy for image improvement in pinhole SPECT. Eur J Nucl Med Mol Imaging. **31** (8): 1166-1172, 2004.
6. Nishizawa S, Iida H, Tsuchida T, Ito H, Konishi J, Yonekura Y: Validation of the dual-table autoradiographic method to quantify two sequential rCBFs in a single SPET session with N-isopropyl-[123I] p-iodoamphetamine. Eur J Nucl Med Mol Imaging. **30** (7): 943-950, 2003.
7. Kim K, Watabe H, Hayashi T, Hayashida K, Katabuchi T, Enomoto N, Ogura T, Shidahara M, Takikawa S, Eberl S, Nakazawa N, Iida H: Quantitative mapping of basal and vasareactive cerebral blood flow using split-dose ^{123}I-Idoamphetamine and single photon emission computed tomography. Neuroimage. **33** (4): 1126-1135, 2006.
8. Morris ED, Yoder KK, Wang C, Normandin MD, Zheng QH, Mock B, Muzic RF, Jr, Froehlich JC: ntPET: a new application of PET imaging for characterizing the kinetics of endogenous neurotransmitter release. Mol Imaging. **4** (4): 473-489, 2005.
9. Iida H, Kanno I, MS, eds. Rapid measurement of cerebral blood flow with positron emission tomography. Exploring the brain functional anatomy with positron tomography, ed. D. J. Chadwick and J. Whelan. 1991, John Wiley & Sons: Chichester. 23-42.
10. Normandin MD, Morris ED: Temporal resolution of ntPET using either arterial or reference region-derived plasma input functions. Conf Proc IEEE Eng Med Biol Soc. **1**: 2005-2008, 2006.
11. Constantinescu CC, Bouman C, Morris ED: Nonparametric extraction of transient changes in neurotransmitter concentration from dynamic PET data. IEEE Trans Med Imaging. **26** (3): 359-373, 2007.
12. Iida H, Kanno I, Miura S, Murakami M, Takahashi K, Uemura K: A simulation study of a method to reduce positron annihilation spread distributions using a strong magnetic field in positron emission tomography. IEEE Trans Nucl Sci. **33**: 597-600, 1986.

飯田　秀博（イイダ　ヒデヒロ）

昭和 59 年筑波大学博士課程物理学修了．理博，医博．秋田脳研研究員を経て国立循環器病センター研究所の現職へ．その間英国ハマースミス病院客員研究員，フィンランドトゥルク大学研究員，デンマークコペンハーゲン大学客員教授，奈良先端科技大学院大学客員教授，大阪大学招聘教授を併任．PET，SPECT の技術開発と臨床応用が専門．英文原著 167 編．日本核医学会賞など．

IOP，PMB，ISCBFM の理事，JNM，および EJNMMI の編集委員など．

銭谷　勉（ゼニヤ　ツトム）

平成 5 年山形大学大学院修士課程修了．同年，(株)日立メディコ入社．平成 14 年山形大学大学院博士後期課程修了．博士（工学）．日本学術振興会特別研究員，国立循環器病センター研究所研究員，奈良先端科学技術大学院大学特任准教授を経て，現在，国立循環器病研究センター研究所画像診断医学部先進診断機器開発研究室室長．奈良先端科学技術大学院大学客員准教授，大阪大学招聘准教授を併任．SPECT イメージングの研究開発に従事．日本医用画像工学会論文賞，日本核医学会研究奨励賞，米国核医学会若手研究者賞など受賞．

越野　一博（コシノ　カズヒロ）

1993 年北見工業大学大学院博士後期課程システム工学専攻修了．現在，国立循環器病研究センター研究所画像診断医学部研究員．医用画像処理の研究に従事．

平野　祥之（ヒラノ　ヨシユキ）

2008 年大阪大学理学研究科博士課程修了．博士（理学）．2008 年国立循環器病研究センター画像診断医学部，流動研究員として着任．主に PET や SPECT の定量技術に関する研究に従事．また高解像度 SPECT 装置の開発も行っている．

10. 分子イメージング臨床用 PET 装置

平野祥之・飯田秀博

臨床用 PET（positron emission tomography）は，主として癌の診断に利用されているが，国立循環器病研究センターでは虚血性疾患の診断に用いている。本稿では脳循環代謝測定において，どのように脳血流などの診断パラメータが計算されるかを紹介する。さらに解析で用いられるコンパートメントモデルの基礎を述べた後，国立循環器病研究センターで開発された DARG（dual-tracer autoradiographic）法について紹介する。DARG 法により検査時間が 30 分程度に短縮された。またマルチモダリティとして，すでに臨床応用されている PET/CT と現在開発が進んでいる MR/PET の問題点や有用性について述べる。

はじめに

PET（positron emission tomography）は，陽電子放出核種を標識した薬剤を投与し，その動態を解析することで病態の理解や診断に用いられている。日本で PET は約 300 施設に設置されており，臨床検査や研究に用いられている。臨床用 PET の主要用途は癌検査であるが，国立循環器病研究センターでは虚血性疾患などの診断に用いている。本稿では，PET の原理を述べた後，国立循環器病研究センターにおいて，臨床検査として主に行われている脳循環代謝測定における解析手法を紹介する。さらにマルチモダリティとして，その有用性が示されている PET/CT や，現在開発が進んでいる MR/PET について述べる。

Ⅰ. PET

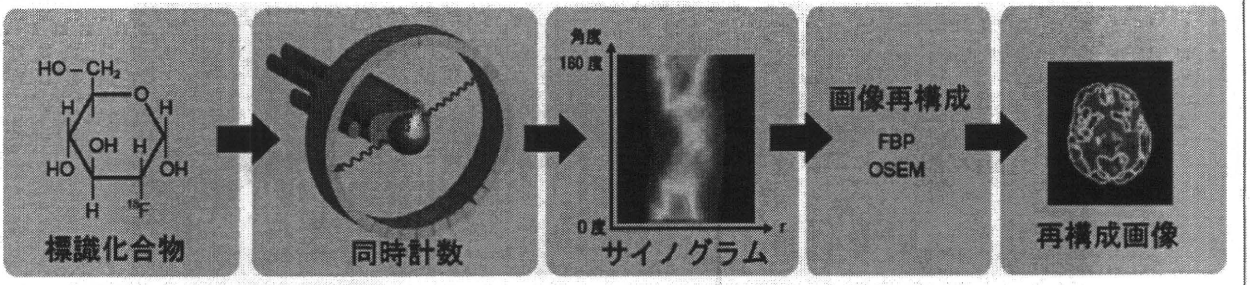
PET は，陽電子放出核種が標識された薬剤（トレーサー）を投与し，その動態を解析することで病態の理解や診断に用いられている。すなわち PET で得られる画像は CT や MRI で得られるような形態画像ではなく，その生体分子の分布や機能を画像化した機能画像である。画像が得られるまでのプロセスを述べると，トレーサーから放出される陽電子は近くの電子と反応し（対消滅），2 本のガンマ線（511keV）を互いに 180 度の方向に放出する。それらをリング状に配置されたシンチレータで検出する。同時に検出（同時計数）したという条件を加えることで，多くのノイズを落とすことができる。ここでわかることは 2 ヵ所の検出位置の対角線上のどこかにトレーサーがあるということである。この対角線のことを LOR（line of response）と呼ぶ。よって角度ごと（0～180 度）にこれらを投影し，この投影画像を画像再構成という数学的なプロセスを経ることで画像ができる（図❶）。画像再構成理論としては FBP（filtered back projection）や OSEM（ordered subsets-expectation maximization）などがある。

癌検査の場合，トレーサーが ^{18}F を標識した FDG（フルオロデオキシグルコース）であり，癌細胞は糖代謝が亢進しているため，FDG 集積箇所が癌の場所と考えられる。また，PET で得ら

key words

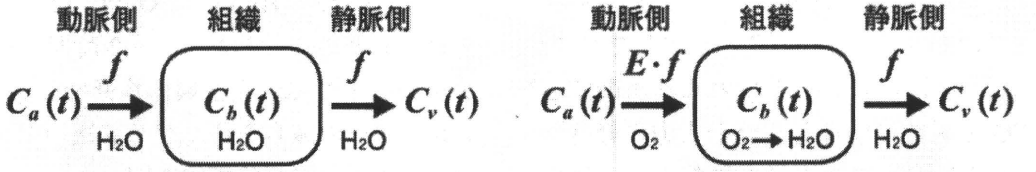
定量測定，DARG 法，コンパートメントモデル，PET/CT，MR/PET，脳循環代謝測定，心筋血流量，モンテカルロシミュレーション，PET の原理

図❶ PET において画像ができるまでの様子



トレーサーから放出される陽電子は近くの電子と反応し（対消滅），2 本のガンマ線（511keV）を互いに 180 度の方向に放出する。それらをリング状に配置されたシンチレータで検出する。ここでわかることは 2 ヵ所の検出位置の対角線上のどこかにトレーサーがあるということである。そして角度ごとにこれらを投影し，投影画像を画像再構成という数学的なプロセスを経ることで画像ができる。

図❷ H_2O，O_2 の動態モデル



A. H_2O の動態モデル　　B. O_2 の動態モデル

H_2O は生体内での挙動が単純で，組織へほぼ 100％取り込まれ，血流量の定量に適している。一方，O_2 は酸素摂取率，血流量に依存して組織に取り込まれ，H_2O に代謝された後，洗い出される。

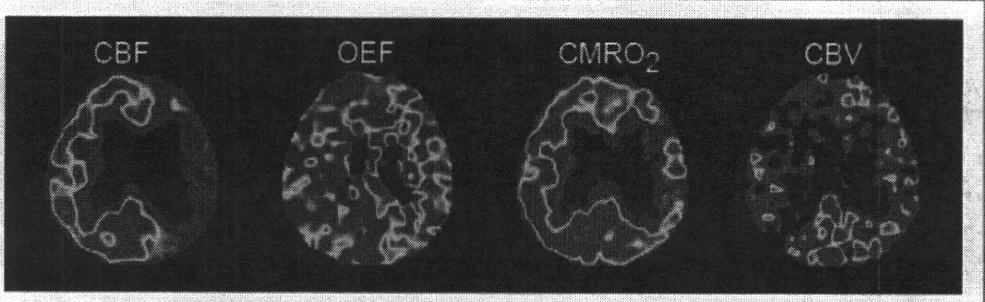
れる関心領域の値は組織放射能濃度［Bq/mL］であり，SUV〔standard uptake value ＝腫瘍や臓器の放射能濃度 /（放射能投与量÷体重）〕という定量値も診断の指標として用いられている。

Ⅱ．臨床検査における脳循環代謝測定

国立循環器病研究センターでは，トレーサーとして ^{15}O を用いて，脳循環代謝量を定量的に測定している。これらの診断結果は，病態把握，血行再建術や血管内治療などの治療法の選択，経過観察に利用されている。脳循環代謝量として，脳血流（CBF：cerebral blood flow），酸素代謝率（$CMRO_2$：cerebral metabolic rate of oxygen），酸素摂取率（OEF：oxygen extraction fraction），脳血液量（CBV：cerebral blood volume）を測定しているが，これらの量はコンパートメントモデルと呼ばれる数学モデルを用いて計算される。ここでコンパートメントモデルによる脳血流の計算方法を簡単に紹介する。脳血流測定に用いられるトレーサーは ^{15}O 標識水（$H_2{}^{15}O$）である。$H_2{}^{15}O$ を静注することもあるが，$C^{15}O_2$ ガスを吸入させ，肺での酵素の働きによって $C^{15}O_2$ は $H_2{}^{15}O$ に変換される。よって $H_2{}^{15}O$ を静注したことと同じになる。$H_2{}^{15}O$ はほぼ 100％脳組織に拡散され，洗い出される。この様子を 1 組織 2 コンパートメントモデルと呼ばれる動態モデルで考える（図❷A）。組織，動脈，静脈の放射能濃度をそれぞれ $C_b(t)$，$C_a(t)$，$C_v(t)$ とする。$C_b(t)$ は PET で得られる画像の関心領域の値から，$C_a(t)$ は入力関数（投与した放射能濃度の時間変化を測定したもの）からわかるが，$C_v(t)$ は知ることができない。そこで脳組織と静脈とのトレーサー濃度は平衡状態にあると仮定し，比例定数を p とすると $C_b(t) = p \cdot C_v(t)$ とかける。よって $C_b(t)$ の時間変化は

$$\frac{dC_b(t)}{dt} = f \cdot C_a(t) - \frac{f}{p} C_b(t) \qquad (1)$$

図❸　脳循環代謝測定による各機能画像



左から脳血流量（CBF），酸素摂取率（OEF），酸素代謝率（$CMRO_2$），脳血液量（CBV）
（グラビア頁参照）

となる。ここでf（mL/g/min）は局所脳血流量（rCBF），pは脳血液分配定数（mL/mL）である。式（1）は，組織中のトレーサー量の時間変化が，組織中に入ってくる量（右辺第一項）と出ていく量（左辺第二項）の差に等しいことを表しており，これはコンパートメントモデルの基本法則でもある。$H_2{}^{15}O$を瞬時に静注し，その入力の経時的変化をPETで測定して血流量を計算する方法はオートラジオグラフィック（ARG法）と呼ばれ，(1)を初期条件$t=0$において$C_b(0)=0$で解くと，組織中の放射能濃度は，

$$C_b(t) = f \cdot C_a(t) \otimes e^{-\left(\frac{f}{p}\right)\cdot t} \qquad (2)$$

となる。⊗は畳み込み積分を表す。よってpが既知であれば血流量fが推定できる。式（2）の直観的な解釈を述べると，組織中のトレーサーは時々刻々と$f \cdot C_a(t)$で流入し，同時に$\exp(-f/p \cdot t)$で流出しており，この状態は⊗で表すことができる。流出を$\exp(-f/p \cdot t)$とかけるのは，組織中トレーサー濃度の減少率は$dC_b(t)/dt = f \cdot C_v(t)$でかけるが，仮定$C_b(t) = p \cdot C_v(t)$により$dC_b(t)/dt = (f/p) \cdot C_b(t)$となる。これは変数分離形の微分方程式で，その解は～$\exp(-f/p \cdot t)$となるからである。

このようにトレーサーとして$C^{15}O_2$（実質上$H_2{}^{15}O$）を用いると，脳血流量が求まり，$^{15}O_2$ガスを用いると酸素代謝率，酸素摂取率が計算できる。$^{15}O_2$は血液中のヘモグロビンと結合し，酸素摂取率に応じて脳組織に取り込まれる。さらに脳組織内で代謝され，代謝水として洗い流される（図❷B）。また，$C^{15}O$ガスを用いると，$C^{15}O$はヘモグロビンと強く結合し，全身に分布する。PETで組織放射能量を測定し，動脈血中$C^{15}O$濃度を測定すれば，組織中の血液量が測定できる。このように，$C^{15}O_2$（$H_2{}^{15}O$），$^{15}O_2$，$C^{15}O$の3検査はワンセットとして行われ，1～2時間の検査時間がかかる。そこで国立循環器病研究センターでは，トレーサーの減衰を待たずして次のトレーサーを投与することで時間短縮を図ったdual tracer ARG法（DARG法）を開発した[1)2)]。ある時間に2つのトレーサーがあってもよいということである。よって，式（2）と同様に組織中の放射能濃度は，

$$C_b(t) = f \cdot F_w \otimes e^{-\left(\frac{f}{p}\right)\cdot t} + E \cdot f \cdot F_o \otimes e^{-\left(\frac{f}{p}\right)\cdot t} + V_B \cdot R_{Hct}(1 - F_v \cdot E)F_o(t) \qquad (3)$$

と書ける。第一項は組織中の$H_2{}^{15}O$からの寄与，第二項は^{15}Oからの寄与，第三項は血管中の^{15}Oを表している。ここで$F_w(t)$，$F_o(t)$はそれぞれ動脈血中の$H_2{}^{15}O$，$^{15}O_2$の放射能濃度（入力関数），Eは OEF，V_Bは CBV，R_{Hct}は小血管と大血管のヘマトクリット比，F_Vは effective venous fraction である。これをそれぞれのPETのスキャン時間で積分すると，

$$\int_w C_b(t)dt = \int_w \left(f \cdot F_w \otimes e^{-\left(\frac{f}{p}\right)\cdot t} + E \cdot f \cdot F_0 \otimes e^{-\left(\frac{f}{p}\right)\cdot t} + V_B \cdot R_{Hct}(1 - F_v \cdot E)F_o(t)\right)dt \qquad (4)$$

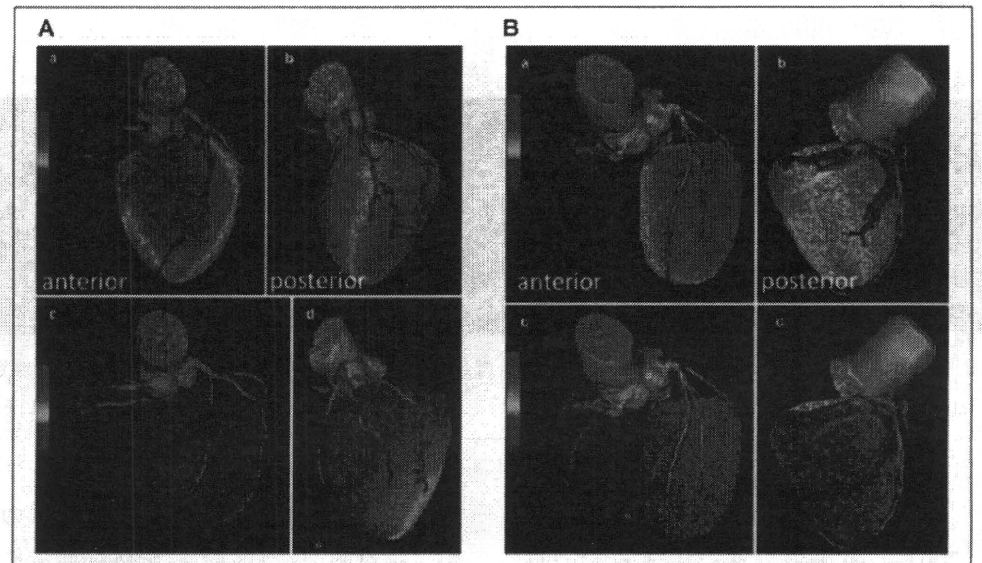
$$\int_o C_b(t)dt = \int_o \left(f \cdot F_w \otimes e^{-\left(\frac{f}{p}\right)\cdot t} + E \cdot f \cdot F_o \otimes e^{-\left(\frac{f}{p}\right)\cdot t} + V_B \cdot R_{Hct}(1 - F_v \cdot E)F_o(t)\right)dt \qquad (5)$$

となる。さらに（5）を変形すると，

$$E = \frac{\int_o \left(C_i(t)dt - f \cdot F_w \otimes e^{-\left(\frac{f}{p}\right)\cdot t} - V_B \cdot R_{Hct} \cdot F_o(t)\right)dt}{\int_o \left(E \cdot f \cdot F_o \otimes e^{-\left(\frac{f}{p}\right)\cdot t} - V_B \cdot R_{Hct} \cdot F_v \cdot F_o(t)\right)dt} \qquad (6)$$

となり，これを式（4）に代入すると，

図❹ PET/CT で得られた ^{15}O による心筋血流分布



CT 画像をボリュームレンダリングし，PET 画像をマッピングしたもの[3]。左右とも冠動脈疾患患者の血流分布で，それぞれ a,b（上 2 つ）は相対画像，c,d（下 2 つ）は絶対画像である。正確な定量測定により，感度・特異度の向上が期待できる。（グラビア頁参照）

$$\int_w C_b(t)dt=\int_w (f\cdot F_w\otimes e^{-\left(\frac{f}{P}\right)\cdot t}+V_B\cdot R_{Hct}\cdot F_o)dt+\int_w (f\cdot F_o\otimes e^{-\left(\frac{f}{P}\right)\cdot t}-V_B\cdot R_{Hct}\cdot F_v\cdot F_o(t))dt \times \frac{\int_o (C_i(t)dt-f\cdot F_w\otimes e^{-\left(\frac{f}{P}\right)\cdot t}-V_B\cdot R_{Hct}\cdot F_o(t))dt}{\int_o (E\cdot f\cdot F_o\otimes e^{-\left(\frac{f}{P}\right)\cdot t}-V_B\cdot R_{Hct}\cdot F_v\cdot F_o(t))dt} \quad (7)$$

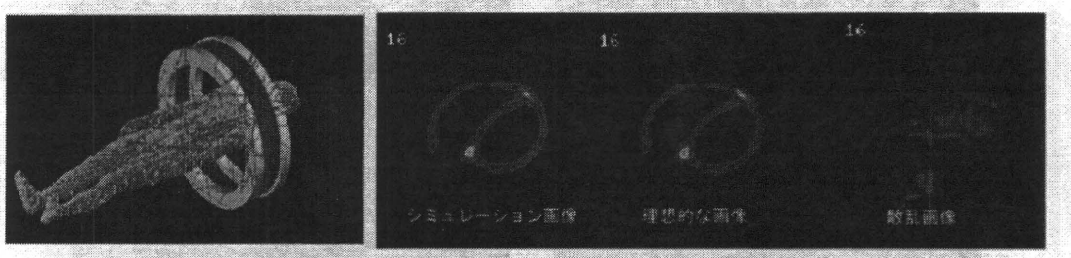
が得られる。これを 2 つのトレーサーを分離した入力関数を用いて，f を参照法（look-up table 法）で推定することができる。さらに式（6）を用いて E（OEF）が計算できる（図❸）。このように国立循環器病研究センターでは，$C^{15}O$ スキャン 6 分，$^{15}O_2$-$H_2{}^{15}O$ 連続スキャン 9 分で，全体として 30 分程度で検査が終了する。この DARG 法に用いられているトレーサーの連続複数投与は，他の臨床および前臨床検査にも応用できる。検査時間の短縮は，患者や実験動物への負担軽減の観点からも望まれる。

ここでは，脳血流代謝測定を例にしてコンパートメントモデルを用いた PET の臨床応用例を紹介した。このコンパートメントは複数あってもよく，コンパートメント間の速度定数が生理学的機能パラメータとなる。このように PET を用いることで，単にトレーサーの分布を知るだけでなく，モデルを工夫することで様々な生理学的機能を評価することができる。

Ⅲ. PET/CT

PET/CT はその名のとおり PET と CT を一体化したもので，明瞭な CT 画像に PET 画像を重ね合わせることで，集積部位の特定が容易になった。これまでもマーカーなどを用いることで異なるモダリティ間の重ね合わせの試みはされているが，やはり同一ベッドで撮像される一体型のほうが重ね合わせのずれは少なく，検査時間の短縮もできる。しかし，PET 画像と CT 画像が完全に一致するわけではなく，秒オーダーの CT 撮像に対して，PET は数分オーダーの撮像時間が必要なため，呼吸や被検者の体動によってずれが生じる。吸収マップに関しては，通常の PET では，$^{68}Ge/^{68}Ga$ のロッドソースによる 10 分程度のトランスミッションスキャンにより吸収マップが作成されるが，PET/CT では CT によって作成されるため，検査時間が短縮される。CT の X 線のエネルギー（40 ～ 100keV）は，511keV に比べて低いが，非線形に外挿することで 511keV の吸収マップが作成できる。しかし，（特に腕を下ろした場合の胸部撮像の場合）CT の視野と PET の視野が異なるため，CT による吸収マップでは補正しきれない

図❺　数値人体モデルを GEANT4 に組み込んだところ（A）とシミュレーションによって得られた心筋画像の例（B）



シミュレーションなので，散乱線を除去したもの（理想的な画像）と散乱線のみで再構成した画像が得られる。（グラビア頁参照）

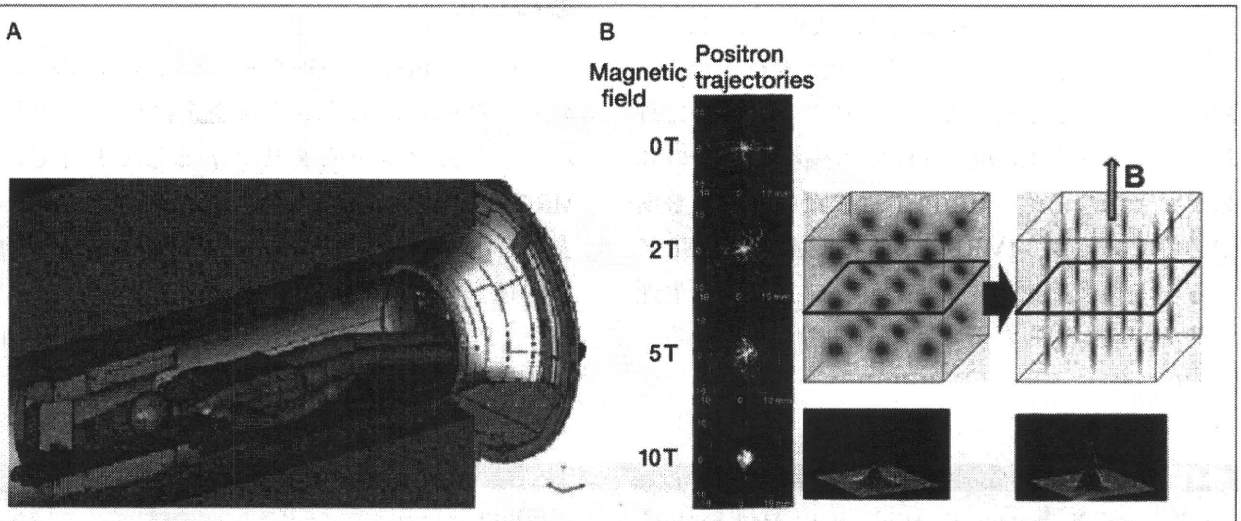
こともある。

PET/CT は 2001 年頃から急速に広まった。日本においても 2003 年には PET/CT の検査数はほぼゼロであったが，2007 年には PET の検査数と並び，2009 年にはほぼ 2 倍になった（日本アイソトープ協会 PET 検査件数に関するアンケート調査報告書のデータから）。今後も TOF（time-of-fright）や DOI（depth-of-interaction）などの技術を導入することで，より高い分解能をもつ PET/CT が開発されるだろう。

図❹に ^{15}O ガスを用いた PET/CT の心筋血流診断画像を示す[3]。これは CT 画像をもとにボリュームレンダリングした 3D 画像に PET の画像をマッピングしたものである。これまでは心筋血流量分布を示すのに，心尖部を中心に円状に心筋を展開したブルズアイ（極座標表示）を用いてきたが，この図は患者にもわかりやすい診断画像といえる。このように PET/CT は癌検査だけでなく，心臓検査においてもその有用性が期待されており，例えば CT によるカルシウムスコアと PET による冠血流予備能の結果を合わせることで，早期冠動脈疾患のリスク評価などがある[4]。

さて，**図❹ A** は労作性狭心症の患者の心筋血流分布であるが，上 2 つは相対画像で，下 2 つは絶対画像（定量画像）である[3]。相対画像においては前壁に大きな血流欠損がみられるが，絶対画像を見ると，側壁にも欠損が確認でき，下側壁のみ正常だといえる。また，**図❹ B** の上 2 つも同様に相対画像，下 2 つは絶対画像であるが，相対画像においては下側壁に血流欠損の疑いがあるが，絶対画像においては全体に血流値が落ちていることがわかる。5 ～ 10％の患者がこのように全体的に血流値が落ちているといわれている。このように血流値などを定量することで，感度（患者が病気にかかっている場合に検査結果が陽性になる確率），特異度（患者が病気にかかっていない場合に検査結果が陰性になる確率）の向上が期待できる。しかし，この定量性を妨げる要因の 1 つとして散乱同時計数がある。これは一方あるいは両方のガンマ線が散乱したのち，同時計数され，間違った LOR が得られることである。この散乱線を補正する手法は様々提案されているが，視野外に強い放射能がある場合においても正確に補正できるかは，あまり調べられていない。特に ^{15}O 心筋血流測定の場合，視野外に位置する肝臓の集積が大きく，ある時間には心臓の約 1.5 倍になることもある。国立循環器病研究センター画像診断医学部では，このような場合でも散乱線補正が有効であるか調べるために，非常にリアルな系でモンテカルロシミュレーションを行い，特に視野外起源の放射能による散乱線の影響を調べている。**図❺**に示すように，情報通信研究機構が開発した数値人体モデル[5]をシミュレーションライブラリー GEANT4 に組み込んで詳細なシミュレーションを行っている。これにより，シミュレーションにおける画像への散乱線の寄与が明確となり，定量値への影響を調べることができる。

図❻ ユーリッヒ研究所における開発中 MR/PET の概念図（文献 6 より）



10 テスラ程度の磁場をかけることで陽電子の飛程が短くなり，画像のコントラストが良くなることを示している[7]。

Ⅳ. MR/PET

PET/CT に続いて，MR/PET の開発が進められている。MR は特に柔組織のコントラストに優れており，放射線の被曝低減からもその臨床応用が期待されている。また，MR 画像を用いた部分容積効果の補正にも使用できる。ヒト用臨床機としては市場に出ていないが，研究用として MRI のボア内側に PET を挿入するタイプ（Siemens BrainPET System）や，数 m 離れたところに PET，MRI がそれぞれ設置され，同一のベッドで移動するタイプ（Philips Gemini TF PET/MR System）がある。しかし MR/PET の場合には，技術的な問題がいくつか挙げられている。

PET に必要な検出器や回路などが磁場を乱したり，反対に MRI に必要な装置（コイルやマグネット）がガンマ線の吸収や散乱に影響を与え，アーチファクトが生じる可能性がある。また PET においてガンマ線の検出は，ガンマ線と相互作用して発光するシンチレータと，そのシンチレーション光を検出する PMT で構成されているが，PMT は磁場の影響を受けやすく，磁場存在下では使用できない。そこで，シンチレーション光を光ファイバーで磁場の影響が少ない場所まで伝送し，PMT を用いるという策が講じられているが，この場合，光ファイバーの接続部などにおける光漏れのため，エネルギー分解能が低下してしまう。よって光センサーとしては，磁場の影響を受けにくく，コンパクトなアバランシェフォトダイオード（APD）や SiPMT（Silicon photomultiplier）の使用が検討されている。他にも，PET における定量測定には動脈採血などが必要であるが，これらにも磁場対策が必要である。

さらに，PET を MR のボアに挿入するタイプの場合，^{68}Ge/^{68}Ga のロッドソースによるトランスミッションを行うスペースがない。そこで新たな吸収マップの作成法が提案されている。1 つは，MRI 画像からセグメンテーションを行い，柔組織，空気，骨などに分け，それぞれの吸収係数を与えて作成するというものである。もう 1 つは MR からテンプレート画像を作成し，それを基にして個人の吸収マップを作る方法がある[6]。**図❻**は開発中のユーリッヒ研究所（ドイツ）にある 9.4 テスラ全身用 MR/PET の概念図である。最新の PET 動態解析手法を駆使することで，fMRI や神経連絡イメージングと同時に PET 受容体賦活検査や，MRS，PET 代謝イメージングなど多くの撮像情報から病態研究が試みられる。さらに，このような高い磁場をかけることで画像のコントラストが向上することが期待きる。トレーサーから放出される陽電子は，組織内で数 mm 程度移動してから対消滅が起きる。よって，たとえ PET

が究極の分解能をもったとしてもこの飛程があるため，トレーサーの位置を正確に決めることはできない。しかし磁場をかけることで，飛程が短くなりコントラストが良くなる。このことはすでに計算されており，10テスラ程度の磁場で，この効果が顕著になる[7]。MR/PETはまだ技術的な整備が必要であるが，fMRIによる機能画像とPETによる機能画像を比較することで，より多くの生理学的な知見が得られることでも期待されている。

おわりに

本稿ではPETの原理を述べ，国立循環器病研究センターでの脳循環代謝測定について紹介した。さらにマルチモダリティとしてPET/CTやMR/PETの現在の状況を簡単に述べた。文献8の表現を借りると，Nuclear Medicineはその不明瞭な画像から“Unclear” Medicineと言われたりするが，PET/CTやMR/PETの出現で“New-Clear” Medicineと呼ばれるであろう。

参考文献

1) Kudomi N, Watabe H, et al : Phys Med Biol 52, 1893-1908, 2007.
2) Kudomi N, Hayashi T, et al : J Cereb Blood Flow Metab, 1-16, 2005.
3) Knuuti J, Kajander S, et al : J Nucl Cardiol 16, 497-506, 2009.
4) Schwaiger M, Ziegler SI, et al : Eur J Radiol 73, 494-503, 2010.
5) Nagaoka T, et al : Phys Med Biol 49, 1-15, 2004.
6) Herzog H, Pietrzyk U, et al : Neuroimage 49, 2072-2082, 2010.
7) Iida H, Kanno I, et al : IEEE Trans Nucl Sci 33, 597-600, 1986.
8) Lonsdale MN, Beyer T : Eur J Radiol 73, 452-460, 2010.

平野祥之

2008年　大阪大学理学研究科博士課程修了，博士（理学）
2008年　国立循環器病研究センター画像診断医学部流動研究員

主にPETやSPECTの定量技術に関する研究に従事。また高解像度SPECT装置の開発も行っている。

Residual Vessel Length on Magnetic Resonance Angiography Identifies Poor Responders to Alteplase in Acute Middle Cerebral Artery Occlusion Patients

Exploratory Analysis of the Japan Alteplase Clinical Trial II

Teruyuki Hirano, MD; Makoto Sasaki, MD; Etsuro Mori, MD; Kazuo Minematsu, MD; Jyoji Nakagawara, MD; Takenori Yamaguchi, MD; for the Japan Alteplase Clinical Trial II Group

Background and Purpose—It remains unknown whether the effects of 0.6 mg/kg alteplase differ with occlusion site of the middle cerebral artery (MCA). We therefore evaluated the effects of 0.6 mg/kg intravenous alteplase in patients with different sites of MCA occlusion.

Methods—An exploratory analysis was made of 57 patients enrolled in the Japan Alteplase Clinical Trial II (J-ACT II), originally designed to evaluate 0.6 mg/kg alteplase in Japanese patients with unilateral occlusion of the MCA (M1 or M2 portion). The residual vessel length (in mm), determined by pretreatment magnetic resonance angiography, was used to reflect the occluded site. The proportions of patients with valid recanalization (modified Mori grade 2 to 3) at 6 and 24 hours and a modified Rankin Scale (mRS) score of 0 to 1 and of 0 to 2 at 3 months were compared between the groups dichotomized according to length of the residual vessel. Multiple logistic-regression models were generated to elucidate the predictors of valid recanalization, mRS 0 to 1, and mRS 0 to 2.

Results—Receiver operating characteristics analysis revealed that 5 mm was the practical cutoff length for dichotomization. In patients with an M1 length <5 mm (n=12), the frequencies of valid recanalization at 6 and 24 hours (16.7% and 25.0%) were significantly lower compared with those (62.1% and 82.8%, respectively) of the 45 patients with a residual M1 length ≥5 mm and an M2 occlusion (P=0.008 for 6 hours, P<0.001 for 24 hours). The proportions of patients who achieved an mRS of 0 to 1 and an mRS of 0 to 2 were also lower for those with an M1 length <5 mm (8.3% and 16.7%, respectively) compared with the other group (57.8% and 68.9%, respectively; P=0.003 for mRS 0 to 1, P=0.002 for mRS 0 to 2). In logistic-regression models, the site of MCA occlusion (<5 mm) was a significant predictor of valid recanalization at 6 and 24 hours and of an mRS of 0 to 1 and of mRS of 0 to 2.

Conclusions—In patients with acute MCA occlusion, a residual vessel length <5 mm on magnetic resonance angiography can identify poor responders to 0.6 mg/kg alteplase.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00412867.

(*Stroke*. 2010;41:2828-2833.)

Key Words: acute ischemic stroke ■ middle cerebral artery occlusion ■ tissue plasminogen activator ■ recanalization ■ magnetic resonance angiography

Intravenous thrombolysis with recombinant tissue plasminogen activator is effective in carefully selected patients with acute ischemic stroke.[1,2] Among patients treated with intravenous alteplase, stroke severity, systolic hypertension, early ischemic changes on computed tomography, persistent arterial occlusion, stroke subtype, and time to thrombolytic treatment have been repeatedly demonstrated as independent predictors of poor outcome.[3–10] Furthermore, the Japan Alteplase Clinical Trial II (J-ACT II) clearly demonstrated that recanalization of the occluded artery represented the most powerful predictor of a favorable outcome at 3 months in selected patients with magnetic resonance angiography (MRA)–documented middle cerebral artery (MCA) occlusions.[11] Information concerning early predictors of recanalization resistance may thus be useful for selecting patients to receive more aggressive reperfusion strategies.

Previous angiographic,[12–14] transcranial Doppler,[15] and MRA[16–18] studies have demonstrated that more proximal

Received June 22, 2010; accepted September 7, 2010.

From the Department of Neurology (T.H.), Faculty of Life Sciences, Kumamoto University, Kumamoto; Advanced Medical Center (M.S.), Iwate Medical University, Morioka; Department of Behavioral Neurology and Cognitive Neuroscience (E.M.), Tohoku University Graduate School of Medicine, Sendai; Department of Stroke and Cerebrovascular Diseases (K.M.), National Cerebral and Cardiovascular Center, Suita, Osaka; Department of Neurosurgery and Stroke Center (J.N.), Nakamura Memorial Hospital, Sapporo; and National Cardiovascular Center (T.Y.), Suita, Osaka, Japan.

Correspondence to Teruyuki Hirano, Department of Neurology, Faculty of Life Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-0811, Japan. E-mail terry07@kumamoto-u.ac.jp

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.110.594333**

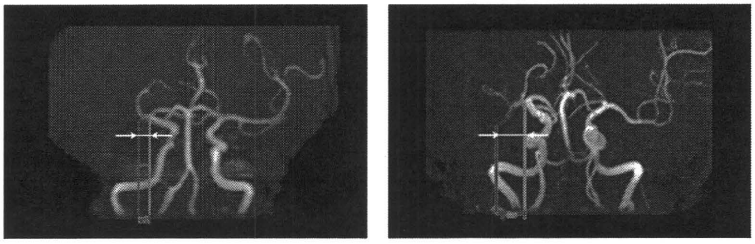


Figure 1. Measurement of residual vessel length in patients with M1 occlusions. Examples are shown of the residual vessel length measured by 3-dimensional time-of-flight MRA. The site of M1 occlusion was determined in an anteroposterior view as the horizontal distance from the ICA bifurcation to the distal end of the flow signal.

occlusions, such as those of the internal carotid artery (ICA)[14,17–20] or tandem ICA/MCA,[21] carry a greater thrombus burden, whereas distal MCA occlusions are more likely to recanalize with systemic alteplase therapy. A meta-analysis revealed that recanalization, either spontaneous or related to thrombolytic or interventional therapies, is less likely with ICA occlusions.[22] ICA occlusion has been shown to predict a poorer clinical outcome compared with MCA occlusion.[14,17,19,20] However, little is yet known about the differences in recanalization rates and response to alteplase among patients with various sites of MCA occlusion. We therefore performed an exploratory analysis of patients with MCA occlusion enrolled in J-ACT II, giving special attention to the residual vessel length as documented on pretreatment MRA.

Methods

J-ACT II is a prospective, single-dose, open-label, multicenter, phase IV trial, originally designed to evaluate 0.6 mg/kg alteplase in Japanese patients with unilateral occlusion of the MCA. Details of the trial have been published previously.[11] In brief, 58 patients with ischemic stroke within 3 hours of onset whose arterial occlusion was identified in the M1 or M2 segment on standardized MRA were enrolled. The results showed that the rates of early and delayed recanalization and a favorable outcome elicited by 0.6 mg/kg alteplase were comparable to the previously reported findings for the regular dose of 0.9 mg/kg.

Site of MCA Occlusion

All baseline MRA data were re-evaluated centrally by 2 reviewers, 1 expert neurologist, and 1 expert neuroradiologist (the image-reading panel), all of whom were blinded to all clinical information except the affected side. For patients with M1 occlusions, the site of occlusion was determined in an anteroposterior view on 3-dimensional time-of-flight MRA as the horizontal distance from the ICA bifurcation to the distal end of the flow signal. The residual vessel length (in mm) was used to reflect the occluded site in the patients with M1 occlusions (Figure 1).

Evaluation of Recanalization

MRA was repeated at baseline, 6 hours, and 24 hours after symptom onset. The time allowance for the 6-hour MRA was between the end of alteplase infusion and 8 hours from symptom onset, and that for the 24-hour MRA was between 24 and 36 hours after symptom onset.

Recanalization was evaluated centrally by the image-reading panel according to the modified Mori grade: grade 0, no reperfusion; grade 1, movement of thrombus not associated with any flow improvement; grade 2, partial (branch) recanalization in <50% of the branches in the occluded arterial territory; and grade 3, nearly complete recanalization with reperfusion in ≥50% of the branches in the occluded arterial territory.[11] The recanalization rate was estimated by regarding grades 2 and 3 as valid recanalization, corresponding to Thrombolysis in Myocardial Infarction grades 2 and 3.

Clinical Evaluation

Functional outcome after 3 months was assessed by the modified Rankin Scale (mRS) score. Patients with an mRS of 0 to 1 at 3 months were regarded as having a favorable outcome. In addition, an mRS of 0 to 2 was judged to be indicative of functional independence, that is, avoiding death or dependency.

Statistical Analysis

The proportions of patients with valid recanalization at 6 and 24 hours after symptom onset, a favorable outcome (mRS 0 to 1), and functional independence (mRS 0 to 2) at 3 months were compared between the groups dichotomized according to length of residual vessel on MRA. Receiver operating characteristics curves were constructed for the patients with M1 occlusions to make comparisons between vessel length and clinical outcome.

The predictors of valid recanalization at 6 and 24 hours, mRS 0 to 1, and mRS 0 to 2 were assessed by multiple logistic-regression analysis. Knowledge of disease-related factors before alteplase administration, such as time from onset, presence of hypertension, diabetes mellitus, baseline National Institutes of Health Stroke Scale score, and Alberta Stroke Program Early Computed Tomography Score (ASPECTS),[6] as well as MCA occlusion site, was included in a stepwise regression analysis, for which age and sex were forcibly entered into the model to adjust for their possible confounding effects.

Table 1. Comparison of Demographic and Baseline Characteristics of the Patients (N=57) According to Site of MCA Occlusion

	Total (N=57)	M1 <5 mm (n=12)	M1 ≥5 mm (n=29)	M2 (n=16)
Mean±SD age, y	70.7±11.2	74.6±9.8	66.4±11.7	75.5±8.2
Female, n	23 (40.4%)	8 (66.7%)	12 (41.4%)	3 (18.8%)
Baseline NIHSS score (range)	12 (5–22)	17 (5–22)	12 (6–22)	11 (5–21)
Stroke subtype, n				
Cardioembolic	49 (86.0%)	10 (83.3%)	25 (86.2%)	14 (87.5%)
Atherothrombotic	5 (8.8%)	2 (16.7%)	2 (6.9%)	1 (6.3%)
Other/not differentiated	3 (5.3%)	0 (0%)	2 (6.9%)	1 (6.3%)
Concomitant diseases				
Hypertension, n	36 (63.2%)	9 (75.0%)	13 (44.8%)	14 (87.5%)
Diabetes	10 (17.5%)	2 (16.7%)	3 (10.3%)	5 (31.3%)
Dyslipidemia	18 (31.6%)	3 (25.0%)	10 (34.5%)	5 (31.3%)
Atrial fibrillation	34 (59.6%)	9 (75.0%)	15 (51.7%)	10 (62.5%)
Previous stroke/TIA	12 (21.1%)	1 (8.3%)	7 (24.1%)	4 (25.0%)
ASPECTS value (range)	9 (3–10)	8 (3–10)	9 (5–10)	9 (7–10)

NIHSS indicates National Institutes of Health Stroke Scale; TIA, transient ischemic attack. Data show the mean (SD), median (interquartile range), or No. (%).

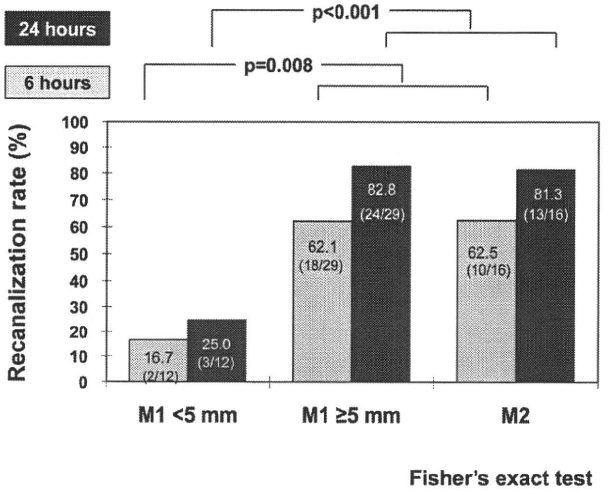


Figure 2. Rate of valid recanalization at 6 and 24 hours by site of vessel occlusion. The rate of valid recanalization was significantly lower in patients with a residual M1 length <5 mm at both 6 and at 24 hours.

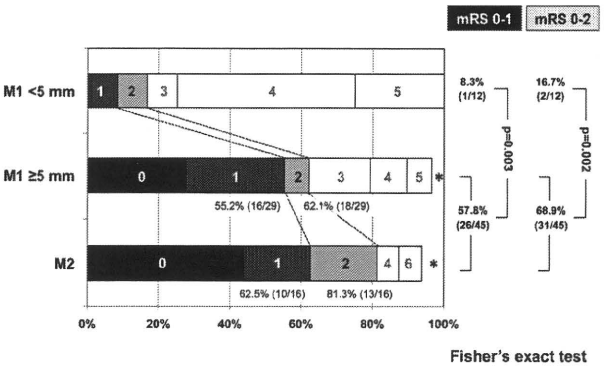


Figure 3. Distribution of scores at 3 months on the mRS scale by site of vessel occlusion. The proportion of patients with a favorable outcome, ie, an mRS score of 0 to 1, was significantly lower in patients with a residual M1 length <5 mm. Similar results were obtained when the frequency of functional independence, ie, an mRS of 0 to 2, was investigated. *Data were not obtained in 1 patient each with a residual M1 length ≥5 mm and M2. These patients were assigned an mRS ≥3.

To examine the possible interaction of MCA occlusion site with recanalization for the 3-month outcome, the following recanalization patterns were evaluated with the logistic model in addition to the disease-related factors: (1) model 1, in which recanalization on 6-hour MRA was entered; (2) model 2, in which recanalization on 24-hour MRA was entered; and (3) model 3, in which recanalization within 6 hours and delayed recanalization (that is, arterial occlusion unchanged on 6-hour MRA but recanalized on 24-hour MRA) were entered. Significance was set at $P<0.05$ in all models. The odds ratio (OR) and 95% CIs were also determined. SAS 9.1.3 was used for statistical analyses.

Results

Of the 58 patients enrolled in the trial, 41 (70.7%) were evaluated as having an M1 occlusion. Their residual M1 length ranged from 0.0 (origin) to 17.7 mm (distal end), whereas the contralateral M1 length ranged from 19.5 to 32.1 mm (mean±SD, 26.1±3.1 mm). One patient was judged to have no occluded artery on baseline MRA by the image-reading panel and was therefore excluded from the present analysis. The remaining 16 patients (27.6%) were evaluated as having an M2 occlusion. Further analyses were therefore performed on 57 patients with MCA occlusion. Table 1 summarizes these patients' characteristics.

The cumulative frequency of valid recanalization at 6 and 24 hours increased as the residual M1 length increased. No patient had recanalization on 6-hour MRA that subsequently disappeared on 24-hour MRA. Receiver operating characteristics analysis revealed that valid recanalization differed between the groups dichotomized by residual vessel length at both 6 (Az 0.701, $P=0.027$) and 24 (Az 0.817, $P=0.001$) hours. The optimal cutoff residual M1 lengths for predicting valid recanalization at 6 and 24 hours were the same, 5.3 mm. When the patients with M1 occlusions were divided into 2 groups (residual vessel length <5 mm or ≥5 mm), the frequency of valid recanalization was significantly lower in the patients with a residual M1 length <5 mm (n=12) compared with the combined group with an M1 length ≥5 mm (n=29) and those with M2 occlusions (n=16) ($P=0.008$ for 6 hours, $P<0.001$ for 24 hours; Fisher's exact test; Figure 2). In logistic-regression models, the site of MCA occlusion (<5 mm) was the only significant predictor of valid recanalization at both 6 (OR=0.076; 95% CI, 0.010 to 0.573) and 24 (OR=0.023; 95% CI, 0.002 to 0.245) hours.

Similarly, receiver operating characteristics analysis demonstrated that the proportions of patients with a favorable outcome (mRS 0 to 1) and functional independence (mRS 0 to 2) were also different among patients with M1 occlusions, with an optimal cutoff length of 5.3 mm. The distribution of scores on the 3-month mRS was different among patients with M1 lengths <5 mm compared with those with an M1 length ≥5 mm and M2 occlusions (Figure 3). On logistic-

Table 2. Predictors of Favorable Outcome and Functional Independence by Multiple Logistic Regression Analysis

	OR	95% CI	*P* Value
mRS 0–1			
Sex (female vs male)	1.011	0.274–3.726	0.9871
Age (by 1 year)	0.989	0.932–1.050	0.7155
Time from onset to treatment (by min)	0.998	0.971–1.027	0.9112
Diabetes	0.891	0.146–5.428	0.9006
Hypertension	1.872	0.465–7.528	0.3773
Baseline NIHSS (by 1 point)	0.878	0.737–1.046	0.1466
Occluded site (<5 mm vs others)	**0.082**	**0.008–0.812**	**0.0325**
ASPECTS value (by 1 point)	1.429	0.788–2.592	0.2392
mRS 0–2			
Sex (female vs male)	0.639	0.152–2.689	0.5416
Age (by 1 year)	1.016	0.952–1.085	0.6290
Time from onset to treatment (by min)	0.978	0.948–1.008	0.1508
Diabetes	0.607	0.080–4.632	0.6302
Hypertension	1.025	0.235–4.473	0.9743
Baseline NIHSS (by 1 point)	0.890	0.746–1.061	0.1925
Occluded site (<5 mm vs others)	**0.125**	**0.020–0.793**	**0.0274**
ASPECTS value (by 1 point)	**2.121**	**1.082–4.158**	**0.0285**

NIHSS indicates National Institutes of Health Stroke Scale. Table entries in bold-faced type are statistically significant.

Table 3. Predictors of Favorable Outcome and Functional Independence by Multiple-Logistic Regression Analysis in 3 Different Models of Posttreatment Recanalization

	Model 1: 6-Hour Recanalization Model			Model 2: 24-Hour Recanalization Model			Model 3: 6-Hour and Delayed Recanalization Model		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
mRS 0–1									
Sex (female vs male)	0.846	0.198–3.619	0.8212	0.814	0.168–3.933	0.7974	0.668	0.137–3.245	0.6167
Age (by 1 year)	0.986	0.924–1.052	0.6689	0.989	0.921–1.062	0.7555	0.973	0.905–1.046	0.4632
Time from onset to treatment (by min)	1.006	0.976–1.037	0.7024	0.997	0.967–1.027	0.8273	1.003	0.972–1.034	0.8721
Diabetes	0.341	0.042–2.783	0.3152	0.456	0.053–3.893	0.4728	0.281	0.028–2.783	0.2779
Hypertension	1.847	0.419–8.147	0.4177	2.919	0.544–15.671	0.2115	2.556	0.449–13.087	0.2602
Baseline NIHSS (by 1 point)	0.903	0.748–1.091	0.2915	**0.797**	**0.643–0.989**	**0.0391**	0.859	0.701–1.054	0.1456
Occluded site (<5 mm vs others)	0.173	0.016–1.901	0.1515	0.544	0.041–7.290	0.6453	0.568	0.040–8.068	0.6759
ASPECTS value (by 1 point)	1.755	0.881–3.497	0.1096	2.111	0.981–4.541	0.0560	2.007	0.940–4.287	0.0718
Recanalization within 6 h	**6.772**	**1.346–34.080**	**0.0203**	...	...	...	**38.972**	**3.222–471.318**	**0.0040**
Recanalization within 24 h	...	...	...	**32.762**	**3.572–300.514**	**0.0020**	...	...	...
Delayed recanalization	...	...	...	...	...	...	**18.607**	**1.357–255.149**	**0.0286**
mRS 0–2									
Sex (female vs male)	0.546	0.113–2.646	0.4521	0.525	0.100–2.763	0.4471	0.522	0.104–2.636	0.4317
Age (by 1 year)	1.007	0.938–1.081	0.8476	1.017	0.947–1.092	0.6420	1.004	0.935–1.079	0.9029
Time from onset to treatment (by min)	0.987	0.955–1.020	0.4274	0.978	0.946–1.010	0.1784	0.986	0.955–1.018	0.3942
Diabetes	0.233	0.021–2.586	0.2357	0.362	0.035–3.713	0.3926	0.228	0.019–2.730	0.2434
Hypertension	1.115	0.236–5.277	0.8906	1.524	0.298–7.802	0.6129	1.288	0.264–6.281	0.7543
Baseline NIHSS (by 1 point)	0.925	0.759–1.127	0.4382	0.850	0.699–1.035	0.1056	0.911	0.746–1.112	0.3594
Occluded site (<5 mm vs others)	0.250	0.035–1.798	0.1684	0.447	0.052–3.821	0.4618	0.363	0.043–3.073	0.3522
ASPECTS value (by 1 point)	**2.683**	**1.217–5.918**	**0.0145**	**2.949**	**1.279–6.798**	**0.0111**	**2.791**	**1.231–6.331**	**0.0140**
Recanalization within 6 h	**7.362**	**1.250–43.371**	**0.0274**	...	...	...	**13.179**	**1.478–117.510**	**0.0209**
Recanalization within 24 h	...	...	...	**15.502**	**1.953–123.034**	**0.0095**	...	...	...
Delayed recanalization	...	...	...	...	...	...	3.132	0.322–30.427	0.3250

NIHSS indicates National Institutes of Health Stroke Scale. Table entries in bold-faced type are statistically significant.

regression analysis including the disease-related factors present before alteplase administration, a residual M1 length <5 mm was the only significant predictor of a favorable outcome (OR=0.082; 95% CI, 0.008 to 0.812; Table 2). A residual M1 length <5 mm (OR=0.125; 95% CI, 0.020 to 0.793), together with a high ASPECTS value (OR=2.121; 95% CI, 1.082 to 4.158), was significantly related to functional independence at 3 months (Table 2).

Possible interactions between the pretreatment residual vessel length and patterns of recanalization were evaluated by multiple logistic-regression analysis (Table 3). Among the models for favorable outcome, recanalization in model 1, recanalization and baseline National Institutes of Health Stroke Scale score in model 2, and 6-hour and delayed recanalization in model 3 were significant predictors. Among the models for functional independence, recanalization and ASPECTS score in model 1, recanalization and ASPECTS score in model 2, and 6-hour recanalization and ASPECTS score in model 3 were significant predictors.

Discussion

In the present exploratory analysis of the J-ACT II cohort, we found that a residual M1 length <5 mm on MRA was a negative predictor of early and delayed recanalizations as well as for a favorable outcome and functional independence at 3 months. Patients with residual M1 lengths <5 mm are poor responders to 0.6 mg/kg alteplase. The site of vessel occlusion was a strong predictor of outcome before systemic alteplase administration.

In a previous magnetic resonance imaging–based, open-label, nonrandomized study, the German Stroke Excellence Network Initiative,[16] the reported recanalization rate of proximal MCA occlusions was comparable with distal MCA and M2 occlusions (76.7% for the proximal MCA, 60.0% for the distal MCA, and 87.5% for M2) in the 76 patients treated with thrombolysis. On the other hand, the difference in recanalization rate was significant between an MCA origin and other sites of MCA occlusion in our study. In addition to the different alteplase doses between Europe and Japan, the lack of a clear definition of "proximal" and "distal" MCA might have led to this discrepancy. In our study, cumulative analysis followed by receiver operating characteristics analysis demonstrated that <5 mm was the practical cutoff length between proximal and distal sites within the M1 portion.

Our results paralleled those of Saqqur et al,[15] who examined the effects of alteplase by transcranial Doppler. They showed that patients with distal MCA occlusions were more likely to recanalize and were twice as likely to achieve an

mRS of 0 to 1 than were those with proximal MCA occlusions. Their transcranial Doppler–based definitions of the occluded site in the MCA and of complete recanalization differed from ours, however. The proportions of patients achieving an mRS of 0 to 1 decreased with more proximal occlusions: distal MCA, 52%; proximal MCA, 25%; tandem ICA/MCA, 21%; and terminal ICA, 18%.

What are the potential reasons for different outcomes between patients with residual M1 lengths <5 mm and others? In terms of thrombus size and the association of thrombi with atherosclerosis, clot size is bigger in patients with a residual M1 length <5 mm, and there may be differences in clot composition between proximal and distal M1 occlusions.[23] Fibrin-rich clots have been shown to display a greater propensity for lysis by alteplase compared with platelet-rich clots.[10] Relative to other stroke subtypes, the rate of complete recanalization has been reported to be higher in patients with cardioembolic stroke.[10] Although there was no statistical difference, atherosclerotic occlusion was found more frequently in patients with proximal M1 occlusions (16.7% in M1 <5 mm; 6.7% in M1 ≥5 mm and M2, P=0.281).

Another possible explanation concerns the number of perforating arteries originating from the M1 portion. Patients with a residual M1 length <5 mm seldom spare perforators that allow a continuous blood stream. Effective delivery and distribution of alteplase into the clot may thus become severely disturbed. Experimental studies have demonstrated that the fibrinolytic rate is dependent on the pressure gradient to which the clot is exposed.[24]

In our first logistic-regression model including only pretreatment factors, the site of vessel occlusion (M1 <5 mm or other) was a strong predictor of 3-month outcome. Once important posttreatment factors, like early and/or delayed recanalization, were included in the second of the 3 different models, the site of vessel occlusion no longer remained as significant. This is reasonable, because the site of vessel occlusion before treatment with alteplase was strongly correlated to posttreatment recanalization. To achieve an mRS of 0 to 1, the key is recanalization immediately after thrombolysis, as repeatedly reported.[25–29] Using the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Register database, Kharitonova et al[30] also noted that disappearance of a hyperdense MCA signs, an indirect marker of recanalization on computed tomography, was significantly related to functional independence and survival.

On the other hand, an mRS of 0 to 2 might be achieved independently of recanalization if the patient has good collateral flow, indicated by a high ASPECTS value.[31] Regarding the influence of pretreatment ASPECTS, the Pro-Urokinase for Acute Cerebral Thromboembolism II trial demonstrated that patients with ASPECTS scores >7 were 3 times more likely to achieve an mRS of 0 to 2.[32]

It might be reasonable to modify our treatment strategy according to the MRA information concerning the site of pretreatment vessel occlusion. We speculate that patients with M1-origin occlusions (residual vessel length <5 mm) as well as those with ICA occlusions may be potential candidates for rescue interventional therapies, such as intra-arterial thrombolysis and mechanical thrombectomy, should intravenous thrombolysis fail to achieve recanalization and reperfusion.

The present study has several limitations. First, the number of patients was relatively small because the target population was strictly limited to MRA-documented M1 or M2 occlusions. Second, we could not evaluate collateral status because MRA was the only required modality for imaging. Good collateral flow up to the distal end of the clot might have accelerated recanalization.[33] Third, the alteplase dose was 0.6 mg/kg, which is the specified dose in the Japanese license.[34] The recanalization rate in patients with a residual M1 length <5 mm could have been improved with the 0.9 mg/kg dose of alteplase, although J-ACT II demonstrated efficacy in terms of vascular and clinical outcomes.[11]

In conclusion, the effect of 0.6 mg/kg intravenous alteplase differs according to the MRA-documented site of MCA occlusion. In patients with acute MCA occlusions, a residual M1 length <5 mm on MRA can identify poor responders to 0.6 mg/kg alteplase.

Sources of Funding

This clinical trial was supported by Kyowa Hakko Kirin Co, Ltd, and Mitsubishi Tanabe Pharma Corporation.

Disclosures

Teruyuki Hirano has received honoraria from Mitsubishi Tanabe Pharma and Kyowa Hakko Kirin. Makoto Sasaki has received honoraria from Mitsubishi Tanabe Pharma, Kyowa Hakko Kirin, and Lundbeck. Etsuro Mori has received a research grant, honoraria, and consulting fees from Mitsubishi Tanabe Pharma; honoraria and consulting fees from Kyowa Hakko Kirin; and consulting fees from Lundbeck. Kazuo Minematsu has received a research grant and honoraria from Mitsubishi Tanabe Pharma and honoraria from Kyowa Hakko Kirin and Lundbeck. Jyoji Nakagawara has received honoraria from Mitsubishi Tanabe Pharma, Kyowa Hakko Kirin, and Lundbeck. Takenori Yamaguchi has received consulting fees from Mitsubishi Tanabe Pharma and research grants from Kyowa Hakko Kirin and Lundbeck.

References

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med.* 1995;333:1581–1587.
2. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med.* 2008;359:1317–1329.
3. Dávalos A, Toni D, Iweins F, Lesaffre F, Bastianello S, Castillo J. Neurological deterioration in acute ischemic stroke: potential predictors and associated factors in the European Cooperative Acute Stroke Study (ECASS) I. *Stroke.* 1999;30:2631–2636.
4. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study. *J Am Med Assoc.* 2000;283:1145–1150.
5. Marler JR, Tilley BC, Lu M, Brott TG, Lyden PC, Grotta JC, Broderick JP, Levine SR, Frankel MP, Horowitz SH, Haley DC, Lewandowski CA, Kwiatkowski TP, for the NINDS rt-PA Stroke Study Group. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology.* 2000;55:1649–1655.
6. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. *Lancet.* 2000;355:1670–1674.

7. Demchuk AM, Tanne D, Hill MD, Kasner SE, Hanson S, Grond M, Levine SR; The Multicentre tPA Stroke Survey Group. Predictors of good outcome after intravenous tPA for acute ischemic stroke. *Neurology*. 2001;57:474–480.
8. Labiche LA, Al-Senani F, Wojner AW, Grotta JC, Malkoff M, Alexandrov AV. Is the benefit of early recanalization sustained at 3 months? a prospective cohort study. *Stroke*. 2003;34:695–698.
9. Hacke W, Donnan GA, Fieschi C, Kaste M, von Kummer R, Broderick JP, Brott T, Frankel M, Grotta JC, Haley EC Jr, Kwiatkowski T, Levine SR, Lewandowski C, Lu M, Lyden P, Marler JR, Patel S, Tilley BC, Albers G, Bluhmki E, Wilhelm M, Hamilton S; ATLANTIS Trials Investigators; ECASS Trials Investigators; NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. 2004;363:768–774.
10. Molina CA, Montanar J, Arenillas JF, Ribo M, Rubiera M, Alvarez-Sabin J. Differential pattern of tissue plasminogen activator–induced proximal middle cerebral artery recanalization among stroke subtypes. *Stroke*. 2004;35:486–490.
11. Mori E, Minamatsu K, Nakagawara J, Yamaguchi T, Sasaki M, Hirano T; for the J-ACT II Group. Effects of 0.6 mg/kg intravenous alteplase on vascular and clinical outcomes in middle cerebral artery occlusion: Japan Alteplase Clinical Trial II (J-ACT II). *Stroke*. 2010;41:461–465.
12. del Zoppo GJ, Poeck K, Pessin MS, Wolpert SM, Furlan AJ, Ferbert A, Alberts MJ, Zivin JA, Wechsler L, Busse O, Greenlee R, Brass L, Mohr JP, Feldmann E, Hacke W, Kase CS, Biller J, Gress D, Otis SM. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. *Ann Neurol*. 1992;32:78–86.
13. Lewandowski CA, Frankel M, Tomsick TA, Broderick J, Frey J, Clark W, Starkman S, Grotta J, Spilker J, Khoury J, Brott T. Combined intravenous and intra-arterial rt-PA versus intra-arterial therapy of acute ischemic stroke: Emergency Management of Stroke (EMS) Bridging Trial. *Stroke*. 1999;30:2598–2605.
14. Linfante I, Llinas RH, Selim M, Chaves C, Kumar S, Parker RA, Caplan LR, Schlaug G. Clinical and vascular outcome in internal carotid artery vs middle cerebral artery occlusions after intravenous tissue plasminogen activator. *Stroke*. 2002;33:2066–2071.
15. Saqqur M, Uchino K, Demchuk AM, Molina CA, Garami Z, Calleja S, Akhtar N, Orouk FO, Salam A, Shuaib A, Alexandrov AV; for CLOTBUST Investigators. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. *Stroke*. 2007;38:948–954.
16. Röther J, Schellinger PD, Gass A, Siebler M, Villringer A, Fiebach JB, Fiehler J, Jansen O, Kucinski T, Schoder V, Szabo K, Junge-Hülsing GJ, Hennerici M, Zeumer H, Sartor K, Weiller C, Hacke W; for the Kompetenznetzwerk Schlaganfall Study Group. Effect of intravenous thrombolysis on MRI parameters and functional outcome in acute stroke <6 hours. *Stroke*. 2002;33:2438–2445.
17. Nakashima T, Toyoda K, Koga M, Matsuoka H, Nagatsuka K, Takada T, Naritomi H, Minematsu K. Arterial occlusion sites on magnetic resonance angiography influence the efficacy of intravenous low-dose (0.6 mg/kg) alteplase therapy for ischaemic stroke. *Int J Stroke*. 2009;4:425–431.
18. De Silva DA, Brekenfeld C, Ebinger M, Christensen S, Barber PA, Butcher KS, Levi CR, Parsons MW, Bladin CF, Donnan GA, Davis SM; for the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) Investigators. The benefits of intravenous thrombolysis relate to the site of baseline arterial occlusion in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET). *Stroke*. 2010;41:295–299.
19. Kim YS, Garami Z, Mikulik R, Molina CA, Alexandrov AV. Early recanalization rates and clinical outcomes in patients with tandem internal carotid artery/middle cerebral artery occlusion and isolated middle cerebral artery occlusion. *Stroke*. 2005;36:869–871.
20. Marks MP, Olivot JM, Kemp S, Lansberg MG, Bammer R, Wechsler LR, Albers GW, Thijs V. Patients with acute stroke treated with intravenous tPA 3–6 hours after stroke onset: correlations between MR angiography findings and perfusion- and diffusion-weighted imaging in the DEFUSE study. *Radiology*. 2008;249:614–623.
21. Rubiera M, Ribo M, Delgado-Mederos R, Santamarina E, Delgado P, Montaner J, Alvarez-Sabín J, Molina CA. Tandem internal carotid artery/middle cerebral artery occlusion: an independent predictor of poor outcome after systemic thrombolysis. *Stroke*. 2006;37:2301–2305.
22. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. *Stroke*. 2007;38:2438–2445.
23. Marder VJ, Chute DJ, Starkman S, Abolian AM, Kidwell C, Liebeskind D, Ovbiagele B, Vinuela F, Duckwiler G, Jahan R, Vespa PM, Selco S, Rajajee V, Kim D, Sanossian N, Saver JL. Analysis of thrombi retrieved from cerebral arteries of patients with acute ischemic stroke. *Stroke*. 2006;37:2086–2093.
24. Blinc A, Francis CW. Transport processes in fibrinolysis and fibrinolytic therapy. *Thromb Haemost*. 1996;76:481–491.
25. Mori E, Yoneda Y, Tabuchi M, Yoshida T, Ohkawa S, Ohsumi Y, Kitano K, Tsutsumi A, Yamadori A. Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke. *Neurology*. 1992;42:976–982.
26. von Kummer R, Hacke W. Safety and efficacy of intravenous tissue plasminogen activator and heparin in acute middle cerebral artery stroke. *Stroke*. 1992;23:646–652.
27. Yamaguchi T, Hayakawa T, Kiuchi H. Intravenous tissue plasminogen activator ameliorates the outcome of hyperacute embolic stroke. *Cerebrovasc Dis*. 1993;3:269–272.
28. Yamaguchi T, Kikuchi H, Hayakawa T. Clinical efficacy and safety of intravenous tissue plasminogen activator in acute embolic stroke: a randomized, double-blind, dose-comparison study of duteplase. In: Yamaguchi T, Mori E, Minematsu K, del Zoppo GJ, eds. *Thrombolytic Therapy in Acute Ischemic Stroke III*. Tokyo: Springer-Verlag; 1995:223–229.
29. Chalela JA, Kang DW, Luby M, Ezzeddine M, Latour LL, Todd JW, Dunn B, Warach S. Early MRI findings in patients receiving tissue plasminogen activator predict outcome: insights into the pathophysiology of acute stroke in the thrombolysis era. *Ann Neurol*. 2004;55:105–112.
30. Kharitonova T, Thorén M, Ahmed N, Wardlaw JM, von Kummer R, Thomassen L, Wahlgren N, for the SITS investigators. Disappearing hyperdense middle cerebral artery sign in ischaemic stroke patients treated with intravenous thrombolysis: clinical course and prognostic significance. *J Neurol Neurosurg Psychiatry*. 2009;80:273–278.
31. Hirano T, Yonehara T, Inatomi Y, Hashimoto Y, Uchino M. Presence of early ischemic changes on computed tomography depends on severity and the duration of hypoperfusion: a single photon emission-computed tomographic study. *Stroke*. 2005;36:2601–2608.
32. Hill MD, Rawley HA, Adler F, Eliasziw M, Furlan A, Higashida RT, Wechsler LR, Roberts HC, Dillon WP, Fischbein NJ, Fieszt CM, Schulz GA, Buchan AM. Selection of acute ischemic stroke patients for intra-arterial thrombolysis with pro-urokinase by using ASPECTS. *Stroke*. 2003;34:1925–1931.
33. Miteff F, Levi CR, Bateman GA, Spratt N, McElduff P, Parsons MW. The independent predictive utility of computed tomography angiographic collateral status in acute ischaemic stroke. *Brain*. 2009;132:2231–2238.
34. Yamaguchi T, Mori E, Minematsu K, Nakagawara J, Hashi K, Saito I, Shinohara Y. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). *Stroke*. 2006;37:1810–1815.

Effects of 0.6 mg/kg Intravenous Alteplase on Vascular and Clinical Outcomes in Middle Cerebral Artery Occlusion

Japan Alteplase Clinical Trial II (J-ACT II)

Etsuro Mori, MD; Kazuo Minematsu, MD; Jyoji Nakagawara, MD; Takenori Yamaguchi, MD; Makoto Sasaki, MD; Teruyuki Hirano, MD; for the J-ACT II Group

Background and Purpose—The purpose of this study was to evaluate further the efficacy of 0.6 mg/kg intravenous alteplase on vascular and clinical outcomes in patients with middle cerebral artery occlusion in a postmarketing Phase IV trial of prospective cohort study design.

Methods—Alteplase was given intravenously at 0.6 mg/kg to patients with ischemic stroke within 3 hours of onset with MR angiography-documented middle cerebral artery occlusion. Vascular outcome was evaluated by MR angiography at 6 and 24 hours after symptom onset based on the modified Mori grade. The primary end points also included a favorable outcome (modified Rankin Scale 0 to 1 at 3 months after onset) and incidence of symptomatic intracranial hemorrhage within 36 hours after treatment. The impact of recanalization on clinical outcome was assessed by stepwise logistic regression analysis.

Results—Fifty-eight patients were enrolled. Recanalization was noted in 51.7% on 6-hour MR angiography and 69.0% on 24-hour MR angiography. A favorable clinical outcome was achieved in 46.6%. None had symptomatic intracranial hemorrhage. In logistic regression models, recanalization on either 6-hour or 24-hour MR angiography was an independent predictor for clinical outcome as well as the baseline National Institutes of Health Stroke Scale score.

Conclusions—Early recanalization of an occluded middle cerebral artery can be provoked by 0.6 mg/kg intravenous alteplase and may induce a favorable clinical outcome. The rates of recanalization and favorable outcome are comparable to that previously reported with the 0.9-mg/kg dose. (***Stroke.* 2010;41:461-465.**)

Key Words: acute ischemic stroke ■ middle cerebral artery occlusion ■ magnetic resonance angiography ■ recanalization ■ tissue plasminogen activator

Based on the Japan Alteplase Clinical Trial (J-ACT) in 2002 to 2003,[1] the Ministry of Health, Labor and Welfare of Japan approved alteplase at 0.6 mg/kg for treating acute ischemic stroke within 3 hours of symptom onset in October 2005. Although the internationally recommended dosage is 0.9 mg/kg, the 0.6-mg/kg dose had been selected according to previous tissue plasminogen activator data in Japan.[2–4] The underlying rationale has been published on the *Stroke* web site (http://stroke.ahajournals.org/cgi/content/full/37/7/1810).[1] In J-ACT, the efficacy and safety of 0.6 mg/kg intravenous alteplase for ischemic stroke were examined in a prospective cohort study and were compared with data reported for 0.9 mg/kg alteplase in North America and the European Union; the efficacy and safety profiles were compatible with those in the National Institute of Neurological Disorders and Stroke study[5] and those in a meta-analysis of data for 0.9 mg/kg. One of the conditions required by the Ministry of Health, Labor and Welfare at the time of approval was that the dosage efficacy, including potential for occluded artery recanalization, should be documented in an angiography-based study. J-ACT II is thus a prospective cohort study, in which vascular outcome, that is, recanalization of an occluded middle cerebral artery, was documented by MR angiography (MRA) as well as clinical outcome. Recanalization of occluded arteries directly reflects the pharmacological effect of thrombolytics, and early recanalization after thrombolytic therapy represents a powerful factor affecting clinical outcome.[6]

Methods

J-ACT II, a prospective, single-dose, open-label, multicenter, Phase IV trial, was performed at 15 centers in Japan between March 2007

Received November 17, 2009; accepted November 26, 2009.

From the Department of Behavioral Neurology and Cognitive Neuroscience (E.M.), Tohoku University Graduate School of Medicine, Sendai, Japan; Cerebrovascular Division (K.M.), National Cardiovascular Center, Suita, Japan; the Department of Neurosurgery and Stroke Center (J.N.), Nakamura Memorial Hospital, Sapporo, Japan; the National Cardiovascular Center (T.Y.), Suita, Osaka, Japan; Advanced Medical Research Center (M.S.), Iwate Medical University, Morioka, Japan; and the Department of Neurology (T.H.), Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan.

Correspondence to Etsuro Mori, MD, Department of Behavioral Neurology and Cognitive Neuroscience, Tohoku University Graduate School of Medicine, 2-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan. E-mail mori@mail.tains.tohoku.ac.jp

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.109.573477

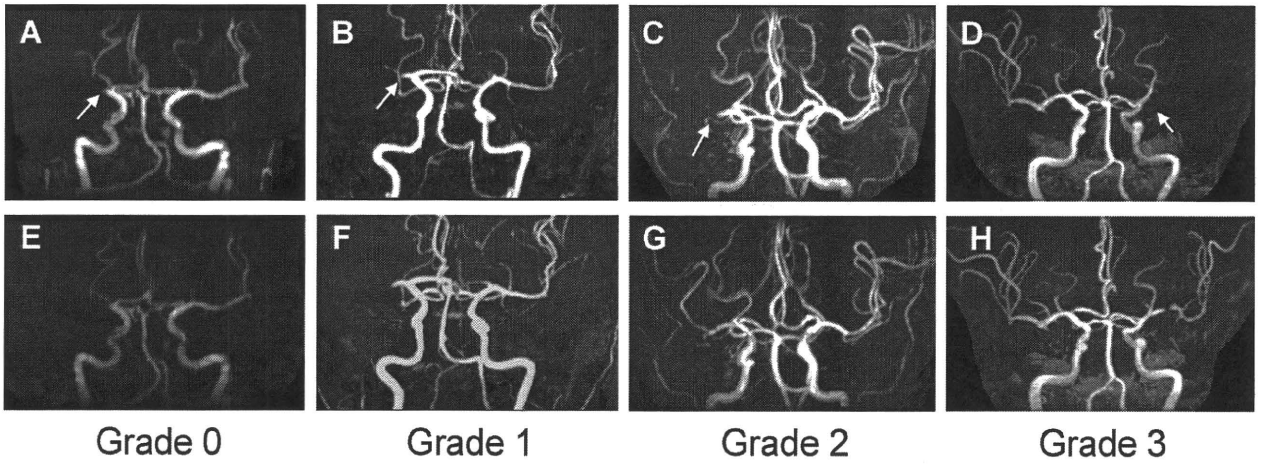


Figure. Modified Mori grades. A–D, Baseline MRA; E–H, follow-up MRA. For details of the grades, see text under "MRA Protocol." The arrow shows the occluded artery.

and July 2008. The protocol was approved by the Institutional Review Board at each center. Written informed consent was obtained from each patient or an appropriate family member before participation in this study. The patients with ischemic stroke within 3 hours of onset whose responsible arterial occlusion was identified in the middle cerebral artery (M1 or M2 segment) by MRA were given 0.6 mg/kg intravenous alteplase with 10% being administered as a bolus followed by continuous infusion of the remainder over 1 hour. Exclusion criteria were adopted from the National Institute of Neurological Disorders and Stroke rtPA Stroke Study[5] and J-ACT.[1] Also excluded were patients whose National Institutes of Health Stroke Scale (NIHSS) score was ≥23, those contraindicated for MRI, those whose MRA demonstrated arterial occlusions other than of the middle cerebral artery, or whose Alberta Stroke Program Early Computed Tomography Score (ASPECTS) was ≤6. Only CT and MRA were considered for subject selection, although diffusion-weighted images were also obtained to investigate their role in selecting patients (data to be reported elsewhere).

MRA Protocol

Before the study, the MRI conditions were standardized to unify the image quality among all participating sites. For MRI and MRA, a 1.5-T echoplanar imaging-equipped scanner was used. Three-dimensional time-of-flight MRA was performed under the following conditions: axial images parallel to the anterior commissure–posterior commissure plane; scanning range from the pontomedullary junction to the corpus callosum; slice thickness 1 to 1.5 mm; and field of view 200 to 240 mm. MRA images were processed by maximum intensity projection to create images of the axial projection and in rotation about the vertical axis (RL rotation, 15° to 18°). MRA was repeated at baseline, 6 hours, and 24 hours after symptom onset. The time allowance for 6-hour MRA was between the end of alteplase infusion and 8 hours from symptom onset and that for 24-hour MRA was between 24 and 36 hours after symptom onset. Arterial occlusion was assessed by 2 reviewers, one expert neurologist and one expert neuroradiologist (the image reading panel) blinded to information except the affected side. Recanalization was evaluated according to the modified Mori grade: Grade 0, no reperfusion; Grade 1, movement of thrombus not associated with any flow improvement; Grade 2, partial (branch) recanalization in <50% of the branches in the occluded arterial territory; and Grade 3, nearly complete recanalization with reperfusion in ≥50% of the branches in the occluded-arterial territory (Figure). Modifications were made to apply the original scheme,[2] which was developed for conventional angiography, to MRA, because distal arterial branches are not visible on MRA. The recanalization rate was estimated by regarding Grades 2 and 3 as valid recanalization corresponding to Thrombolysis in Myocardial Infarction Grades 2 and 3.

Clinical Evaluations

As a primary outcome, the functional outcome after 3 months was assessed by the modified Rankin Scale (mRS). Symptomatic intracranial hemorrhage was designated as CT evidence of intracranial hemorrhage accompanied by apparent neurological deterioration defined as conditions that could be documented objectively or were increased by ≥4 points from the latest NIHSS score. CT images obtained at 24 to 36 hours were assessed by the image reading panel. According to the European Cooperative Acute Stroke Study CT criteria, the panel classified hemorrhagic transformation as none, hemorrhagic infarction (HI-1 and HI-2), or parenchymal hematoma (PH-1 and PH-2).

End Points

The primary end points were modified Mori Grade 2 and 3 recanalization on 6-hour MRA and 24-hour MRA and a favorable outcome of mRS 0 to 1 at 3 months. The safety primary end point was symptomatic intracranial hemorrhage within 36 hours. If data were missing at any follow-up time point, data were imputed using the "last observation carried forward."

To test the hypothesis, we used a similar strategy to the one-arm trial, J-ACT[1]: the incidences of the primary end points were compared with the results of a meta-analysis of published data on thrombolysis. First, we searched MEDLINE and Current Contents as of March 2006 using the following key words: (acute stroke OR ischemic stroke) AND tPA AND angiography. Publications incorporating information concerning the present primary end points were selected to determine the target reference values. Based on the 5 publications selected,[2,3,7–9] we determined a target value for the recanalization rate on 6-hour MRA; the weighted average recanalization rate was 45.1% in 113 patients. The 90% CI of the recanalization rate in 50 patients (the target patient number for this study) was estimated to be 33.5% to 56.8% (normal approximation without sequential correction). In the present study, the treatment aim was thus for a recanalization rate of not <33.5%, the lower limit of the 90% CI. Similarly, we determined a target value for the recanalization rate on 24-hour MRA of not <57.7% based on one publication.[10]

Second, we repeated the database survey with a different search strategy: (acute stroke OR ischemic stroke) AND middle cerebral artery AND (tissue plasminogen activator OR urokinase OR prourokinase). Based on the 2 publications found in the literature search[11,12] and unpublished data from the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT-J), which was published during this study,[13] we estimated the weighted mean proportion of patients with a favorable outcome at 3 months to be 33.6% and the 90% CI in 50 patients to be 22.6% to 44.6%. From data in 3 publications[12,14,15] and MELT-J,[13] we estimated the

Table 1. Demographics and Baseline Characteristics of Patients (n=58)

Age, years	70.3 (11.5)
Sex, females	23 (39.7%)
Body weight, kg	62.1 (11.7)
Baseline NIHSS	12 (5–22)
Stroke subtype	
Cardioembolic	49 (84.5%)
Atherothrombotic	5 (8.6%)
Other/not differentiated	4 (6.9%)
M1 occlusion	41 (70.7%)
Systolic blood pressure, mm Hg	148.5 (16.2)
Diastolic blood pressure, mm Hg	81.2 (12.1)
Blood glucose, mg/dL	132.9 (46.2)
Time elapsed, hours	
Onset to treatment	2.2 (0.4)
Onset to 6-hour MRA	5.9 (1.4)
End of tPA infusion to 6-hour MRA	2.7 (1.3)
Onset to 24-hour MRA	27.1 (2.7)
End of tPA infusion to 24-hour MRA	23.9 (2.7)

Data show the mean (SD), median (range), or no. (%).
tPA indicates tissue plasminogen activator.

weighted mean incidence of symptomatic intracranial hemorrhage to be 8.2% and the 90% CI in 50 patients to be 1.8% to 14.6% for use as reference values.

Statistical Analysis

The effect of recanalization on clinical outcome was assessed by comparing the proportion of a favorable outcome at 3 months between patients with and without recanalization using Fisher exact test, which was also expressed as the ORs and 95% CI. To examine the effects of baseline characteristics and recanalization on clinical outcome, disease-related factors, including time from onset, hypertension, diabetes mellitus, baseline NIHSS, occluded site (M1 or M2), and ASPECTS, and recanalization on either 6-hour MRA or 24-hour MRA were included in a stepwise regression analysis, in which age and sex were forcibly entered into the model to adjust for their possible confounding effects. To assess the possible interaction of recanalization with severity of disease/ischemia, interaction terms between recanalization and NIHSS, ASPECTS, or occlusion site were entered into the model. Furthermore, to examine the effect of delayed recanalization (ie, arterial occlusion unchanged on 6-hour MRA but recanalized on 24-hour MRA), a similar analysis was repeated, in which both delayed recanalization and early recanalization on 6-hour MRA were entered into the model. Significance was set at $P<0.05$ in all final models. The OR and 95% CI were also determined. SAS 9.1.3 was used for the statistical analyses.

Results

Fifty-eight patients were enrolled in this study and were included in the full analysis set both for primary safety and for primary efficacy. One patient had no occluded artery on baseline MRA according to the image reading panel and was excluded from further analysis. Table 1 summarizes the patients' characteristics.

The recanalization rate on 6-hour MRA was 51.7% (Table 2). The recanalization rate did not differ significantly between M1 and M2 occlusions (48.8% versus 62.5%, respectively; $P=0.391$). In all except 2 patients who were withdrawn or had an obstacle for MRI, 24-hour MRA was available. The recanalization rate on 24-hour MRA was 69.0% (Table 2). Delayed recanalization was noted in 10 patients (17.5%). No patient had recanalization on 6-hour MRA that subsequently disappeared on 24-hour MRA.

Table 2. Vascular Conditions and Recanalization After Thrombolysis

Modified Mori Grade	0	1	2	3	Recanalization Rate (95% CI)*
6-hour MRA (n=58)					51.7 (38.9–64.6)
n	21†	7	3	27	
Percent	36.2	12.1	5.2	46.6	
24-hour MRA (n=58)					69.0 (57.1–80.9)
n	12†	6	4	36‡	
Percent	20.7	10.3	6.9	62.1	

*Valid recanalization (Mori Grade 2 or 3) and 95% CI.
†Including one patient whom the image reading panel judged as having no occlusion on baseline MRA.
‡Including 2 patients in whom data were imputed using the "last observation carried forward" for missing 24-hour MRA.

Three-month clinical outcomes were unavailable in 2 patients; one withdrew consent and the other was discharged earlier with an mRS of 4. Both were categorized as having an "unfavorable outcome." The proportion of a favorable outcome at 3 months was 46.6% (95% CI, 33.7% to 59.4%). Death within 3 months after onset occurred in one patient (1.7%), who died of septic shock at 50 days after entry. An alteplase-related serious adverse event occurred in one patient, who had an ischemic stroke on the side opposite to the original stroke 12 hours after alteplase infusion.

The proportion of a favorable outcome was significantly higher in patients with recanalization than in those without recanalization on either 6-hour or 24-hour MRA (Table 3). In a logistic regression model with 6-hour MRA entered as an independent variable, recanalization (OR, 6.030; 95% CI, 1.730 to 21.011) and baseline NIHSS (OR, 0.841; 95% CI, 0.719 to 0.983) emerged as independent predictors of a favorable outcome. In another model with 24-hour MRA entered, recanalization (OR, 21.231; 95% CI, 3.318 to 135.859) and baseline NIHSS (OR, 0.796; 95% CI, 0.672 to 0.943) were also independent predictors of a favorable outcome. The model with delayed recanalization revealed 6-hour recanalization (OR, 23.036; 95% CI, 3.474 to

Table 3. Relationship Between Vascular Outcome and Clinical Outcome at 3 Months

Time	Favorable (mRS 0–1)	Unfavorable (mRS ≥2)	OR [95% CI] Probability
6-hour MRA			
Recanalized	20 (66.7%)	10 (33.3%)	5.714 [1.814–18.004]
Not recanalized	7 (25.9%)	20 (74.1%)	$P=0.003$
24-hour MRA			
Recanalized	25 (62.5%)	15 (37.5%)	12.500 [2.503–62.428]
Not recanalized	2 (11.8%)	15 (88.2%)	$P<0.001$

152.753), delayed recanalization (OR, 15.949; 95% CI, 1.710 to 148.762), and baseline NIHSS (OR, 0.801; 95% CI, 0.675 to 0.951) as independent predictors of a favorable outcome.

No patient had symptomatic intracranial hemorrhage within 36 hours. Asymptomatic intracranial hemorrhage was present in 19.0% of patients (11 of 58) on CTs at 24 to 36 hours, but no patient had parenchymal hematoma 2.

Discussion

This is the first prospective multicenter clinical trial to evaluate recanalization of occluded arteries by MRA shortly after tissue plasminogen activator administration and at 24 hours. The recanalization rates immediately (2.7 hours on average) after treatment and at 24 hours (23.9 hours on average) after treatment were 51.7% and 69.0%, respectively, exceeding the predetermined thresholds. A systematic review in May 2009 revealed that the weighted average of the recanalization rate in the placebo arm of randomized controlled trials of thrombolysis examined by conventional angiography or MRA was 19.8% up to 8 hours after onset.[2,3,12,16] The recanalization rate in the present study was thus considered likely to be much higher than the rate of spontaneous recanalization.

Concerning clinical outcomes, the proportion of a favorable outcome at 3 months (46.6%) fairly well exceeded the predetermined threshold. The systematic review in May 2009 revealed that the weighted average of the proportion of a favorable outcome (mRS 0 or 1) for patients with middle cerebral artery occlusion in the placebo arm of randomized controlled trials of thrombolysis was 22.3%.[11–13,16] The proportion of a favorable outcome in the present study was considered likely to be much higher than that in the natural course of patients with middle cerebral artery occlusion.

The present findings indicated that 0.6 mg/kg intravenous alteplase is, as expected, effective in terms of vascular and clinical outcomes. The most critical limitations of this study arise from the lack of a control group, a postmarketing clinical trial of open-label design, and comparison of results with published data, which could generate various biases. Although primary vascular outcome was assessed centrally by raters independent from the participating sites, rater prejudice cannot be excluded. Nevertheless, the MRA imaging conditions were standardized among all participating sites, and 2 expert raters reviewed the images blinded to the clinical information, probably ensuring quality of image acquisition and evaluation.

Concerning safety, we did not encounter symptomatic intracranial hemorrhage in this trial, which was much better than expected. However, this could reflect the small sample size used. In the Phase III clinical study (J-ACT),[1] symptomatic intracranial hemorrhage occurred in 5.8% of patients, whose arterial occlusions were not documented. Asymptomatic intracranial hemorrhage was noted in 19% of the present subjects, which was comparable to that in the previous trial (17%).[1]

Recanalization immediately after any form of thrombolysis has repeatedly been indicated to predict clinical outcome.[2–4,7,9] A recent systematic review of cerebral artery recanalization has confirmed a strong correlation between recanalization and clinical outcome in acute ischemic stroke.[6] Several investigations have also suggested that the baseline severity of symptoms as measured by NIHSS represents an independent predictor for clinical outcome in patients treated with intravenous alteplase.[11,17,18] Similar to previous thrombolysis studies, the present results demonstrated a strong relationship between vascular outcome and functional outcome as well as baseline stroke severity. Recanalization on either 6-hour or 24-hour MRA was an independent predictor for a favorable clinical outcome. Our data indicated that recanalization on 24-hour MRA was a much stronger predictor of clinical outcome than that on 6-hour MRA. These findings should be interpreted cautiously; they do not necessarily imply that delayed recanalization is far more effective than early recanalization, because recanalization on 24-hour MRA is a cumulative result. Nevertheless, delayed recanalization (recanalization occurring between 6 and 24 hours after treatment) was also a modest but independent predictor for a favorable outcome. The prognostic value of the 24-hour cumulative recanalization is supported by a transcranial Doppler study.[19] Delayed as well as early recanalization may thus have a favorable impact on clinical outcome.

In conclusion, early recanalization of an occluded middle cerebral artery can be provoked by 0.6 mg/kg intravenous alteplase and may induce a favorable clinical outcome. The rates of recanalization and a favorable outcome are comparable to that previously reported with the 0.9-mg/kg dose.

Appendix

Steering Committee

T. Yamaguchi, National Cardiovascular Center; E. Mori, Tohoku University Graduate School of Medicine; K. Minematsu, National Cardiovascular Center; J. Nakagawara, Nakamura Memorial Hospital.

Image Reading Panel

M. Sasaki, Iwate Medical University; T. Hirano, Graduate School of Medical Sciences, Kumamoto University.

Investigators and Institutions

T. Nagao, Tokyo Metropolitan HMTC Ebara Hospital; J. Nakagawara, Nakamura Memorial Hospital; T. Yonehara, Saiseikai Kumamoto Hospital; E. Furui, Kohnan Hospital; K. Kimura, Kawasaki Medical School Hospital; T. Terasaki, Japanese Red Cross Kumamoto Hospital; B. Mihara, Mihara Memorial Hospital; N. Sakai, Kobe City Medical Center General Hospital; A. Suzuki, Research Institute for Brain and Blood Vessels Akita; K. Minematsu, H. Naritomi, National Cardiovascular Center; S. Takagi, Tokai University Hospital; Y. Kitagawa, Tokai University Hachioji Hospital; Y. Okada, National Hospital Organization Kyushu Medical Center; S. Irie, Kushiro Kojinkai Memorial Hospital; Y. Itou, TOYOTA Memorial Hospital.

Safety Monitoring Committee

S. Kobayashi, Shimane University Hospital; I. Nagata, Nagasaki University Graduate School of Biomedical Science.

Medical Adviser

M. Takagi, Tokyo Saiseikai Central Hospital.

Sources of Funding

This clinical trial was supported by Kyowa Hakko Kirin Co, Ltd and Mitsubishi Tanabe Pharma Corporation.