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もやもや病と過灌流現象 — 過灌流における脳循環動態

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もやもや病に対する血行再建術後の局所過灌流が最近注目されているが，その病態，特に過灌流時の脳循環動態については不明な点が多い．今回，術後急性期に^{15}O-gas PETを施行し脳循環代謝の評価を行ったので，結果について報告するとともに過灌流の病態について考察する．

Key Words: もやもや病，過灌流，脳循環代謝，PET

Ⅰ．はじめに

もやもや病は頭蓋内の主要動脈の狭窄と側副血行路の発達を特徴とする疾患であり，脳虚血症状や出血性合併症を生じることが知られている[1)]．虚血症状を呈する例に対しては浅側頭動脈（STA）－中大脳動脈（MCA）吻合術などの直接バイパスや種々の間接バイパスが有効な治療として確立している[2, 3)]．良好な治療成績が報告されている一方で，直接バイパス術後急性期にはバイパス吻合部周囲の局所的高灌流が一過性の神経症状や痙攣，頭痛などの原因となっており，術後の過灌流現象として注目されている[4-10)]．血行再建術後の過灌流は頚動脈内膜剥離術（CEA）後の合併症として認知されており，その病態は脳組織のデマンドに対しての過剰な脳血流の増加と考えられている[11, 12)]．脳循環動態の評価は正確にはPET検査によって行われるべきだが，最近では^{123}I-IMP-ARG法[13)]などのような簡便で精度の高い脳血流SPECT定量画像が臨床応用され代用されていることが多い．過灌流の評価も脳血流SPECTで行われるのが一般的で，過灌流時の脳循環代謝についての詳細な報告はない．本研究では，STA-MCAバイパス術後の過灌流症候群について^{15}O-gas PETを用いて評価を行った．

Ⅱ．対象・方法（図1）

対象は2009年4月から2011年7月の期間に国立循環器病研究センターで治療を行った成人もやもや病34例（15～70歳：平均39.3歳）42半球である．小児例は除外した．全症例に対してSTA-MCAバイパス術を行い，術中は脳血流dopplerおよびindocyanine green（ICG）video-angiographyを用いてバイパスの開存を確認した

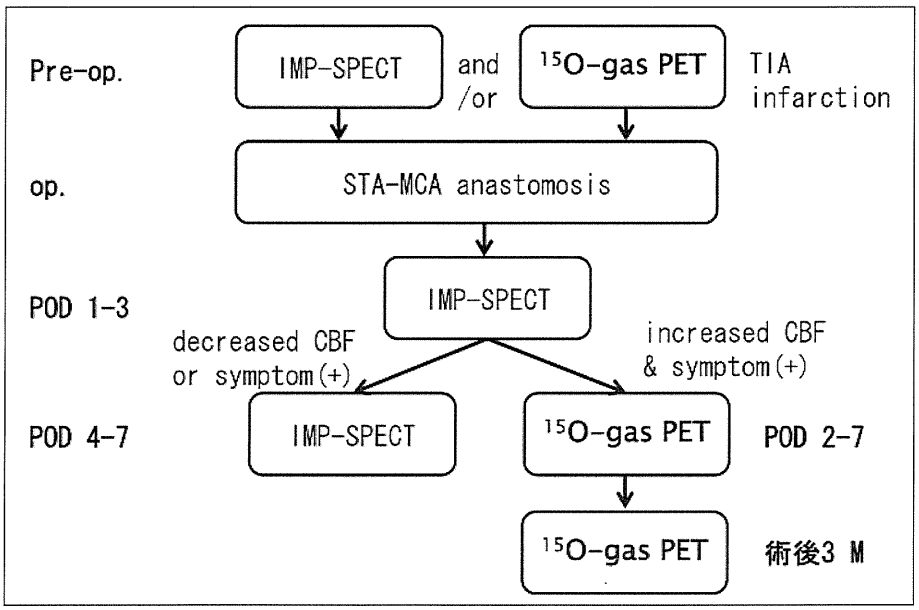

図1　脳血流検査のプロトコール

(図2). 術前に ^{123}I-IMP SPECT もしくは ^{15}O-gas PET を行い脳循環動態の評価を行った. 特に, 術前に虚血症状が強い20例23半球に対しては積極的に ^{15}O-gas PET を施行した. 術後は全例で術後1～3日以内に ^{123}I-IMP SPECT を施行し, 術前に比べ脳血流の増加かつ神経症状を呈する例では症候性過灌流と判断し術後急性期に ^{15}O-gas PET を施行, また術後3カ月目にも ^{15}O-gas PET を施行した (図1). 術前, 術後2～7日, 術後3カ月での PET パラメータの評価を行った.

Ⅲ. 過灌流症候群の定義

STA-MCA バイパス術後の局所過灌流についての明確な定義はない. そこで, 症候性の過灌流を術後の ^{15}O-gas PET での脳血流定量値が正常値 + 2SD (57.8 mL/100 g/min) 以上で, バイパス吻合部位周囲の局所的高灌流が原因と考えられる一過性の局所神経脱落症状や強い頭痛, 痙攣を呈するものと定義した.

Ⅳ. 結　果

術前の血行力学的脳虚血ステージを PET[14] もしくは SPECT[30] で評価を行ったところ, stage Ⅰ相当が18半球, stage Ⅱ相当が24半球であった. 症候性過灌流は5例6半球 (6/42, 14.3%) に認めた. 症例と経過の一覧を表1に示す. 術後に症候性過灌流を呈した5例はいずれも虚血発作での発症であり, 術前の血行力学的ステージは stage Ⅰ相当が1半球 (1/18, 5.9%), stage Ⅱ相当が5半球 (5/24, 20.8%) で, stage Ⅱでは高率に術後過灌流を呈した. 過灌流を呈した部位は STA-MCA バイパス吻合部周囲で, 症状は痙攣,

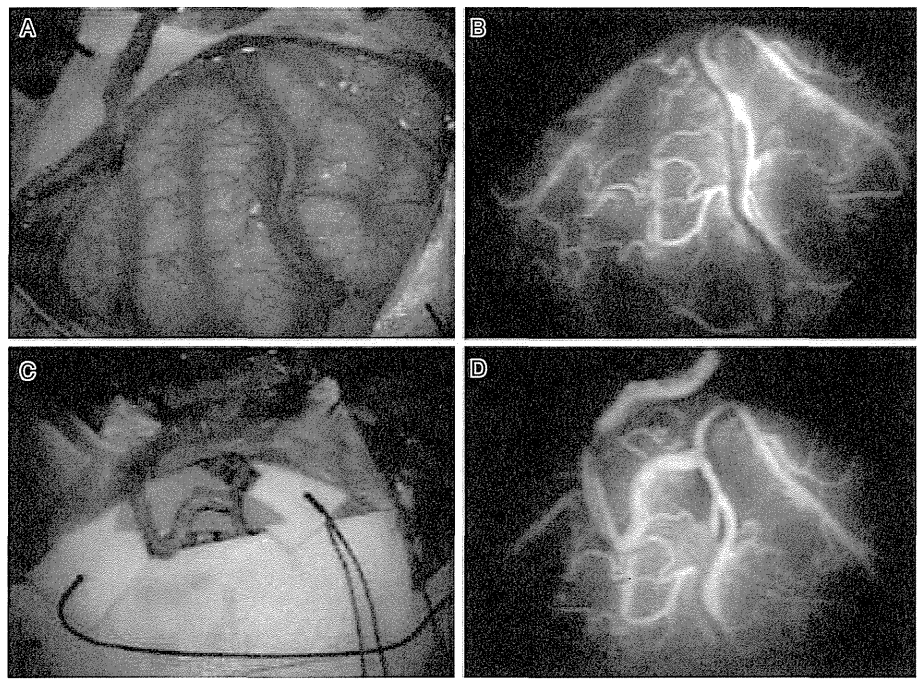

図2　症例 no. 5 の術中画像，左 STA-MCA バイパス
A：吻合前．脳表には拡張した細動脈を多数認める．
B：吻合前の ICG videoangiography．動脈相での脳表の濃染が疎である．
C：STA parietal branch と M4 の吻合を施行．
D：吻合後の ICG videoangiography．バイパスからの血流により動脈相での脳表の濃染像が改善している．ただし，この時点で術後の過灌流を予測することは困難である．

感覚障害，失語症状がそれぞれ 2 例ずつであった．過灌流の症状は術後 1 ～ 4 日目の早期に出現し，持続期間は 4 ～ 14 日であった．術後 3 カ月での mRS はいずれも良好であった．

V．PET 定量値

表 2 に示す．脳血流量 CBF は術前 37.6 ± 5.1 mL/100 g/min（n = 4）に比べ過灌流 77.6 ± 10.7 mL/100 g/min（n = 6）では有意に増加を認めた．脳血液量 CBV は術前 5.83 ± 1.88 mL/100 g，過灌流 6.80 ± 1.46 mL/100 g と術前からの高値が持続していた．脳酸素代謝量 $CMRO_2$ は術前 3.70 ± 0.31 mL/100 g/min で，過灌流では 4.42 ± 0.88 mL/100 g/min と増加を認めた．術後過灌流を呈した 6 例中 4 例の $CMRO_2$（3.83 ± 0.33 mL/100 g/min）は正常域で推移したが，痙攣を呈した 2 例では $CMRO_2$（5.60 ± 0.10 mL/100 g/min）の著明な上昇を認めた．CBF の著明な上昇と $CMRO_2$ の軽度上昇の結果，酸素摂取率 OEF は術前 0.58 ± 0.05 の高値から過灌流では

表1　過灌流症候群をきたした5例6半球の臨床像

症例 no.	年齢，性別	発症形式	術前の血行力学的ステージ	左右	術後過灌流の範囲	症候	過灌流の発症時期	持続期間（days）	mRS score 術後 3M
1	37，M	TIA	stage Ⅰ*	R	central & parietal	痙攣	POD 4	4	0
2	44，F	梗塞	stage Ⅱ	L	central	痙攣	POD 3	7	1
3	44，F	梗塞	stage Ⅱ	R	central	感覚障害	POD 3	11	1
4	41，F	TIA	stage Ⅱ	R	central	感覚障害	POD 3	7	0
5	60，F	梗塞	stage Ⅱ	L	pre- & central	失語	POD 1	11	0
6	51，M	TIA	stage Ⅱ*	L	pre-，central & parietal	失語	POD 3	14	0

POD = post-operative day，pre- = precentral，mRS = modified Rankin Scale
症例2と3は同一患者，* IMP-SPECT での脳血流評価.

表2　PET パラメータの推移

	pre op.（n = 4）	hyper-（n = 6）	post op.（n = 6）	P value hyper- vs. pre op.	P value hyper- vs. post op.
CBF（mL/100 g/min）	37.5 ± 5.1	77.6 ± 10.7*	44.2 ± 4.2	<0.01	<0.01
CBV（mL/100 g）	5.83 ± 1.87*	6.80 ± 1.46*	4.27 ± 0.40*	n.s.	0.021
$CMRO_2$（mL/100 g/min）	3.70 ± 0.31	4.42 ± 0.89	3.58 ± 0.44	n.s.	0.034
OEF	0.58 ± 0.05*	0.40 ± 0.08	0.48 ± 0.04	<0.01	0.024
CBF/CBV（min^{-1}）	7.37 ± 1.93	12.5 ± 4.09	12.0 ± 2.45	n.s.	n.s.

* Values out of the mean ± 2SD range of controls
hyper- = hyperperfusion，n.s. = not significant
3群間の検定には ANOVA にて $p<0.01$，各群間についての有意差検定は Scheffe 検定にて行った.

0.40 ± 0.08 と有意に低下した．脳灌流圧 CPP の指標である CBF/CBV は術前 7.4 ± 1.9 min^{-1} と低値であったが，過灌流では 12.5 ± 4.1 min^{-1} と増加を認めた．術後3カ月では，CBF，$CMRO_2$，OEF は正常域となり，CBV，CBF/CBV は術前に比べ改善した．

Ⅵ．代表例

41歳，女性（症例 no. 4）．5年前から左半身の脱力発作を自覚していたが，最近になりその頻度

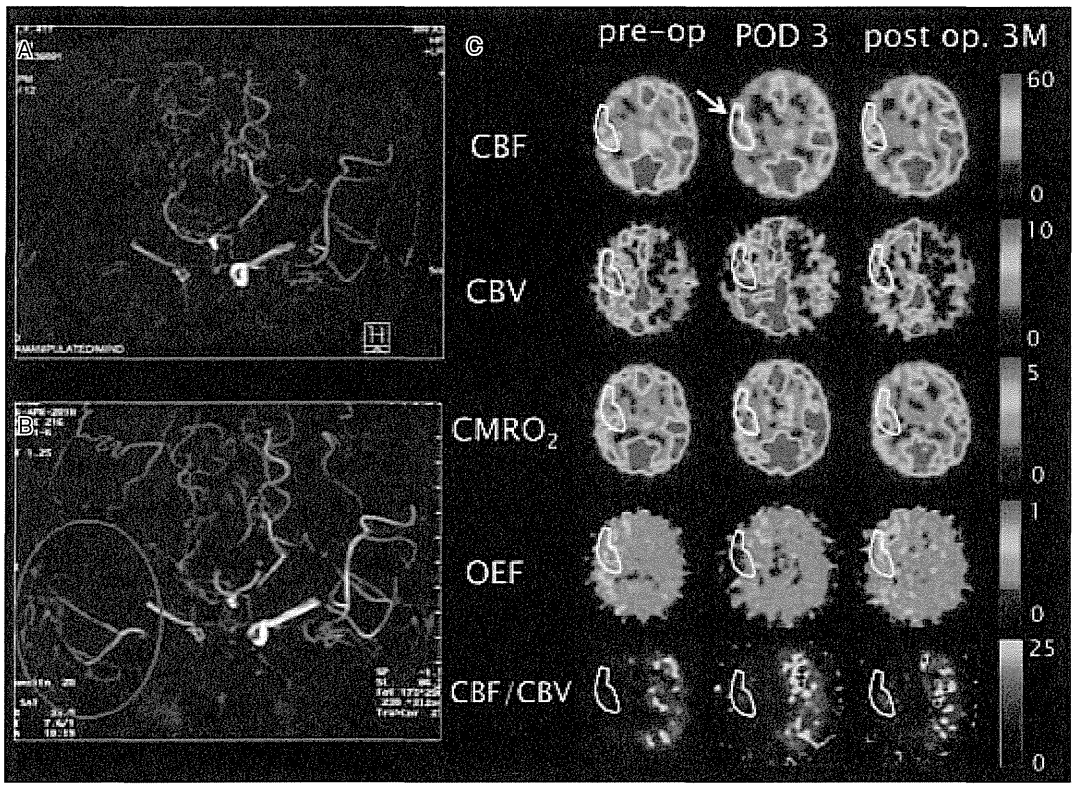

図3　症例 no. 4

A：術前 MRA，B：術後 MRA．バイパスの patency は良好である．
C：PET パラメータの推移．左側：術前は右半球で著明な CBF の低下を認め，CBV は上昇，$CMRO_2$ は正常であるが，OEF は上昇し，いわゆる misery perfusion の状態である．脳灌流圧の指標となる CBF/CBV は対側に比べ著明に低下している．中央：術後3日目（POD 3）では CBF は著明に増加し（矢印），CBV の高値は持続，$CMRO_2$ はわずかに増加，OEF は低下している．右側：術後3カ月では，CBF，$CMRO_2$，OEF は正常となり，CBV と CBF/CBF は術前に比べ改善を認める．

が増えたため精査を行った．頭部 MRI/A，脳血管撮影でもやもや病の確定診断となった．^{15}O-gas PET では右半球の貧困灌流を認めた（図3）．右半球に対して STA-MCA バイパス術を施行した．術後2日目までは特に症状なく経過していたが，術後3日目より左半身のしびれ感を自覚，30分程度のものが1日に数回出現した．術後3日目の PET ではバイパス吻合部周囲に著明な CBF の増加を認め，過灌流症候群の診断で厳重な血圧管理を行った．術後7日目まで症状は続いたが自然に消失し，術後10日目には独歩退院となった．

Ⅶ. 考　察

1）過灌流症候群

もやもや病に対する血行再建術後の俗にいう過灌流症候群は，これまでの成人例での報告では自験例を含めて 14.3～21.5%に認めた[4, 8]．最近では，脳血流定性 SPECT での術後評価で無症候性

過灌流の存在も言われており，潜在的には高い頻度で過灌流を呈するものと推測する．症候性の過灌流について，CEA 術後の過灌流症候群の古典的 3 徴は頭痛，痙攣，脳出血であるが[11, 12, 15]，STA-MCA バイパス術後の一過性の神経脱落症状を過灌流症候群に含めてよいものであろうか．周術期には虚血性合併症も起こりえるが[7, 16]，今回の神経脱落症状（感覚障害，失語など）は局所の脳血流増加部位に起因するものと判断し，これらを過灌流症候群と定義した．

2）もやもや病における過灌流のメカニズム

術後過灌流では CBF は著明に増加するが，CEA/carotid artery stenting（CAS）術後の過灌流は術前の 100%（定量値で術前値の 2 倍）以上の増加とする[11, 12]のが一般的である．自験例では術前に比べ CBF は一過性に 53 ～ 120%（平均 106%）増加したが，100%未満の CBF の増加であっても症候性過灌流が起こり得ると言える．CBV 値の上昇は細動脈の拡張と関係があり[17, 18]，血管狭窄に伴う CBV 上昇は脳灌流圧の低下を引き起こす．自験例では術前の CBV 値は高値であり，過灌流でも CBV 高値は持続していた．術後 3 カ月の時点では術前に比べ CBV 値の低下を認めた．CEA/CAS 後の過灌流で報告されているように[19, 20]，術後急性期に CBV 値の回復の遅延はもやもや病においても術後過灌流の重要なメカニズムであると考えられる．過灌流の状態では CBF が上昇し脳灌流圧が上昇しているにもかかわらず CBV が低下しないのは，細動脈が術後早期には収縮しないためと考えられる．すなわち，自動調節能の障害による vasopararesis の状態が続いており，過灌流に伴う臨床症状は術後 1 日目から 14 日目まで継続したが，その間は vasopararesis が持続するものと推測される．それゆえ，過灌流時には血圧の上昇が脳血流の増加を助長するため厳重な血圧管理が必要となる[6]．また，TIA や脳梗塞など虚血発作で発症するもやもや病では CBV 値は著明に高値であり[21]，術前の CBV 高値は術後過灌流の予測因子と推測される．

脳灌流圧 CPP は一般的に脳血管予備能 CVR を反映し，CVR 低下例は CEA 術後の症候性過灌流の予測因子である[19, 22]．本研究において術前の CPP（CBF/CBV）は低値であり，術後急性期には増加を認めた．CPP は CBV 値と強く相関しており，術前 CPP の高度低下は術後過灌流のリスクファクターと考えられる．

過灌流時には $CMRO_2$ は増加し OEF は有意に低下した．しかし，67 %（4/6 例）は過灌流時に $CMRO_2$ は正常域であったが，痙攣を呈した 2 例では $CMRO_2$ は著明に高値であった．痙攣発作は脳酸素代謝量の過剰な上昇をきたす異常な生理的状態であり[23]，痙攣発作中は $CMRO_2$ の増加に応じて CBF は増加する[24-27]．注意すべくは，術後過灌流を呈した例には痙攣発作のために 2 次的に脳血流が増加した例も存在する可能性があることである．脳血流 SPECT での測定だけでは過灌流が痙攣発作によるものなのどうかの判断は困難である．

Marchal ら[28]は脳梗塞後の再灌流障害・過灌流（postischemic hyperperfusion）について PET を用いた脳循環動態の評価を行い，患側では健側に比べ CBF，CBV，$CMRO_2$ の増加，OEF の低下を認め，総合的に hypermetabolic state である

と結論付けている．Postischemic hyperperfusionとSTA-MCAバイパス術後の局所過灌流を単純には比較できないが，本研究では術後痙攣発作を呈さなかった例では$CMRO_2$は過灌流でわずかに増加したが正常域で経過した．$CMRO_2$はCBFの増加に対して対数関数的に増加する[29]ため，過灌流では必ずしもCBFと$CMRO_2$がミスマッチの状態ではないと考えられる．また，過灌流の脳循環動態は脳組織のデマンドに対しての過剰な脳血流の増加[11, 12]と考えられてきたが，本研究の結果からは必ずしもそうではないようである．もやもや病に対する血行再建術後の過灌流現象については，脳循環代謝の解析では評価できないその他の因子も関与していると考えられ，さらなる研究が必要と思われる．

Ⅷ. まとめ

過灌流は，血行再建術後の急激な血流再開により自動調節能が障害された脳血管がただちに反応できず一時的な血流増加をきたすことと考えられてきたが，今回のPETでの脳循環動態の検討からはおそらくこれは正しいと考えられる．痙攣発作を除く症候性の過灌流の脳循環動態は，脳血流の著明な増加，脳血液量の高値持続および脳酸素代謝量の正常域での推移であり，結果として酸素摂取率は著明に低下する．

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5. 大脳白質病変例における脳循環代謝と脳血管反応性の検討

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要　旨

大脳白質病変の進展に関連した脳循環代謝病態は不明である．頭蓋内外主幹脳動脈に50%以上の狭窄性病変を有さない慢性期のラクナ梗塞18例を対象に，白質病変重症度とPET（迅速法）を用いた脳循環代謝諸量およびアセタゾラミド（ACZ）負荷脳血管反応性との関連を比較した．白質病変重症群（9例，75±3歳）は軽症群（9例，74±4歳）に比べて半卵円中心での脳血流量（20.6±4.4 vs. 29.9±8.2 ml/100 g/min，p=0.008），酸素代謝量（1.95±0.41 vs. 2.44±0.42 ml/100 g/min，p=0.025）が低く，酸素摂取率が高かった（55.2±7.4 vs. 46.7±5.3%，p=0.013）．ACZ負荷脳血管反応性は白質病変の重症度と無関係であり（R^2=0.06，p=0.316），酸素摂取率とアセタゾラミド負荷脳血管反応性に関連性は認めなかった（R^2=0.04，p=0.422）．白質病変の進展には，慢性脳低潅流が関与していると考えられ，重症白質病変例であってもACZ脳血管反応性は保たれていた．

（脳循環代謝　22：72～77，2011）

キーワード：白質病変，PET，脳血管反応性，アセタゾラミド

はじめに

大脳白質病変は加齢，高血圧，糖尿病に関連し，高次脳機能障害を伴う場合が多い[1,2]．白質病変の進展には，慢性脳低潅流や血行力学的不全などの関連が示唆されているが[1]，白質病変の脳循環代謝病態は不明である．白質病変の重症度と脳血管反応性に関しても，重症白質病変例では血管反応性が低下していたという報告がある一方[3~8]，白質病変と血管反応性は関連がなかったという報告も散見される[9,10]．本研究では慢性期のラクナ梗塞患者を対象に，脳循環代謝評価方法としてpositron emission tomography（PET）を用い，大脳白質病変の重症度別に，高次脳機能，大脳白質，皮質の脳循環代謝と脳血管反応性を比較した．

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対象と方法

頭蓋内外主幹脳動脈に50%以上の狭窄性病変を有さない発症3カ月以上経過したラクナ梗塞18例（男14例，平均74歳）を対象とした．診療録より，危険因子（脳卒中の既往，高血圧，糖尿病，脂質代謝異常）の有無を調べた．全例に1.5テスラMRI（MAGNETOM Visionまたは MAGNETOM Sonata, Siemens Medical Systems, Erlangen, Germany）を撮像し，白質病変の重症度を，FLAIR画像を用いてFazekas分類で評価した[11]．Fazekas 0，1を軽症群，Fazekas 2，3を重症群とし，両群の性，年齢は一致させた．白質体積は，Dr. View/Linuxソフトウェアを用いてマニュアルで計測した．高次脳機能検査としては，Mini Mental State Examination（MMSE），Frontal Assessment Battery（FAB），日本語版Alzheimer's Disease Assessment Scale（ADAS-J cog），Clinical Dementia Rating（CDR）を行った．

脳循環代謝評価は，rapid dual autoradiography method[12]，いわゆる迅速PETを用いたガスPETによるCBF，脳血液量（CBV），酸素摂取率（OEF），

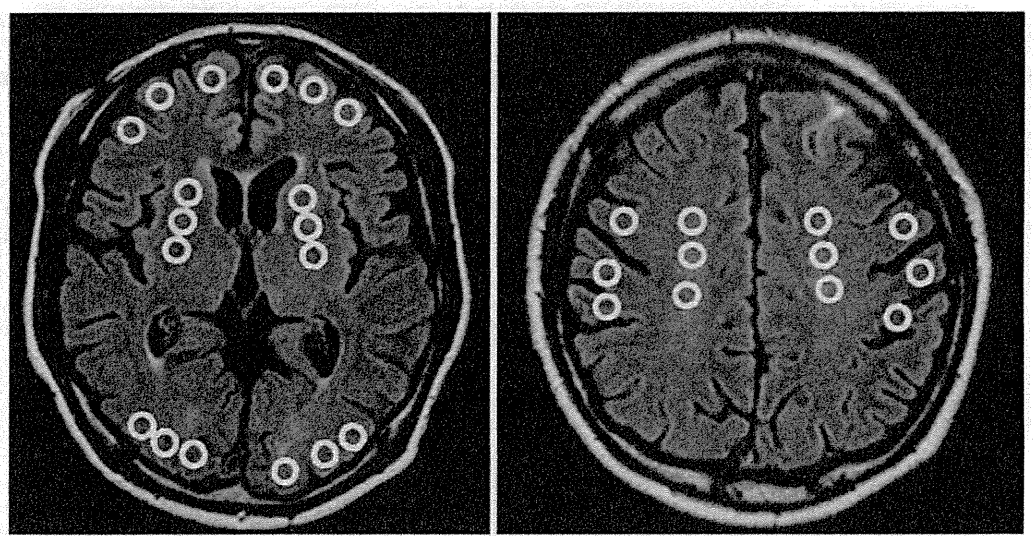


図1. FLAIR画像での関心領域（前頭葉，頭頂葉，後頭葉，基底核，半卵円中心に左右対称に直径10mmの円形を合計30個）

表1. 患者背景

	重症白質病変群（n＝9）	軽症白質病変群（n＝9）	P
年齢（years）	75.2±3.3	73.6±4.2	0.359
男性（%）	6（66.7）	8（88.9）	0.577
喫煙（%）	7（77.8）	7（77.8）	0.999
高血圧（%）	9（100）	8（87.9）	0.999
糖尿病（%）	3（33.3）	3（33.3）	0.999
脂質代謝異常（%）	6（66.7）	6（66.7）	0.999
白質病変体積（cm^3）	52.6±43.2	3.0±1.9	0.003
脳卒中既往（%）	3（33.3）	2（22.2）	0.999
MMSE	23.2±17.0	27.3±2.4	0.116
FAB	10.7±4.2	15.7±1.9	0.005
ADAS-J.cog	13.6±12.2	8.5±4.1	0.258
CDR	0.56±0.68	0.17±0.25	0.128

t-test, $\chi 2$ test, or Mann-Whitney U test

MMSE：mini-mental state examination
FAB：frontal assessment battery
ADAS-J.cog：日本語版 Alzheimer's Disease Assessment Scale
CDR：clinical dementia rating

酸素代謝量（$CMRO_2$）の測定と，^{15}O標識の水を用いたアセタゾラミド（ACZ）負荷PETによるACZ脳血管反応性を評価した．ACZ脳血管反応性はACZ負荷前後のCBFの差を負荷前のCBFで除したものとした．脳循環代謝諸量の平均値は，MRI画像とPET画像をSPM 5ソフトウェアで重ね合わせを行い，FLAIR画像をもとに前頭葉，頭頂葉，後頭葉，基底核，半卵円中心に直径10 mmの円形の関心領域をマニュアルで置き（図1），各領域にて算出した．

統計学的解析にはJMPソフトウェア（SAS，Ver 7，USA）を用いた．2群間比較では正規分布する連続変数はt検定，カテゴリー変数はχ^2検定，非連続変数はMann-WhitneyのU検定を行った．白質病変体積と脳循環代謝諸量，脳血管反応性の関連性はPearsonの相関係数で評価した．$P<0.05$を有意差ありとした．

結　果

患者背景を表1に示す．重症白質病変群と軽症白質病変群は性，年齢，心血管リスクファクター，脳卒中既往の有無に差はなかった．前頭葉機能バッテリーで

表2. 各領域におけるO-15 gas PETの脳循環代謝諸量

		重症白質病変群（n=9）	軽症白質病変群（n=9）	P
前頭葉	CBF	35.7±9.0	37.8±8.5	0.630
	CBV	3.0±0.9	3.0±0.6	0.969
	OEF	54.1±14.7	48.3±5.2	0.275
	$CMRO_2$	3.24±0.49	3.26±0.73	0.946
頭頂葉	CBF	40.2±6.9	44.1±11.6	0.403
	CBV	2.8±0.7	3.1±0.5	0.284
	OEF	50.6±6.9	46.3±4.9	0.146
	$CMRO_2$	3.53±0.35	3.62±0.80	0.743
後頭葉	CBF	40.4±8.6	47.4±16.1	0.266
	CBV	3.5±0.9	3.7±1.5	0.745
	OEF	55.8±8.8	50.4±4.5	0.116
	$CMRO_2$	3.88±0.63	4.22±1.16	0.442
基底核	CBF	45.1±9.4	49.5±13.1	0.426
	CBV	2.3±0.7	2.5±0.5	0.521
	OEF	52.8±7.9	50.5±6.3	0.505
	$CMRO_2$	4.14±0.66	4.43±0.90	0.441
半卵円中心	CBF	20.6±4.4	29.9±8.2	0.008
	CBV	1.2±0.4	1.4±0.3	0.217
	OEF	55.2±7.4	46.7±5.3	0.013
	$CMRO_2$	1.95±0.41	2.44±0.42	0.025

t-test

CBF（ml/100g/min）：脳血流量
CBV（ml/100g）：脳血液量
OEF（%）：酸素摂取率
$CMRO_2$（ml/100g/min）：酸素代謝量

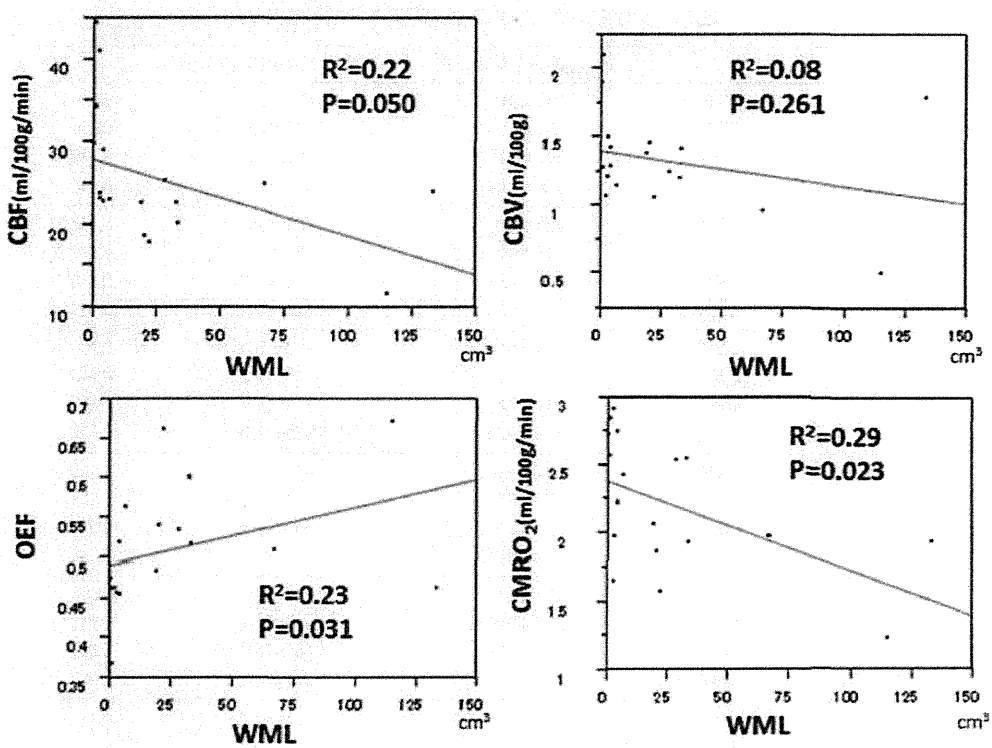
あるFABが重症群で低値であったが（10.7±4.2 vs. 15.7±1.9, p=0.005），その他の高次脳検査では両群間で差はなかった．O-15 gas PETの脳循環代謝諸量に関しては，前頭葉，頭頂葉，後頭葉の皮質，基底核のCBF，CBV，OEF，$CMRO_2$は両群間に有意差はなく，半卵円中心では重症群でCBF（20.6±4.4 vs. 29.9±8.2 ml/100 g/min, p=0.008），$CMRO_2$（1.95±0.41 vs. 2.44±0.42 ml/100 g/min, p=0.025）が低く，OEFが高かった（55.2±7.4 vs. 46.7±5.3%, p=0.013）（表2）．更に，半卵円中心ではCBFと$CMRO_2$は白質病変体積と負に相関し（R^2=0.22, p=0.050, R^2=0.29, p=0.023），OEFは正に相関した（R^2=0.23, p=0.031）（図2）．一方，ACZ脳血管反応性はいずれの部位でも両群間で差を認めず（表3），白質病変体積との関連はなかった（R^2=0.06, p=0.316）．OEFとACZ脳血管反応性にも関連は見られなかった（R^2=0.04, p=0.422）．

考　察

今回，我々は主幹脳動脈高度狭窄・閉塞のないラクナ梗塞例を対象とし，迅速法で行ったPETを用いて，性，年齢を一致させた白質病変の重症度と高次脳機能，脳循環代謝諸量およびACZ脳血管反応性との関連を調べた．高次脳機能に関して，重症白質病変群ではFABが有意に低かった．脳循環代謝諸量に関しては，半卵円中心において白質病変の重症度とCBF低下，OEF上昇，$CMRO_2$低下が関連したが，いずれの部位においてもACZ脳血管反応性とは関連がなかった．

大脳白質病変は認知症と関連することがメタアナリシスより明らかにされており[13]，高次脳機能の中では特に遂行機能障害と関連するとされている[2,14]．本検討ではMMSE，ADAS-J cog，CDRには両群間に差はなかったが，遂行機能を評価するFABのみが重症白質病変群で有意に低く，矛盾しない結果であった．FABは簡便に行える検査であり[15]，大脳白質病変の高次脳機能検査を評価する上で有用であると考えられた．

主幹脳動脈病変を有さない例における白質病変の脳循環代謝諸量に関し，Hatazawaら[16]は，心血管リスクを合併した無症候性白質病変例では白質病変を有さない対照例と比較して，白質と基底核でCBFが低くOEFが上昇していたと報告している．我々の研究で



Pearson's correlation

CBF：脳血流量

CBV：脳血液量

OEF：酸素摂取率

$CMRO_2$：酸素代謝量

WML：白質病変

図 2. 半卵円中心での脳循環代謝諸量と白質病変体積との関係

表 3. 各領域における脳血流量（CBF）とアセタゾラミド（ACZ）負荷反応性

		重症白質病変群（n＝9）	軽症白質病変群（n＝9）	P
前頭葉	CBF 負荷前	36.1 ± 7.2	40.2 ± 7.3	0.244
	負荷後	58.5 ± 10.2	59.9 ± 10.3	0.770
	ACZ 反応性（%）	64.6 ± 28.5	49.7 ± 14.9	0.183
頭頂葉	CBF 負荷前	39.7 ± 4.8	45.7 ± 10.5	0.136
	負荷後	62.0 ± 7.1	66.9 ± 14.6	0.387
	ACZ 反応性（%）	57.2 ± 17.1	47.1 ± 13.5	0.181
後頭葉	CBF 負荷前	38.1 ± 7.1	45.7 ± 11.5	0.109
	負荷後	61.7 ± 13.3	70.1 ± 17.0	0.259
	ACZ 反応性（%）	62.2 ± 21.5	54.2 ± 16.6	0.392
基底核	CBF 負荷前	47.1 ± 9.8	54.6 ± 11.3	0.148
	負荷後	73.7 ± 10.5	85.7 ± 24.6	0.200
	ACZ 反応性（%）	60.9 ± 31.0	55.7 ± 22.9	0.694
半卵円中心	CBF 負荷前	19.0 ± 4.1	29.8 ± 9.2	0.005
	負荷後	28.5 ± 5.9	41.8 ± 10.9	0.005
	ACZ 反応性（%）	48.6 ± 22.6	42.5 ± 17.2	0.524

t-test

CBF（ml/100g/min）：脳血流量

ACZ：アセタゾラミド

は，穿通枝と皮質枝の終末領域であり，もっとも潅流圧低下を生じやすい半卵円中心において，重症白質病変例でCBF低下，OEF上昇，$CMRO_2$低下が観察された．白質病変例は高齢者や高血圧患者に多いという疫学的調査や[17]，重症白質病変例における深部白質での脳虚血変化に関する病理学的な検討もあり[1]，白質病変の進展には長年にわたる慢性脳低潅流が関連していると考えられる．

主幹脳動脈病変例においては，single photon emission tomography（SPECT）におけるACZ脳血管反応性低下はPETにおけるOEF上昇と関連することが知られている[18]．PETを用いた研究からは，主幹脳動脈病変を合併したラクナ梗塞例ではOEFの上昇と白質病変重症度が関連したが，ラクナ梗塞のない例では両者の関連は見られなかったという[19]．一方，主幹脳動脈病変のない例では，ACZ脳血管反応性と白質病変重症度との関連には一定した見解はない．この原因の一つに，脳血管反応性の評価がSPECTやtrans-cranial Doppler（TCD）など方法が様々であること，脳血管反応性の定義が異なることが考えられる[3~10]．ACZ脳血管反応性とPETによる脳循環代謝諸量を同時に測定した研究も見あたらない．我々の研究結果より，CBF低下とOEF上昇が明らかであった半卵円中心において，CBVの上昇はなく，局所的な脳潅流圧は低下していたと考えられる．しかし，重症白質病変例での半卵円中心においてもACZ脳血管反応性は保たれていた．主幹脳動脈病変例を合併した片側大脳半球の脳潅流圧低下と，主幹脳動脈病変のない重症白質病変の終末領域に見られる局所の脳潅流圧低下では，ACZ脳血管反応性が異なることを示していると考えられた．

本検討より，主幹脳動脈病変を合併しないラクナ梗塞例では，最も脳潅流圧が低下する終末領域においてOEFの上昇がみられたことから，白質病変の進展には，慢性脳低潅流が関与していると考えられた．主幹脳動脈病変を有しない白質病変の進展は，細小血管障害による局所のCBF低下とCBF低下に伴う神経脱落による$CMRO_2$低下が並行して慢性的に進行した結果なのかもしれない．白質病変の病態の適切な評価方法の確立は，白質病変の治療に新たな方向性を示す可能性があり，今後さらなる研究が期待される．

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Reduced Estimated Glomerular Filtration Rate Is Associated with Stroke Outcome after Intravenous rt-PA: The Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) rt-PA Registry

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Key Words
Infarction · Intracerebral hemorrhage · Renal dysfunction · rt-PA · SAMURAI

Abstract
Background: The aim of this study was to determine whether renal dysfunction affects the outcome of stroke patients treated with recombinant tissue plasminogen activator (rt-PA). ***Methods:*** A retrospective, multicenter, observational study was conducted to identify the effects of underlying risk factors on intravenous rt-PA therapy using 0.6 mg/kg alteplase in 10 stroke centers in Japan. Consecutive stroke patients with a premorbid modified Rankin Scale (mRS) score ≤3 who received rt-PA were studied. Renal dysfunction was defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 on admission. The outcome measures were any intracerebral hemorrhage (ICH) and symptomatic ICH within the initial 36 h; favorable (mRS 0–1) outcome, poor outcome (mRS 4–6) and mortality at 3 months. ***Results:*** Of a total of 578 patients (372 men; 64.4%, 71.4 ± 11.7 years old), renal dysfunction was present in 186 patients (32.2%). These patients were older and more commonly had hypertension, atrial fibrillation, prior ischemic heart disease and prior use of antithrombotic agents than patients without renal dysfunction. ICH (27.4 vs. 16.6%) and symptomatic ICH (8.1 vs. 2.6%) was more common in patients with renal dysfunction than in those without. At 3 months, patients with renal dysfunction had higher median mRS scores than those without (3 vs. 2). After multivariate adjustment for established outcome predictors, renal dysfunction was related to any ICH (odds ratio 1.81, 95% confidence interval 1.16–2.84), symp-

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tomatic ICH (2.64, 1.10–6.56), poor outcome (1.55, 1.01–2.38), and mortality (2.94, 1.38–6.42). ***Conclusions:*** Reduced eGFR was associated with early ICH and 3-month unfavorable outcome in stroke patients receiving intravenous rt-PA.

Introduction

Renal dysfunction is increasingly noted as a risk factor for stroke in the general population [1, 2], as well as in high-risk patients having diabetes mellitus [3], essential hypertension [4], and preexisting atherothrombotic disease [5, 6]. In a large cohort of patients with acute stroke, renal dysfunction was an independent predictor for long-term mortality and poor outcome [7–9].

Though intravenous (IV) thrombolysis is a standard therapy for acute stroke patients, the effect of renal dysfunction on vital and functional outcome measures following therapy is inconclusive. As far as we know, only one study (involving 196 stroke patients) reported that a high admission serum creatinine level was independently predictive of a modified Rankin scale (mRS) score ≥3 at 3 months after IV recombinant tissue plasminogen activator (rt-PA) [10]. This study also reported that an impaired estimated glomerular filtration rate (eGFR), defined as <90 ml/min/1.73 m^2, tended to be associated with symptomatic intracerebral hemorrhage (ICH). Since renal dysfunction appears to be an important predictor for stroke outcome, its significance for rt-PA-treated patients should be ascertained in a larger cohort using a multicenter design.

To identify adequate risk factor control in acute stroke patients treated with thrombolysis, a multicenter study group [Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) Study Group] was formed. Here, we determined the association of renal dysfunction based on admission eGFR with stroke outcome after IV rt-PA using the database of this study group.

Patients and Methods

The SAMURAI rt-PA Registry Trial had a multicenter, hospital-based, retrospective, observational, cohort design [11]. Details of this study have been described previously [11, 12]. In brief, this study involved 600 consecutive patients with acute ischemic stroke receiving IV rt-PA from October 2005 to July 2008. Of these, 22 patients were ineligible for analysis; 17 patients had dependent activity of daily living before onset, corresponding to an mRS score ≥4, and 5 patients had incomplete 3-month mRS score data. Thus, the remaining 578 patients were included in the present study. Each local ethics committee approved the research protocol. Each patient received a single IV alteplase dose of 0.6 mg/kg, with 10% given as a bolus within 3 h of stroke onset, followed by a continuous IV infusion of the remainder over 1 h [13].

From the database of the SAMURAI rt-PA registers, the data listed in table 1 were extracted for this study. Neurological deficits were assessed using the National Institutes of Health Stroke Scale (NIHSS) score just before and 24 h after rt-PA. Ischemic stroke subtype according to the TOAST categories was elucidated based on information of non-contrast computed tomography (CT), diffusion-weighted magnetic resonance imaging (MRI), magnetic resonance angiography, CT angiography, cervical/transcranial ultrasound, transthoracic or transesophageal echocardiography, and 24-hour Holter monitoring in addition to neurological findings [14].

Kidney function was evaluated based on the eGFR using a revised equation for the Japanese population [15]; eGFR (ml/min/1.73 m^2) = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ × 0.739 (for women). To calculate eGFR, admission serum creatinine was used. According to the Kidney Disease Outcomes Quality Initiative guidelines of the National Kidney Foundation [16], renal dysfunction was defined as a reduced eGFR (<60 ml/min/1.73 m^2). The stage of renal dysfunction was classified as follows: stage 3 (eGFR 30–59 ml/min/1.73 m^2), stage 4 (15–29 ml/min/1.73 m^2), and stage 5 (<15 ml/min/1.73 m^2 or dialysis).

The major outcome measures were: any ICH defined as CT or MRI evidence of new ICH within the initial 36 h; symptomatic ICH with neurological deterioration corresponding to an increase of ≥1 point from the baseline NIHSS score (Cochrane/National Institute of Neurological Disorders and Stroke definition); favorable and poor outcome at 3 months, and mortality at 3 months. To assess favorable and poor outcome, definitions in the subanalyses of the National Institute of Neurological Disorders and Stroke rt-PA Trial (an mRS of 0–1 and 4–6, respectively) were used [17–20].

Statistical Analysis

Statistical test results were considered significant if $p < 0.05$. All analyses were performed using JMP statistical software (version 7.0.1; SAS Institute, Cary, N.C., USA). Baseline clinical characteristics and stroke features were compared using Student's unpaired t test for parametric continuous variables, Mann-Whitney's U test for nonparametric variables, and Fisher's exact test and the χ^2 test for categorical variables. To identify independent predictors of ICH within 36 h and stroke outcome at 3 months, multivariate logistic regression analysis was performed. For each outcome, sex, age, and renal dysfunction were initially entered, and the other variables listed in table 1 were chosen by a backward selection procedure using $p > 0.10$ in the likelihood ratio test for exclusion.

Results

A total of 578 patients (372 men, 71.4 ± 11.7 years old) were studied. Of these, 186 (32.2%) patients had renal dysfunction with eGFR <60 ml/min/1.73 m^2; 163 (28.2%)

Table 1. Baseline clinical characteristics

Baseline characteristics	Renal dysfunction (eGFR <60 ml/min/1.73 m^2) (n = 186)	No renal dysfunction (eGFR ≥60 ml/min/1.73 m^2) (n = 392)	p value
Male patients	113 (60.8)	259 (66.1)	0.227
Age, years	76.0 ± 9.8	69.2 ± 12.0	<0.001
Body mass index	22.7 ± 3.2	23.0 ± 3.4	0.397
Hypertension	137 (73.7)	219 (55.9)	<0.001
Diabetes mellitus	37 (19.9)	70 (17.9)	0.568
Dyslipidemia	35 (18.8)	89 (22.7)	0.329
Atrial fibrillation	97 (52.2)	148 (37.8)	0.001
Liver disease	8 (4.3)	9 (2.3)	0.194
Prior ischemic heart disease	37 (19.9)	37 (9.4)	<0.001
Prior ischemic stroke	39 (21.0)	62 (15.8)	0.129
Prior use of antithrombotic agents	92 (49.5)	125 (31.9)	<0.001
Systolic blood pressure, mm Hg	150 ± 20	151 ± 20	0.613
Diastolic blood pressure, mm Hg	80 ± 16	83 ± 15	0.077
Stroke subtype			
Large-artery atherosclerosis	24 (12.9)	65 (16.6)	0.141
Cardioembolism	128 (68.8)	236 (60.2)	
Lacune	5 (2.7)	23 (5.9)	
Other	29 (15.6)	68 (17.4)	
Internal carotid artery occlusion	29 (15.6)	59 (15.2)	0.902
Blood glucose, mmol/l	7.68 ± 2.77	7.61 ± 2.61	0.787
Hemoglobin A1c, %	5.8 ± 1.0	5.8 ± 1.1	0.995
Total cholesterol, mmol/l	4.68 ± 1.07	5.01 ± 1.01	<0.001
Triglyceride, mmol/l	1.30 ± 0.72	1.32 ± 0.95	0.809
HDL cholesterol, mmol/l	1.27 ± 0.36	1.38 ± 0.40	0.003
LDL cholesterol, mmol/l	2.83 ± 0.88	3.01 ± 0.87	0.043
Time to treatment onset, min	145 (121–167)	146 (122–166)	0.991
Admission NIHSS score	13 (7–19)	12 (7.25–18)	0.423

Numbers of patients (%) are shown except otherwise indicated; data are means ± SD or medians (IQR).

patients belonged to stage 3, 15 (2.6%) to stage 4, and 8 (1.4%) to stage 5. Four patients with stage 5 were on maintenance hemodialysis.

The patients with renal dysfunction were older ($p < 0.001$) and more commonly had hypertension ($p < 0.001$), atrial fibrillation ($p = 0.001$), prior ischemic heart disease ($p < 0.001$), and prior use of antithrombotic agents ($p < 0.001$) than patients without renal dysfunction (table 1). Serum total cholesterol ($p < 0.001$), HDL cholesterol ($p = 0.003$), and LDL cholesterol ($p = 0.043$) levels were lower in patients with renal dysfunction than in those without. NIHSS scores were not significantly different between patients with renal dysfunction and those without immediately before [median (interquartile range, IQR); 13 (7–19) vs. 12 (7.25–18), $p = 0.423$] and 24 h after IV rt-PA [9 (3–18) vs. 7 (3–15), $p = 0.070$; fig. 1a].

Any ICH [51 (27.4%) vs. 65 patients (16.6%), $p = 0.004$] as well as symptomatic ICH within 36 h from IV rt-PA therapy [15 (8.1%) vs. 10 patients (2.6%), $p = 0.004$], was more common in the patients with renal dysfunction than in those without. After multivariate logistic regression analysis, renal dysfunction was significantly related to both any ICH (odds ratio, OR, 1.81, 95% confidence interval, CI, 1.16–2.84, $p = 0.009$) and symptomatic ICH (2.64, 1.10–6.56, $p = 0.031$; table 2). When the value of eGFR (a continuous variable) was used instead of eGFR <60 ml/min/1.73 m^2 (a categorical variable) as an indicator of renal dysfunction, it was related to any ICH (OR 0.89, 95% CI 0.80–0.99 per 10-ml/min/1.73 m^2 increase, $p = 0.029$) but not symptomatic ICH (0.89, 0.73–1.08, $p = 0.231$).

At 3 months, the patients with renal dysfunction had higher mRS scores than those without [median (IQR); 3

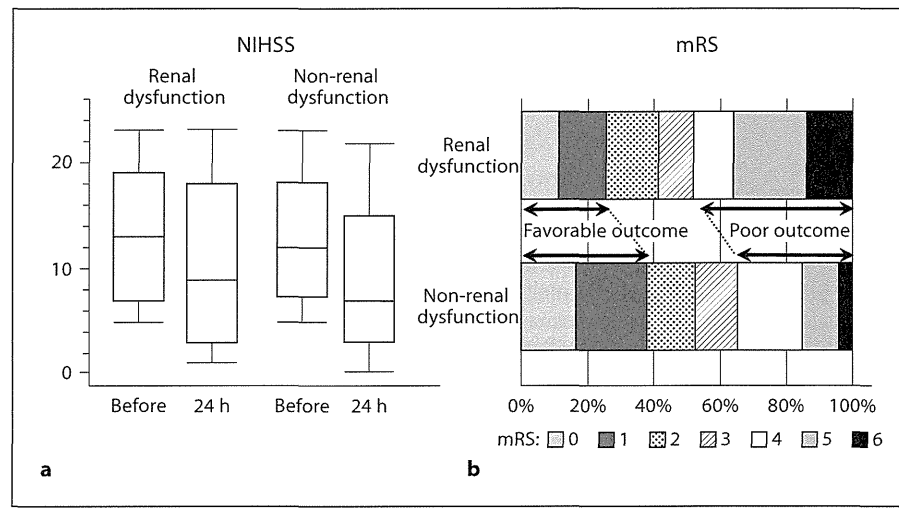

Fig. 1. Neurological deficits and outcome of patients with and without renal dysfunction. NIHSS score just before and 24 h after IV rt-PA therapy (**a**) and mRS score at 3 months (**b**) in patients with and without renal dysfunction. **a** Horizontal lines in boxes = Median NIHSS score; boxes = IQR; whiskers = upper and lower 90% ranges.

Table 2. Characteristics associated with ICH within 36 h

Characteristics	Any ICH			Symptomatic ICH		
	OR	95% CI	p value	OR	95% CI	p value
Male	1.12	0.71–1.78	0.638	1.99	0.74–6.32	0.201
Age (per year)	0.99	0.97–1.01	0.423	1.00	0.96–1.04	0.868
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)	1.81	1.16–2.84	0.009	2.64	1.10–6.56	0.031
Atrial fibrillation	1.93	1.24–3.01	0.004	–	–	–
Liver disease	1.53	0.40–4.79	0.488	–	–	–
Prior use of antithrombotic agents	–	–	–	4.31	1.72–12.06	0.003
Blood glucose (per mmol/l)	1.06	0.98–1.14	0.153	1.11	0.96–1.26	0.126
Triglyceride (per mmol/l)	–	–	–	1.00	0.99–1.01	0.174
Admission NIHSS score (per point)	1.03	0.99–1.06	0.069	–	–	–

– = The variable was not included after the backward selection procedure.

Table 3. Characteristics associated with outcome at 3 months

Characteristics	Favorable outcome (mRS 0–1)			Poor outcome (mRS 4–6)			Death		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Male	1.14	0.74–1.76	0.545	0.84	0.55–1.29	0.430	0.68	0.32–1.48	0.331
Age (per year)	0.97	0.96–0.99	0.005	1.04	1.02–1.06	<0.001	1.01	0.97–1.05	0.718
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)	0.70	0.44–1.09	0.114	1.55	1.01–2.38	0.046	2.94	1.38–6.42	0.006
Prior ischemic heart disease	–	–	–	–	–	–	4.33	1.84–10.05	<0.001
Internal carotid artery occlusion	0.24	0.10–0.51	<0.001	6.07	3.38–11.39	<0.001	4.32	2.00–9.36	<0.001
Blood glucose (per mmol/l)	0.91	0.84–0.99	0.024	1.08	1.01–1.17	0.033	1.17	1.04–1.31	0.007
Admission NIHSS score (per point)	0.91	0.88–0.94	<0.001	1.11	1.08–1.15	<0.001	1.09	1.04–1.15	<0.001

– = The variable was not included after the backward selection procedure. For favorable outcome analysis, patients with premorbid mRS score 2–3 were excluded.

(1–5) vs. 2 (1–4), $p < 0.001$; fig. 1b]. Twenty-five patients (13.4%) with renal dysfunction had died; of these, 5 died of stroke, 6 of heart disease (4 heart failure, 1 myocardial infarction, and 1 infectious endocarditis), 6 of severe infection (3 sepsis and 3 pneumonia), and 8 of unknown causes. In contrast, 15 patients (3.8%, $p < 0.001$) without renal dysfunction had died; of these, 9 died of stroke, 2 of pneumonia, and 4 of unknown causes. Similarly, favorable outcome was less common [48 (25.8%) vs. 149 patients (38.0%), $p = 0.004$], and poor outcome was more common [89 (47.9%) vs. 136 patients (34.7%), $p = 0.003$] in patients with renal dysfunction than in those without. After multivariate logistic regression analysis, renal dysfunction was significantly related to poor outcome (OR 1.55, 95% CI 1.01–2.38, $p = 0.046$) and mortality (OR 2.94, 95% CI 1.38–6.42, $p = 0.006$), although it was not related to favorable outcome (OR 0.70, 95% CI 0.44–1.09, $p = 0.114$; table 3). When the value of eGFR was used instead, it was significantly related to mortality (OR 0.81, 95% CI 0.67–0.96 per 10-ml/min/1.73 m^2 increase, $p = 0.020$), but not to favorable outcome (OR 1.09, 95% CI 0.99–1.20, $p = 0.081$) or poor outcome (OR 0.95, 95% CI 0.86–1.04, $p = 0.268$).

Discussion

In this observational study, we determined the influence of renal dysfunction on early ICH and the long-term outcome of ischemic stroke patients receiving IV rt-PA therapy. The major finding was that renal dysfunction, defined as reduced eGFR (<60 ml/min/1.73 m^2), which was calculated using the admission creatinine level, was related to any ICH and symptomatic ICH within 36 h, as well as poor outcome (mRS 4–6) and death at 3 months, although it was not related to favorable outcome (mRS 0–1).

According to the result of the largest postmarketing surveillance on rt-PA, the Safe Implementation of Thrombolysis in Stroke-Monitoring Study [21], advanced age, body weight, atrial fibrillation, high systolic blood pressure, hyperglycemia, admission NIHSS score, and current infarction on baseline imaging scans were associated with symptomatic ICH. In addition, advanced age, male sex, use of antiplatelet agents other than aspirin, congestive heart failure, higher diastolic blood pressure, hyperglycemia, higher NIHSS score, current infarction, and premorbid dependency were related to death at 3 months. Similar results have been reported in several other studies [22–26]. However, these studies did not assess renal dysfunction as a potential factor affecting stroke outcome. The present study is unique in that renal dysfunction was included as a potential factor and was proven to be associated with patient outcome after rt-PA.

Alteplase is metabolized by the liver, and liver function affects the half-life of alteplase [27]. In this study, liver disease was not associated with stroke outcome. In contrast, renal dysfunction might not prolong the half-life of alteplase. For example, the plasma concentration-time profile of alteplase was not altered after bilateral nephrectomy in rat models [28].

Renal dysfunction is a bystander of stroke, since it is associated with traditional vascular risk factors, including aging, hypertension, diabetes mellitus, dyslipidemia, and smoking [29]. In addition, renal dysfunction is now known to be an independent predictor for stroke [1, 2, 5, 30, 31], partly via nontraditional vascular risk factors, e.g. inflammatory factors, and homocysteinemia. However, the effect of these nontraditional risk factors on stroke outcome has not been clarified, in particular after rt-PA. In patients with acute stroke not receiving IV rt-PA, albuminuria was independently associated with hemorrhagic transformation [32]. Since ICH is a major cause of poor outcome for thrombolysed patients, renal dysfunction may affect chronic outcome after rt-PA via increasing ICH risk. Moreover, renal dysfunction might impair endothelial release of t-PA [33], and increase plasminogen activator inhibitor-1 activity [34] and plasma levels of lipoprotein(a) [35]; these abnormalities might obstruct the reperfusion phenomenon and worsen stroke outcome after IV rt-PA.

An interesting finding regarding the patients who died was that indirect death other than stroke was common as the cause of death for patients with renal dysfunction, though direct stroke death accounted for most of the causes of death for patients without renal dysfunction. This finding suggests that patients with renal dysfunction often had heart problems and susceptibility to infection, developed dependency and died due to non-stroke complications.

Certain limitations need to be considered prior to interpretation of the present results. First, patients who did not receive IV rt-PA were not included in this study. Thus, the influence of renal dysfunction on stroke outcome could not be compared between patients who were treated with rt-PA and those who were not. Second, renal dysfunction was correlated with older age, hypertension, atrial fibrillation, prior ischemic heart disease, and prior use of antithrombotic agents, and this multicolineality may inflate the variances of the parameter estimates. Thus, the present association of renal dysfunction with outcome measures after multivariate analyses may be

overestimated to some extent. Third, eGFR was not measured prior to stroke onset, and therefore eGFR may have been affected by stroke. Fourth, eGFR was calculated using admission creatinine levels, which may have been impaired by acute stroke effects. Repeated assessment in the chronic stroke stage is needed to ascertain that the present patients with reduced eGFR have chronic kidney disease. Fifth, urinary albumin was not measured. Generally, urinary albumin increases during acute ischemic stroke [36]. Finally, the present results based on low-dose rt-PA therapy (0.6 mg/kg) may not be applicable to the regular dose therapy (0.9 mg/kg).

In conclusion, reduced eGFR based on the admission creatinine level was predictive of an unfavorable outcome after IV rt-PA in acute stroke patients. In patients with renal dysfunction, additional therapeutic strategies to improve the efficacy of rt-PA are needed.

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