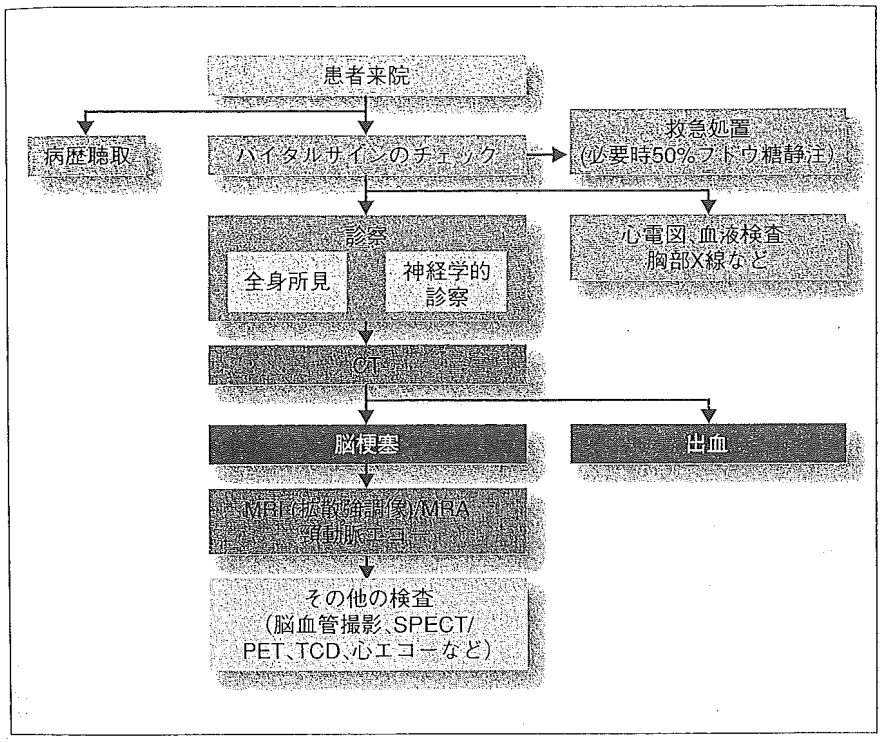

図1　脳卒中急性期の診断の流れ

3. 診察

①一般身体所見

特に心血管系の評価が特に重要である。心音、血管雑音(bruit)、末梢の動脈の触知、四肢の色調など。

①神経学的所見

片麻痺、感覚障害、種々の程度の意識障害、あるいは半盲、失語などの高次脳機能障害を生じることが多い。**表1**に脳血管障害で主にみられる症状を示す[1]。臨床的重症度判定は日本脳卒中学会が作成したJapan Stroke Scale (**表2**)[2]やNIH stroke scaleが有用である。意識障害合併例では局所神経症候をとらえることがしばしば困難である。また糖尿病患者ではラクナ梗塞が多く、特有のラクナ症候群を呈するが、軽微な症状のため臨床症状のみからは診断が難しい場合があり、しばしば無症候となる。運動症状(pure motor hemiplegia；純粋運動性片麻痺)のみや、感覚症状(pure sensory stroke；純粋感覚性発作)のみのこともあることに留意する必要がある。純粋運動性片麻痺が50～60%で感覚運動発作が15～20%と両者でラクナ梗塞の大半を占める。**表3**に軽微な麻痺のみかたについて示した。

Japan Stroke Scale

虚血	頸動脈系	顔面、上肢と（または）下肢の脱力 顔面、上肢と（または）下肢の感覚障害 失語 単眼の視力低下（一過性あるいは永続性）
	椎骨脳底動脈系	上肢と（または）下肢の脱力 上肢と（または）下肢の感覚障害 顔面と反対側の半身の感覚障害 構音障害 両側性の視力低下 めまい 複視 平衡障害 嚥下障害 意識レベルの低下
出血	頭蓋内出血	進行性の重度の頭痛 意識障害 進行する神経脱落症状
	クモ膜下出血	突発する激しい頭痛 項部硬直 眼窩部痛 脳神経麻痺（特に動眼神経） 硝子体出血

表1　局所性脳虚血と出血でしばしばみられる症状と症候(文献1より引用)

患者名：　　年齢：　　歳　男・女　発症日時：／／　時頃　検査日：／／

診断名：　　麻痺側：（右，左，両）　利き手（右，左，両）　検者：

1　Level of Consciousness（意識）：

a）Glasgow Coma Scale

開眼（Eyes Open）
4　自発的に開眼する
3　呼びかけにより開眼する
2　痛み・刺激により開眼する
1　全く開眼しない

言語（Best Verbal Response）
5　見当識良好
4　混乱した会話
3　不適切な言葉
2　理解不能の応答
1　反応なし

運動（Best Motor Response）
6　命令に従う
5　疼痛に適切に反応
4　屈曲逃避
3　異常屈曲反応
2　伸展反応（除脳姿勢）
1　反応なし

E＋V＋M＝Total
（　　）＋（　　）＋（　　）＝□

A：15　B：14～7　C：6～3

b）Japan Coma Scale：

Ⅰ刺激しなくても覚醒している状態
9　全く正常
8　大体意識清明だが、今一つはっきりしない（Ⅰ-1）
7　時・人・場所がわからない（見当識障害）（Ⅰ-2）
6　自分の名前、生年月日が言えない（Ⅰ-3）

Ⅱ刺激すると覚醒する状態
5　普通の呼びかけで容易に開眼する（Ⅱ-10）
4　大きな声または体を揺さぶることにより開眼する（Ⅱ-20）
3　痛み・刺激を加えつつ呼びかけを繰り返すとかろうじて開眼する（Ⅱ-30）

Ⅲ刺激しても覚醒しない状態
2　痛み・刺激に対し払いのけるような動作をする（Ⅲ-100）
1　痛み・刺激で少し手足を動かしたり顔をしかめる（Ⅲ-200）
0　痛み・刺激に全く反応しない（Ⅲ-300）

A：9　B：8～3　C：2～0

□ A＝7.74
□ B＝15.47
□ C＝23.21

表2　Japan Stroke Scale調査票[2)]

(表2の続き)

2. Language（言語）

1. 口頭命令で拳をつくる（両側麻痺の場合は口頭命令で開眼する）
2. 時計を見せて“時計”と言える
3. “サクラ”を繰り返して言える
4. 住所、家族の名前が上手に言える

A：All　B：3/4 or 2/4　C：1/4 or 0/4（None）

☐ A=1.47
☐ B=2.95
☐ C=4.42

3. Neglect（無視）：（可能な限り裏面の線分を使用のこと）

A. 線分二等分試験正常
B. 線分二等分試験で半側空間無視
C. 麻痺に気づかない。あるいは一側の空間を無視した行動をする

＊註：実際のカードには裏面に長さ25cmの太線が印刷してあるが、紙面の都合上省略。

☐ A=0.42
☐ B=0.85
☐ C=1.27

4. Visual Loss or Hemianopia（視野欠損または半盲）

A. 同名性の視野欠損または半盲なし
B. 同名性の視野欠損または半盲あり

☐ A=0.45
☐ B=0.91

5. Gaze Palsy（眼球運動障害）

A. なし
B. 側方視が自由にできない（不十分）
C. 眼球は偏位したままで反対側へ側方視できない（完全共同偏視または正中固定）

☐ A=0.84
☐ B=1.68
☐ C=2.53

6. Pupillary Abnormality（瞳孔異常）

A. 瞳孔異常（対光反射and/or瞳孔の大きさ異常）なし
B. 片側の瞳孔異常あり
C. 両側の瞳孔異常あり

☐ A=1.03
☐ B=2.06
☐ C=3.09

7. Facial Plasy（顔面麻痺）

A. なし
B. 片側の鼻唇溝が浅い
C. 安静時に口角が下垂している

☐ A=0.31
☐ B=0.62
☐ C=0.93

8. Plantar Reflex（足底反射）

A. 正常
B. いずれとも言えない
C. 病的反射（BabinskiまたはChaddock）陽性（1回でも認めたら陽性）

☐ A=0.08
☐ B=0.15
☐ C=0.23

9. Sensory System（感覚系）

A. 正常（感覚障害がない）
B. 何らかの軽い感覚障害がある
C. はっきりした感覚障害がある

☐ A=−0.15
☐ B=−0.29
☐ C=−0.44

10. Motor System（運動系）（臥位で検査する）

Hand（手）　A：1　B：2 or 3　C：4 or 5

1. 正常
2. 親指と小指で輪を作る
3. そばに置いたコップが持てる
4. 指は動くが物はつかめない
5. 全く動かない

☐ A=0.33
☐ B=0.66
☐ C=0.99

Arm（腕）　A：1　B：2 or 3　C：4 or 5

1. 正常
2. 肘を伸ばしたまま腕を挙上できる
3. 肘を屈曲すれば挙上できる
4. 腕はある程度動くが持ち上げられない
5. 全く動かない

☐ A=0.66
☐ B=1.31
☐ C=1.97

Leg（下肢）　A：1．B：2 or 3　C：4 or 5

1. 正常
2. 膝を伸ばしたまま下肢を挙上できる
3. 自力で膝立てが可能
4. 下肢は動くが膝立てはできない
5. 全く動かない

☐ A=1.15
☐ B=2.31
☐ C=3.46

TOTAL　＝ ☐
CONSTANT　−14.71
SCORE　＝ ☐

手回内試験	両手を軽く握らせて前腕を曲げて手を肩につけるように命ずると、健側では手掌面が肩に近づくのに、障害側では回内して手背面が肩に近づく。
第5指徴候	手掌を下にして腕と手を水平前方に突き出させた時に麻痺側の小指が外側にそれる。
バレー徴候(上肢)	手掌を上にして手を水平にさせたときに片麻痺側が回内しつつ落下する徴候。
バレー徴候(下肢)	腹臥位として、両下腿を膝関節が135度くらいに開くような位置に保持させる。麻痺側が自然に落下する。
Mingazzini試験	仰臥位にて両下肢を、股・膝関節ともにそれぞれ約90度屈曲させて空中に保持させる。障害側下肢は自然に落下してくる。
足の外旋位	仰臥位で患側は健側に比べ外旋位になる

表3 軽微な麻痺のみかた

4. 画像検査

脳血管障害の診断における各種画像検査の占める意義は大きく、その進歩は脳卒中臨床を大きく変えてきた。

①CT

出血を発症直後から高吸収域として確実に診断できる点と撮影時間がMRIに比べると短いため、多くの施設で脳血管障害時に第一に行う画像検査としている。急性期出血の診断感度はきわめて高いが、亜急性期以降は等吸収となり梗塞その他の病変との鑑別は難しくなる。

脳梗塞巣はCTでは低吸収域として描出されるが、病変が明瞭化してくるのは発症約6時間後であり、急性期梗塞の同定は難しいことが多い。また、骨に囲まれた後頭蓋窩の構造(脳幹、小脳など)はアーチファクトのため判別に苦慮する場合も多い。

②MRI

骨のアーチファクトがなく、空間解像能に優れるため、後頭蓋窩の病変やラクナのような小さな病変の診断はCTより優れている。またMRアンギオグラフィー(MRA)によって造影剤を用いずに血管を評価することも可能である。T2強調像など種々の撮像法があるが、なかでも分子の拡散運動を反映する拡散強調像(diffusion-weighted image ; DWI)は、虚血病巣を細胞障害性浮腫(cytotoxic edema)の段階で高輝度病変として描出するので、脳虚血巣を超早期(数十分後より)かつCTより確実に診断しうる[3]。また新旧が混在した多発梗塞巣を有する場合の責任病巣の同定にも有用である(図2)。 DWI

③超音波

ベッドサイドで施行できる簡便な検査であり、反復性に優れ低コスト・低侵襲である点より超急性期においても広く使用されている。脳卒中の超音波診断には、(a)頸動脈エコー、(b)経頭蓋超音波ドプラ(TCD)、(c)経食道・経胸

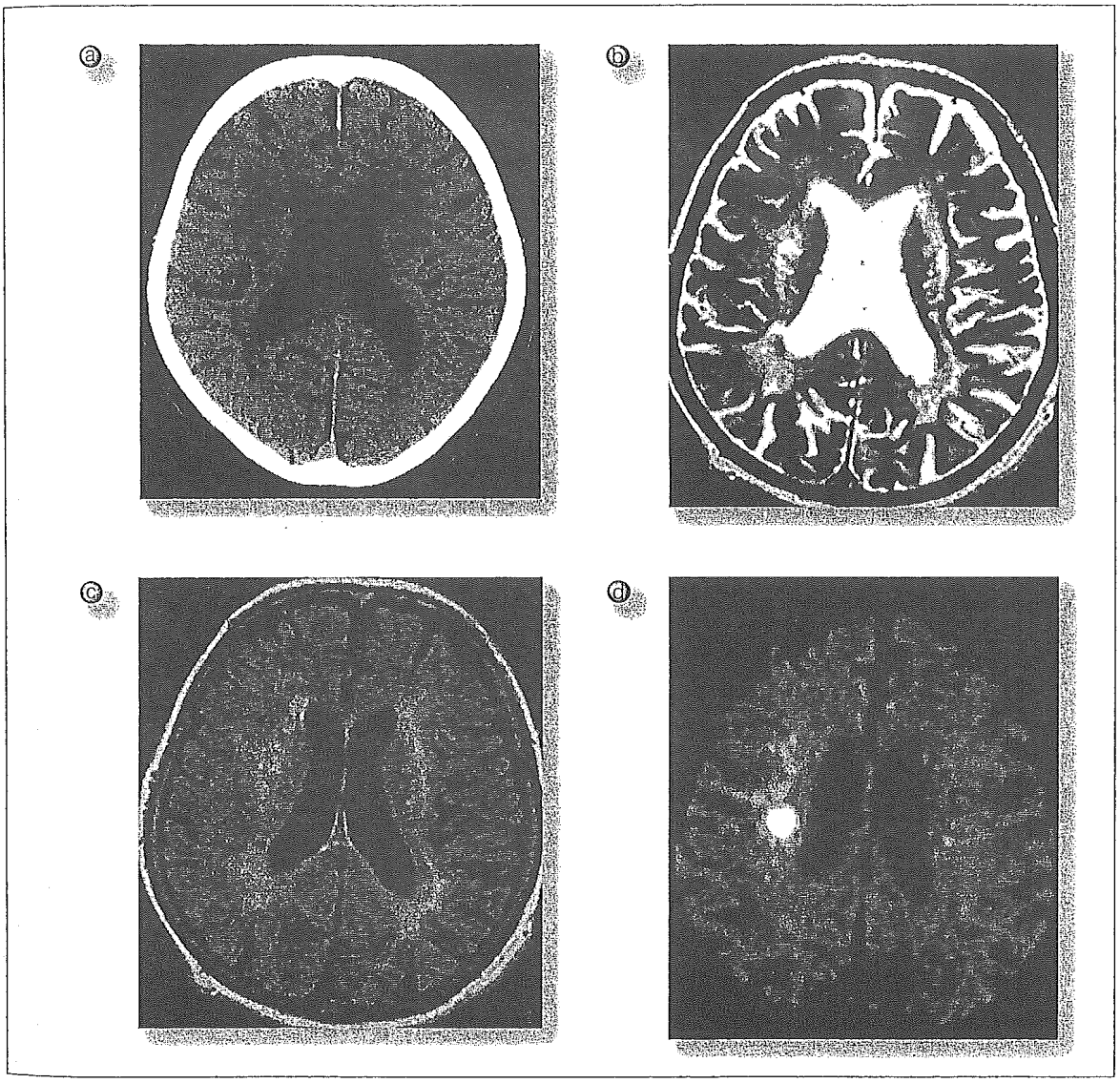

図2　82歳女性(脳梗塞発症後5時間)
a：CT、b：T2強調像、c：FLAIR像、d：拡散強調像(DWI)
CT、T2、FLAIR像では新鮮梗塞巣が明らかではないが、DWIでは右放線冠の急性期梗塞巣が明瞭に描出されている。

壁心エコーなどがある。頸動脈エコーは頭蓋外頸部動脈の狭窄・閉塞の評価、動脈硬化の評価に有用である。TCDは頭蓋内主幹動脈の評価や塞栓子をリアルタイムに観察することが可能である。経食道・経胸壁心エコーは塞栓源の検索や心機能評価に有用である。

④SPECT；single photon emission computed tomography/
PET；positron emission tomography
脳の核医学検査であり、脳血流の評価が可能であり、脳虚血領域の範囲の

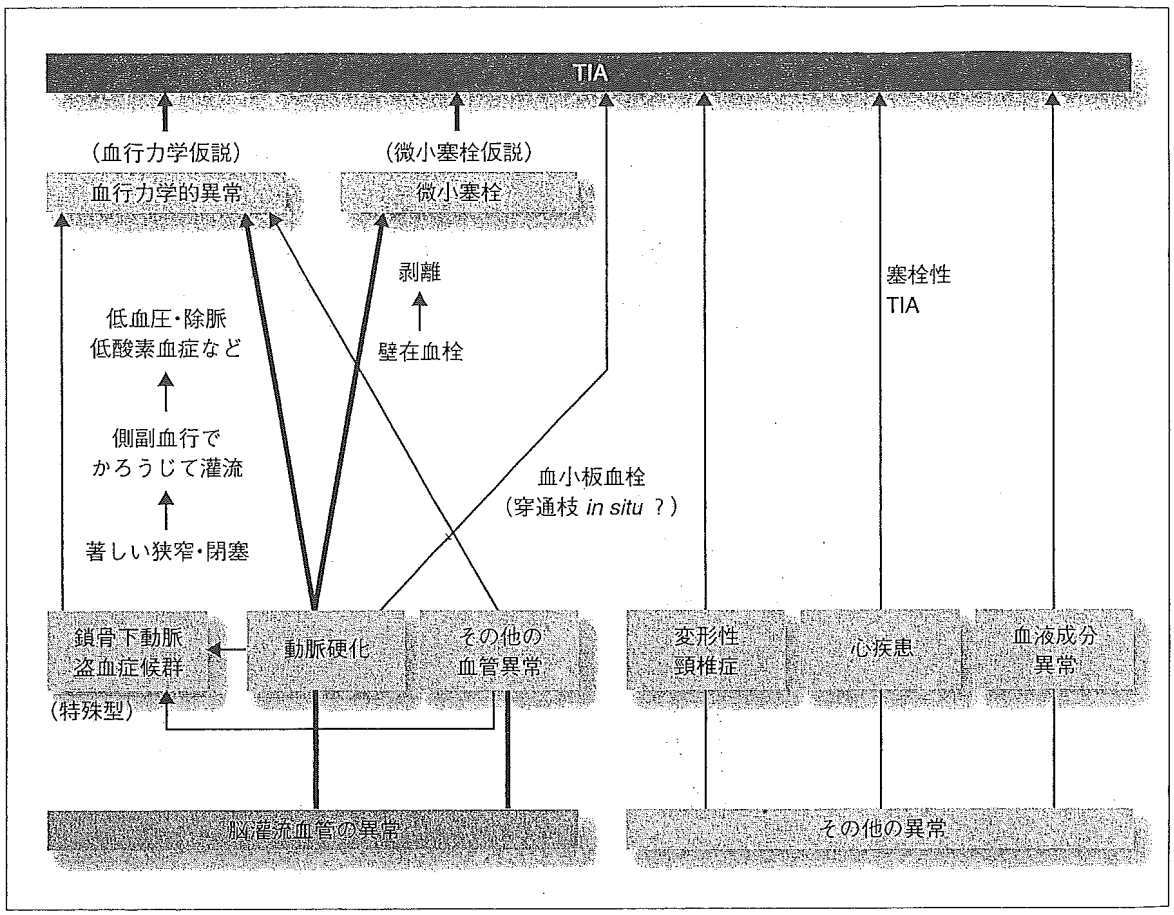

図3　一過性脳虚血発作(TIA)の成因(文献6より引用)

評価が可能である。梗塞巣の範囲と虚血領域を比較することで、救済可能な領域(虚血 penumbra)の評価と血栓溶解時の出血リスクの推測が可能であるが[4]、30分程度の検査時間が必要であるのが難点である。このほかの脳血流評価法として近年進歩したperfusion MRIや、perfusion CTが虚血penumbraの同定に有用との報告が相次いでおり、大規模な前向き研究が待たれる。

penumbra

⑤脳血管の画像

血管障害の責任血管評価のためには、脳血管のimagingが不可欠である。従来は脳血管撮影のみであったが、近年では前述の頸動脈エコー、MRA、あるいはCT アンギオグラフィー(CTA)といった非侵襲的血管画像の発達がめざましい。急性期脳梗塞においてはまずこれらの検査を行い、さらに血行動態の把握が必要な場合やインターベンションの適応がある場合に緊急脳血管撮影を行うことが多い。

2. 一過性脳虚血発作(transient ischemic attack；TIA)

TIAとは運動障害、視力消失、感覚障害、失語などの脳虚血による局所神経症状が24時間以内に完全に消失するものをいう。多くは2分以内に極期に達し、繰り返すことも多い。TIAが生じたあとの1ヵ月以内に脳梗塞を発症するリスクが高いので、その症状を理解し、予防を図ることが重要である。拡散強調MRI(DWI)を行うと、不可逆性あるいは時に可逆性の病変を検出できることが報告されている[5]。診断は原則として症状と経過により行うが、内頸動脈系TIAと椎骨動脈系TIAに大別される。失調、回転性めまい、平衡障害、複視、嚥下障害、構音障害などがあれば、椎骨動脈系TIAの可能性が高いが、これらの症状や失神が単独で生じてもTIAとはみなさないことに注意する必要がある。発症機序は脳梗塞同様多様であるが、以下の2つが多くを占める(図3)[6]。一つは頸動脈分岐部に形成されたアテローム硬化病変から剥れた微小栓子がつまる場合である。他方は頭蓋外脳動脈や、脳底部主幹動脈の高度狭窄/閉塞病変を有する例にさらなる血流不全が加わることによる(脱水や血圧低下など)血行力学的な機序である。両機序とも動脈硬化を背景としており、頸部超音波やMRAによる頭蓋内外の血管病変のチェックが必要である。

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循環器疾患等総合研究事業

脳血管疾患の再発に対する高脂血症治療薬 HMG-CoA還元酵素阻害薬の予防効果に関する研究

Japan Statin Treatment Against Recurrent Stroke (J-STARS)

平成17年度　総括・分担研究報告書

3/5

雑誌（I）

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Ⅲ．研究成果の刊行物・別刷

雑　　誌（Ⅰ）

（平成17年度）

Original Article

Hemodynamic Influences of Losartan on the Brain in Hypertensive Patients

Naohiko OKU, Kazuo KITAGAWA*, Masao IMAIZUMI*, Masashi TAKASAWA*, Risyu PIAO*, Yasuyuki KIMURA, Katsufumi KAJIMOTO*, Masayasu MATSUMOTO**, Masatsugu HORI*, and Jun HATAZAWA

The effects of angiotensin II receptor blockers on cerebral hemodynamics in humans have not been well elucidated. The present study evaluated the effects of losartan on cerebral hemodynamics in hypertensive patients using positron emission tomography. Ten patients with essential hypertension (mean age, 60.8 years) were examined. In each patient, regional cerebral blood flow was measured by [O-15] labeled water positron emission tomography before and after the oral administration of losartan for 8 to 23 weeks. In 8 patients, the baseline regional cerebral blood flow measurement was followed by 1,000 mg of acetazolamide challenge to measure the cerebral perfusion reserve. Systemic blood pressures before and after treatment were 153.8±10.8/96.0±6.5 mmHg (systolic mean±SD/diastolic mean±SD) and 133.4±11.2/83.6±6.5 mmHg, respectively; this difference was significant. The baseline global cerebral blood flow values before and after treatment were 38.4±6.9 ml/min/100 g and 38.2±8.2 ml/min/100 g, respectively; this difference was not significant. The results of the global cerebral blood flow response to the acetazolamide challenges were not statistically different before and after treatment. A regional analysis showed no statistical difference in regional cerebral blood flow or cerebral perfusion reserve throughout the brain before and after treatment. Losartan's effect on reducing the blood pressure did not affect either the baseline regional cerebral blood flow or the cerebral perfusion reserve in patients with mild to moderate hypertension. The inclusion of losartan in anti-hypertensive regimens could be advantageous for cerebral circulation in patients with essential hypertension. (*Hypertens Res* 2005; 28: 43–49)

Key Words: **cerebral blood flow, hypertension, losartan, positron emission tomography, cerebrovascular reactivity**

Introduction

Angiotensin II receptor blockers are the latest generation of anti-hypertensive drugs. Losartan, an angiotensin II receptor blocker, has been reported to have protective effects against hypertensive organ damage as well as on systemic blood pressure. The LIFE study (*1*) was a prospective, double-blinded and randomized clinical trial in which losartan was shown to be more effective at preventing cardiovascular morbidity and death than atenolol. In the LIFE study, interest was focused on the preventive effects of losartan on primary fatal or non-fatal strokes. Losartan appeared to have beneficial effects on cerebral vessels beyond a reduction in blood pressure.

The effect of angiotensin II receptor blockers on cerebral hemodynamics is still controversial. Previous studies have suggested that angiotensin II receptor blockers do not influence cerebral blood flow under baseline conditions.

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Table 1. Characteristics of the Subjects

Patient No.	Age (years old)	Gender	Losartan dose (mg/day)	Duration (weeks)	Brain MRI	Coexisting disease
1	61	M	50	23	asym WMI	hyperchol
2*	60	F	100	20	ns	ns
3	60	M	50	19	ns	ns
4*	64	M	50	9	lacunar inf	ns
5	62	F	100	22	asym WMI	hyperchol
6	52	M	50	12	ns	ns
7	59	M	50	12	asym WMI	ns
8	62	M	100	11	asym WMI	ns
9	65	M	100	8	ns	ns
10	63	F	100	18	ns	hyperchol

M, male; F, female; MRI, magnetic resonance imaging; asym WMI, asymptomatic white matter ischemic lesion; lacunar inf, lacunar infarction; hyperchol, hypercholesterolemia; ns, not specific. *Patient refused to undergo acetazolamide challenge. Duration means the therapy period from the start of losartan administration to the second cerebral blood flow measurement.

Vraamark *et al.* (*2*) reported that candesartan shifted the autoregulation curve towards the left in hypertensive rats. Strömberg *et al.* (*3*) reported that losartan shifted the upper limit of the autoregulation curve towards the right in rats with experimental hypertension induced by angiotensin II. Finally, in an experiment by Näveri *et al.* (*4*), losartan increased cerebrovascular resistance in rats with acute hypotension induced by hemorrhage.

However, these previous results were based on animal models and some observed acute effects of angiotensin II receptor blockers on cerebral blood flow. Few reports have evaluated the chronic effects of losartan on cerebral hemodynamics in hypertensive patients. The purpose of this paper was to elucidate the hemodynamic status before and after losartan administration using positron emission tomography and an acetazolamide challenge.

Methods

Subjects

Subjects were selected from patients with essential hypertension, defined according to the criteria of the VIth Joint National Committee (*5*). We excluded patients who met any of the following conditions: age under 40 years; severe hypertension (systolic blood pressure >200 mmHg or diastolic blood pressure >120 mmHg) or uncontrolled diabetes (HbA1c >8%); a history of stroke within the previous 3 months; angina pectoris or myocardial infarction; heart failure; renal failure (serum creatinine >2 mg/dl); severe stenosis (>50%) of the carotid artery and/or middle cerebral artery (assessed by ultrasonography and magnetic resonance angiography); currently taking anti-hypertensive drugs; atherosclerosis obliterans; any type of dementia; or currently taking tranquilizers, histamine blockers, analgesics, or diuretics.

Eighteen patients were nominated for the study. Of these 18 patients, 10 patients agreed to participate in the study and provided their written informed consent after receiving a detailed explanation of the study, including the irradiation dosage used in the positron emission tomography procedure. The profiles of these patients are shown in Table 1. The mean age of the patients was 60.8±3.4 (mean±SD) years. Of the 10 patients, one had a non-disabling pure motor hemiparesis due to lacunar infarction and four had mild asymptomatic white matter ischemic lesions (Fazekas (*6*) grade 1, minimal patchy white matter foci), as revealed by brain magnetic resonance imaging. Three patients had hypercholesterolemia, and none had diabetes. All portions of the study were performed in agreement with the ethical guidelines of the hospital.

Drug Control

On enrollment in the study, the clinical history of the patients was thoroughly checked. The administration of drugs that might influence the baseline cerebral blood flow was prohibited during the study period. Prescriptions for chronic diseases such as hypercholesterolemia were continued unchanged throughout the study period. Patients underwent an initial cerebral blood flow measurement using positron emission tomography with [O-15] labeled water. Subsequently, the patients received a daily oral dose of losartan (NU-LOTAN™; Banyu Pharmaceutical Co., Ltd., Tokyo, Japan) titrated to 50 mg. Follow-up examinations were performed every 2 to 4 weeks, and the drug dosage was increased up to 100 mg a day unless the patient reached a target sitting blood pressure of less than 140/90 mmHg. When the sitting blood pressure reached the target range and stabilized with losartan administration, the patient underwent a second cerebral blood flow measurement.

Table 2. Syetemic Blood Pressure, Pulse Rate, and Arterial Gas Tension during Cerebral Blood Flow Measurement

	Before losartan			After losartan		
	Baseline (n=10)	ACZ_{10} (n=8)	ACZ_{20} (n=8)	Baseline (n=10)	ACZ_{10} (n=8)	ACZ_{20} (n=8)
SBP (mmHg)	153.8±10.8	159.2±15.5	159.5±16.6	133.4±11.2*	138.0±15.8*	138.8±17.5*
DBP (mmHg)	96.0±6.5	95.9±6.3	97.6±7.2	83.6±6.5*	82.8±7.7*	84.5±6.5*
Pulse (bpm)	64.4±7.9	64.3±6.7	64.9±5.0	61.0±7.0	61.3±7.2	63.4±7.2
pH	7.409±0.021	7.426±0.023	7.423±0.033	7.406±0.014	7.416±0.010	7.412±0.019
$PaCO_2$ (mmHg)	38.7±2.8	37.2±2.9	36.7±4.3	39.5±2.1	37.9±2.2	37.6±1.8
PaO_2 (mmHg)	81.6±8.7	87.9±13.8	91.0±15.6	80.5±6.6	85.8±9.5	87.3±9.9

SBP and DBP, systolic and diastolic blood pressure, respectively; $PaCO_2$ and PaO_2, arterial gas tension for carbon dioxide and oxygen, respectively; ACZ_{10} and ACZ_{20}, 10 and 20 min after acetazolamide injection, respectively; bpm, beats per minute. Data are listed in mean±SD. *$p<0.01$ *vs.* baseline in before losartan.

Cerebral Blood Flow Measurement

All patients underwent two cerebral blood flow measurements. As described above, the first and second measurements were performed before and after the administration of losartan, respectively. We used a high-performance positron emission tomography scanner (SET-2400W; Shimadzu Co., Kyoto, Japan) that uses 63 slices (slice thickness of 3.1 mm) and a spatial resolution of 3.7 mm full width at half maximum. Regional cerebral blood flow was quantitatively measured using positron emission tomography, an [O-15] labeled water injection, and an autoradiographic method (*7*). During each session, the patient was asked to lie on the scanner bed in a supine position in a quiet, dimly lit room. One session consisted of four scans. First, two consecutive scans were performed for the baseline condition. Then, after the intravenous administration of acetazolamide titrated to 1,000 mg, two additional scans were performed at an interval of 10 min. At the end of every scan, the patient's blood pressure, pulse rate, and arterial blood gas tension were measured. The data obtained for the baseline condition were averaged using the two measurements.

Blood Pressure Measurements

Blood pressure was measured using a mercury sphygmomanometer and a 6-inch cuff, with the patient lying supine on the scanner bed. Systolic and diastolic blood pressure (Korotkoff phase I and phase V, respectively) were averaged using two readings obtained 3 min apart.

Cerebral Blood Flow Image Analysis

The regional cerebral blood flow image data set obtained by the positron emission tomography scanner was transformed stereotaxically into an identical normal brain template using statistical parametric mapping-99 software (*8*) (SPM99; Wellcome Department of Cognitive Neurology, University College London, London, UK) running in a MATLAB™ (The MathWorks Inc., Natic, USA) environment. Identical regions of interest (the whole cerebrum, whole cerebellum, bilateral upper and lower frontal lobes, bilateral temporal lobes, bilateral occipital lobes, bilateral parietal lobes, bilateral basal ganglia areas, and bilateral thalami) were drawn on standardized cerebral blood flow images. Except for the whole cerebrum and whole cerebellum, the regions of interest were drawn on the gray matter of each region and consisted of multiple small circular regions of interest (20 mm in diameter) linked together.

Statistical Analysis

Blood pressure, pulse rate, arterial blood gas tensions, and baseline cerebral blood flow measurements obtained before and after treatment were compared using paired t-tests. The effects of acetazolamide on systemic conditions and an increased cerebral blood flow were analyzed using a one-way repeated-measure analysis of variance (ANOVA) followed by Bonferroni's multiple comparison. These analyses were performed using statistical analysis software (SPSS 11.5J; SPSS Japan Inc., Tokyo, Japan) on a personal computer running Windows™. Differences were considered to be significant when the statistical p value was less than 0.05.

Results

Losartan was well tolerated by all the patients and no complications or adverse effects occurred. The period of losartan therapy ranged from 8 to 23 weeks, and the final losartan dosages required to control the patients' blood pressures were 50 mg/day in 5 patients and 100 mg/day in 5 (Table 1). Of the 10 patients in the study, 8 patients safely underwent two acetazolamide challenges; the examination was well tolerated in these patients. Two patients (Nos. 2 and 4 in Table 1) refused to undergo the acetazolamide challenge. Thus, the physiological parameters and baseline regional cerebral blood flow were assessed in 10 patients, while the changes in these parameters after an acetazolamide challenge were assessed in

Table 3. Changes of Individual Cerebral Blood Flow, Response to Acetazolamide, and Systemic Parameters before and after Losartan Administration

PtNo	Baseline gCBF (ml/min/100 g)		INC%max (%)		Mean BP (mmHg)		P_{CO_2} (mmHg)	
	Before	After	Before	After	Before	After	Before	After
1	31.7	32.3	29	42	114.3	111.7	41.2	41.4
2	39.0	41.1			111.1	98.2	37.8	36.2
3	34.7	35.4	42	39	116.5	94.2	37.1	38.5
4	48.0	50.3			130.7	105.3	35.0	42.0
5	48.6	39.9	65	58	113.5	109.8	44.6	40.5
6	31.6	38.8	29	41	112.8	104.3	38.8	37.4
7	28.1	28.2	23	28	109.7	87.5	39.0	38.4
8	40.4	29.6	34	50	110.3	93.2	37.7	40.3
9	40.4	33.7	68	47	107.2	94.3	39.8	38.1
10	41.1	52.6	49	39	126.3	103.5	35.9	42.6

gCBF, global cerebral blood flow; INC%max, maximum percent increase of gCBF from baseline after acetazolamide injection; BP, systemic blood pressure; P_{CO_2}, arterial partial pressure of carbon dioxide; PtNo, patient number.

8 patients.

Table 2 shows the physiological data for the patients. The baseline systemic blood pressures before and after losartan administration were 153.8±10.8/96.0±6.5 (systolic mean±SD/diastolic mean±SD) mmHg and 133.4±11.2/83.6±6.5 mmHg, respectively. Both the systolic and diastolic blood pressures decreased significantly after losartan administration. Arterial blood gas tensions, arterial pH, and the pulse rate measured before and after losartan administration did not change significantly. Although a slight elevation in blood pressure was observed during the acetazolamide challenges, both before and after losartan administration, the effect of the acetazolamide challenge on the baseline blood pressure values was not significant.

None of the regional cerebral blood flow images obtained during the positron emission tomography examinations showed major abnormalities, and all of the images were successfully transformed into standardized normal brain images using the SPM99 software.

As the peak response time (*i.e.*, 10 or 20 min after acetazolamide injection) to acetazolamide differed by patient, we selected individual maximum cerebral blood flow value for the analysis. Table 3 shows the individual changes in global cerebral blood flow, the maximum percent increase in cerebral blood flow (INC%max) induced by acetazolamide, mean systemic blood pressure, and arterial partial pressure of carbon dioxide. In 3 patients (Nos. 5, 8, and 9), there was a considerable decrease in global cerebral blood flow after losartan administration. In contrast, the other 2 patients (Nos. 6 and 10), showed considerable increases in global cerebral blood flow after losartan administration. Table 4 shows the mean global and regional baseline cerebral blood flow values and the INC%max for the two conditions. The mean baseline global cerebral blood flow values obtained before and after losartan administration were 38.4±6.9 ml/min/100 g and 38.2±8.2 ml/min/100 g, respectively; these values were not significantly different. The mean global INC%max before and after losartan administration were 42.4±17.0% and 43.0±8.9%, respectively. No significant differences among the mean global INC%max values were observed. The same relationships were seen for every brain region examined, *i.e.*, there were no significant differences in the baseline cerebral blood flow and INC%max values obtained before and after losartan administration.

Discussion

In the present study, losartan was shown to reduce blood pressure without deteriorating baseline cerebral blood flow or the cerebral blood flow response to acetazolamide in patients with essential hypertension. No regional differences in this effect were observed in the brain. Only a few previous studies have evaluated the effect of losartan on the brain in hypertensive patients. Matulla *et al.* (*9*) indirectly suggested that losartan did not change the resting global cerebral blood flow in normal individuals, based on ultrasonography findings. This previous study measured blood flow velocities in the middle cerebral artery, not the cerebral blood flow, and only evaluated the acute effects of losartan. The present clinical study evaluated the chronic effects of losartan on regional cerebral blood flow. In this study, three patients (Nos. 5, 8, and 9) out of 10 showed considerable decrease in baseline cerebral blood flow after losartan administration. In one patient (No. 5), the decrease might be explained by the change in arterial carbon dioxide gas tension. In the rest 2, although it was possible that losartan affected the baseline cerebral blood flow, it was also possible that the drift in cerebral blood flow measurement by positron emission tomography partially influenced the result. The reproducibility of the method has been reported to have a SD of almost 10% (*10*).

Positron emission tomography, [O-15] labeled water, and SPM99 software were used in this study. These methods offer

Table 4. Regional Cerebral Blood Flow at Baseline and Cerebral Perfusion Reserve

Region	Before losartan		After losartan	
	Baseline CBF (ml/min/100 g) (n=10)	INC%max (%) (n=8)	Baseline CBF (ml/min/100 g) (n=10)	INC%max (%) (n=8)
Cerebrum global	38.4±6.9	42.4±17.0	38.2±8.2	43.0±8.9
Cerebellum global	44.0±8.7	45.9±11.4	42.8±8.7	51.0±16.6
Frontal Base Rt	41.9±8.9	44.3±17.6	40.9±8.1	45.4±7.8
Top Rt	43.5±9.2	42.3±11.3	41.2±8.4	43.0±7.3
Base Lt	42.0±8.4	47.5±20.8	41.7±8.8	49.9±13.4
Top Lt	43.2±9.2	46.0±16.0	41.7±9.1	46.5±10.8
Temporal Rt	39.0±6.1	43.1±19.0	39.4±7.2	47.1±9.3
Lt	39.1±6.8	42.3±19.7	39.2±9.2	52.1±14.0
Parietal Rt	42.2±8.5	39.0±13.7	41.0±8.2	45.3±7.0
Lt	42.5±7.2	39.9±16.4	41.6±8.7	45.9±8.4
Occipital Rt	41.4±5.5	39.8±23.5	42.9±9.1	38.8±10.9
Lt	43.0±5.6	35.0±19.7	44.3±11.0	41.5±10.6
Basal ganglea Rt	50.8±9.9	51.4±18.6	50.8±11.5	52.9±11.7
Lt	49.4±9.9	53.5±26.1	49.7±13.1	62.3±19.4
Thalamus Rt	54.4±14.0	50.8±18.1	50.4±13.0	53.8±17.1
Lt	52.9±9.6	56.3±20.9	51.5±15.2	58.1±15.9

INC%max, maximum percent increase of regional cerebral blood flow from baseline after acetazolamide injection; Rt, right; Lt, left.

some advantages for this type of study. Regional cerebral blood flow measurement using positron emission tomography and [O-15] labeled water is a reliable and quantitative method. A single measurement requires only 2 min to perform, and measurements can be repeated every 10 min because the half-life of [O-15] is as short as 2 min. This characteristic enabled us to measure both the baseline cerebral blood flow and the cerebral blood flow after an acetazolamide challenge within about 1 h. To quantify the regional cerebral blood flow, we used a region of interest-based analysis. This type of analysis using native cerebral blood flow images is limited by positional changes of the head from session-to-session and by inter-subject differences in the shape of the brain. SPM99 have been developed as an analysis tool for detecting areas with statistically significant signal changes among images obtained under different scanning conditions and for different individuals. Using the SPM99 module enabled us to correct for inter-scan head motion and to minimize inter-individual structural differences in the head. Using these techniques, corresponding regions of interest were obtained in all of the patients.

Theoretically, organ blood flow is determined by blood pressure and vascular resistance. Our data indicated that losartan reduced the cerebral vascular resistance whereas the blood pressure reduced. Unlike in the present study, Näveri *et al.* (*4*) reported that the administration of losartan in a hemorrhagic hypotensive animal model increased cerebrovascular resistance. These conflicting results may be explained by the fact that Näveri *et al.* examined the acute effects of losartan in an experimental animal model, whereas our data were focused on the chronic effects of losartan in humans in a clinical environment.

Under physiological conditions, global cerebral blood flow is controlled by autoregulation, irrespective of changes in systemic blood pressure. The vascular responses of large arteries and the resistance of small cerebral vessels play pivotal roles in this mechanism. Furthermore, the renin-angiotensin system is known to have a large effect on the regulation of vascular tonus (*2–4, 11*). It is thus of concern that losartan administration may have shifted the cerebral autoregulation curve to the left or right. However, elucidating the upper and lower limits of the cerebral autoregulation curve is difficult in real patients. In the present study, patients were categorized as having mild or moderate hypertension, and thus the average right shift of the autoregulation curve was likely to be small. It remains unclear whether or not losartan affects the cerebral hemodynamics in patients with severely impaired autoregulation.

Instead of elucidating the autoregulation range, we applied an acetazolamide challenge to test cerebral vasomotor reactivity. The intravenous administration of acetazolamide titrated to 1,000 mg causes a dramatic dilatation in the cerebral resistant vessels as a result of extracellular acidosis (*12*), which in turn causes the regional cerebral blood flow to increase to its maximum possible value. This effect has been used to evaluate cerebral vasomotor reactivity and the cerebral perfusion reserve (*13*). The cerebral perfusion reserve is considered a safety margin against a drift in cerebral perfusion pressure. This idea has been supported by several previous studies (*14–16*) which concluded that compromised

cerebral perfusion reserve was associated with an increased risk of cerebral ischemic events. Our data suggested that losartan did not affect the cerebral perfusion reserve. This property is thought to be beneficial to patients with cerebral ischemic lesions, such as those seen in the present study.

Stroke prevention is a major goal in the treatment of hypertension. Inada *et al.* (*17*) reported that candesartan treatment reduced the incidence of stroke in stroke-prone spontaneously hypertensive rats. In the LIFE (*1*) losartan was more effective at preventing fatal and non-fatal stroke events than atenorol (adjusted risk reduction, 24.9%) and resulted in fewer adverse events. The results raise the question of whether angiotensin II receptor blockers are superior to angiotensin-converting enzyme inhibitors. In patients with symptomatic heart failure (*18*) or acute myocardial infarction (*19*), losartan was equally beneficial but not superior to captopril. Which of these drugs is superior for stroke management remains uncertain, but both drugs owe their protective effects to the inhibition of the renin-angiotensin system. Many experimental studies have proved that the inhibition of the renin-angiotensin system modulates vascular tonus (*2–4*, *10*), prevents (*20*) or improves (*21*, *22*) vascular wall remodeling or improves endothelial functions (*23*, *24*). In a human study, candesartan reduced oxidative stress and inflammation (*25*), which were related to organ damage. Angiotensin II receptor blockers as well as angiotensin converting enzyme inhibitors seem to be promising for the prevention of stroke.

In conclusion, losartan has been accepted as an effective anti-hypertensive drug with good tolerability. Our results showed that losartan effectively lowered the blood pressure without affecting the baseline cerebral blood flow or cerebral perfusion reserve in patients with mild to moderate hypertension. This characteristic protects the brain from unexpected episodes of hypotension during treatment with losartan. The effect of this drug on the brain in patients with stroke or in those with severe hypertension awaits further study.

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Critical Analysis of Hemodynamic Insufficiency by Head-up Tilt in Patients With Carotid Occlusive Disease

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Background The objective of this study was to evaluate the diagnostic value of the head-up-tilt (HUT) test for detecting cerebral hemodynamic insufficiency in patients with major cerebral artery occlusion disease because such patients may benefit from extracranial–intracranial bypass surgery.

Methods and Results In 13 cases of transient ischemic attacks in patients with carotid or middle cerebral artery occlusive disease, the HUT test was used to determine whether or not the symptoms appear during induced hypotension before investigating cerebral hemodynamics with positron emission tomography. Three of the 13 patients showed focal symptoms such as hemiparesis and limb shaking during the HUT test. In all 3 patients, the oxygen extraction fraction (OEF) increased beyond 53.3% (ie, misery perfusion), whereas only 2 of the other 10 patients without focal symptoms showed an increase in OEF during HUT.

Conclusions The HUT test was highly useful for screening patients with cerebral hemodynamic insufficiency in carotid occlusive disease. (*Circ J* 2005; **69:** 971–975)

Key Words: Cerebral hemodynamics; Head-up-tilt; Positron emission tomography; Transient ischemic attack

In patients with ischemic cerebrovascular disease (CVD), atherothrombotic occlusion or severe stenosis of the major cerebral arteries can cause chronic hypoperfusion in the border zone area[1,2] However, the cause of ischemic stroke associated with previously occluded major vessels such as the internal carotid artery (ICA) would be largely emboli either from the distal or proximal stump of the occluded vessel or from atherosclerotic plaque[3] For management of patients with transient ischemic attacks (TIA) or minor stroke with major vessel occlusion, it is critically important to clarify which mechanism, embolic or hemodynamic, underlies the pathophysiology. Cerebral hemodynamics can be assessed precisely with positron emission tomography (PET), and patients with misery perfusion[4] characterized by an increased oxygen extraction fraction (OEF), are at high risk for subsequent stroke[5,6] Although hemodynamic CVD is unlikely to occur in patients with normal hemodynamics, embolic TIA can occur in patients with hemodynamic cerebrovascular insufficiency. Therefore, careful history taking is also essential for diagnosing hemodynamic TIA; however, the number, stereotype, duration of neurological symptoms are unreliable indicators of impaired cerebral hemodynamics[7] Head-up tilt (HUT) tests have been often used to examine cerebral autoregulation in patients with vasovagal syncope[8] Because focal neurological signs in hemodynamic TIA are often precipitated by standing up[9–11] orthostatic stress with HUT tests may reproduce the clinical symptoms in patients with cerebral hemodynamic insufficiency.

We have investigated the clinical symptoms with HUT test and cerebral hemodynamics with PET in carotid TIA patients with major cerebral artery occlusive disease for determining an operation indication of extracranial–intracranial (EC-IC) bypass surgery. The purpose of this study was to determine the diagnostic value of HUT tests in detecting hemodynamic insufficiency (ie, misery perfusion).

Methods

Enrollment in this study began in February 2000, and ended in December 2001. A total of 26 carotid TIA patients were hospitalized during this period at the Osaka University Hospital. Carotid TIA was diagnosed according to the National Institute of Neurological Disorders and Stroke classification of CVD III[12] Each subject underwent neurological and neuroradiological evaluations, including an evaluation for occlusive CVD by duplex carotid ultrasonography (US),[13] magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and cerebral angiography. The MRI examination was performed in 5-mm-thick sections along the orbitomeatal plane with a 1.5-T unit. Infarction was defined as a focal area with prolonged T1 and T2 relaxation times. After evaluation of major cerebral vessels with US, MRA or angiography, 14 patients (9 men, 5 women; mean±SD age, 57.9±12.3 years) with occlusion or stenosis of the ICA or the main trunk of the middle cerebral artery (MCA) were included in this study. The patients gave written informed consent to undergo

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Table 1 Patient Characteristics and HUT and PET-OEF Parameters

Patient no.	Age (years)	Sex	Transient neurological deficit	Angiographic findings	MRI	HUT					PET OEF (%)
						Minimal/basal MBP (mmHg) (% reduction)	NTG	CMS	Duration to target MBP (min)	Symptoms	
1	64	M	L. amaurosis fugax	L. ICAS	L. occipital	66/120 (45%)	+	–	19	Presyncope	41.1
2	55	M	L. hemiparesis	Bil. MCAO	R. CR	63/116 (46%)	–	–	15	Presyncope	39.4
3	56	F	L. hemiparesis	R. ICAO	R. CR	69/108 (36%)	+	+	33	–	58.4
4	52	M	L. upper limb monoparesis	R. MCAO	None	70/105 (32%)	–	+	26	–	44.1
5	40	F	L. hemiparesis and dysarthria	Bil. MCAO	R. BG	71/104 (32%)	–	+	17	–	50.6
6	62	M	L. hemiparesis and dysarthria	R. MCAS	None	57/116 (51%)	+	–	30	Presyncope	43.2
7	69	F	L. upper/lower limb shaking	R. MCAO	None	73/126 (42%)	+	+	36	L. upper/lower limb shaking	60.7
8	66	M	R. upper limb monoparesis	L. ICAO	L. temporal	70/116 (40%)	+	+	36	–	47.4
9	63	M	R. hemiparesis	L. MCAO	L. CR	72/104 (31%)	–	–	28	R. upper limb weakness	58.1
10	71	M	L. hemiparesis	R. ICAO	None	84/105 (20%)	–	+	18	–	58.0
11	59	F	L. upper/lower limb shaking	R. MCAO	None	56/102 (45%)	+	–	52	Presyncope	47.4
12	28	F	L. hemiparesis	Bil. MCAS	None	68/99 (31%)	–	–	23	–	40.7
13	68	M	L. hemiparesis and dysarthria	Bil. MCAO	Bil. BG-CR	80/107 (25%)	–	–	10	L. upper limb shaking	63.8

HUT, head-up-tilt test; PET, positron emission tomography; OEF, oxygen extraction fraction; MRI shows the lesions of cerebral infarction; MBP, mean blood pressure; NTG, nitroglycerin (0.3 mg) s.l.; CSM, carotid sinus massage; ICAS, internal carotid artery stenosis; Bil, bilakeral; MCAO, middle cerebral artery occlusion; CR, corona radiatal; ICAO, internal carotid artery occlusion; MCAS, middle cerebral artery stenosis; BG, basal ganglia.

HUT test, PET and angiography for determining an operation indication of EC-IC bypass surgery. The study protocol was in accordance with the standard ethics guidelines of Osaka University Graduate School of Medicine.

HUT Test

Stepwise reduction of systemic blood pressure was accomplished by passive postural changes on a head-up tilting table[8,14–17] Patients were allowed to rest quietly in the supine position after instrumentation had been completed. Catheterization of the radial artery of each patient allowed us to monitor continuously the arterial blood pressure. After the patients had rested for a minimum of 10 min, they were then tilted head-up to an angle of 60° for 30 min or until syncope was imminent. The imminence of syncope was recognized by the presyncopal symptoms such as dizziness, nausea, diaphoresis, blurred vision and diplopia. All presyncopal subjects were returned to the supine position before loss of consciousness. When patients showed focal neurological symptoms such as hemiparesis, hemianopia, dysarthria or limb shaking during HUT tests, patients were recognized as positive by HUT test and returned to the supine position. If blood pressure was not sufficiently reduced by this method, patients were given nitroglycerin (0.3 mg, s.l.), and then received carotid sinus massage because this technique can be safely performed even in elderly patients[18] The goal level of mean blood pressure during HUT in the present study was 80 mmHg, above the lower limit of cerebral blood flow (CBF) autoregulation in normal subjects.

PET Imaging

All patients were scanned with a Headtome V/SET 2400W system (Shimadzu Co Ltd), which acquires 63 slices with slice thickness of 3.1 mm, as described previously[19] All scans were performed at a resolution of 3.7 mm full-width at half-maximum in the transaxial direction and at 5 mm in the axial direction. For the ^{15}O-labeled gas steady-state method, $C^{15}O$ (550 MBq/min) and $^{15}O_2$ (1,300 MBq/min) were inhaled through a mask. The scan time was 9 min and arterial blood was manually sampled from the radial artery 4 times during each scan. The concentration of the radiotracer activity in the whole blood and plasma was measured with a well counter; the arterial blood hematocrit, hemoglobin concentration, PaO_2, and $PaCO_2$ were also measured. Inhalation of 2,000 MBq $C^{15}O$ and a 9-min scanning period were used to measure the cerebral blood volume (CBV). Arterial sampling was manually performed 3 times during the scanning, and the radiotracer activity in whole blood was measured. The CBF, cerebral metabolic rate of oxygen ($CMRO_2$), and OEF were calculated from the steady-state method, and $CMRO_2$ and OEF were corrected according to the CBV. All PET data were analyzed with the Dr View pro5.0 image analysis software system (Asahi Kasei Joho System Co Ltd) running on a UNIX system and an Indigo 2 station (Silicon Graphics). Circular regions-of-interest, 20 mm in diameter, were placed over the cortex at the level of the parietal lobe (upper MCA territory) in the PET images of each patient. As the normal values we used PET parameter values obtained from 7 patients without either infarction or severe stenosis/occlusion (<50%) who were suffering from nonspecific brain symptoms without focal signs: CBF, $46.9\pm11.3\ ml\cdot100\ g^{-1}\cdot min^{-1}$ (mean±SD); OEF, 44.1±4.62%; $CMRO_2$, $3.39\pm0.82\ ml\cdot100\ g^{-1}\cdot min^{-1}$; CBV, 4.22±0.75%. The misery perfusion group was identified as OEF >53.3% (mean±2 SD of the mean OEF value). The increased OEF value was compatible with that beyond the upper 95% confidence limits defined in healthy volunteers[6]

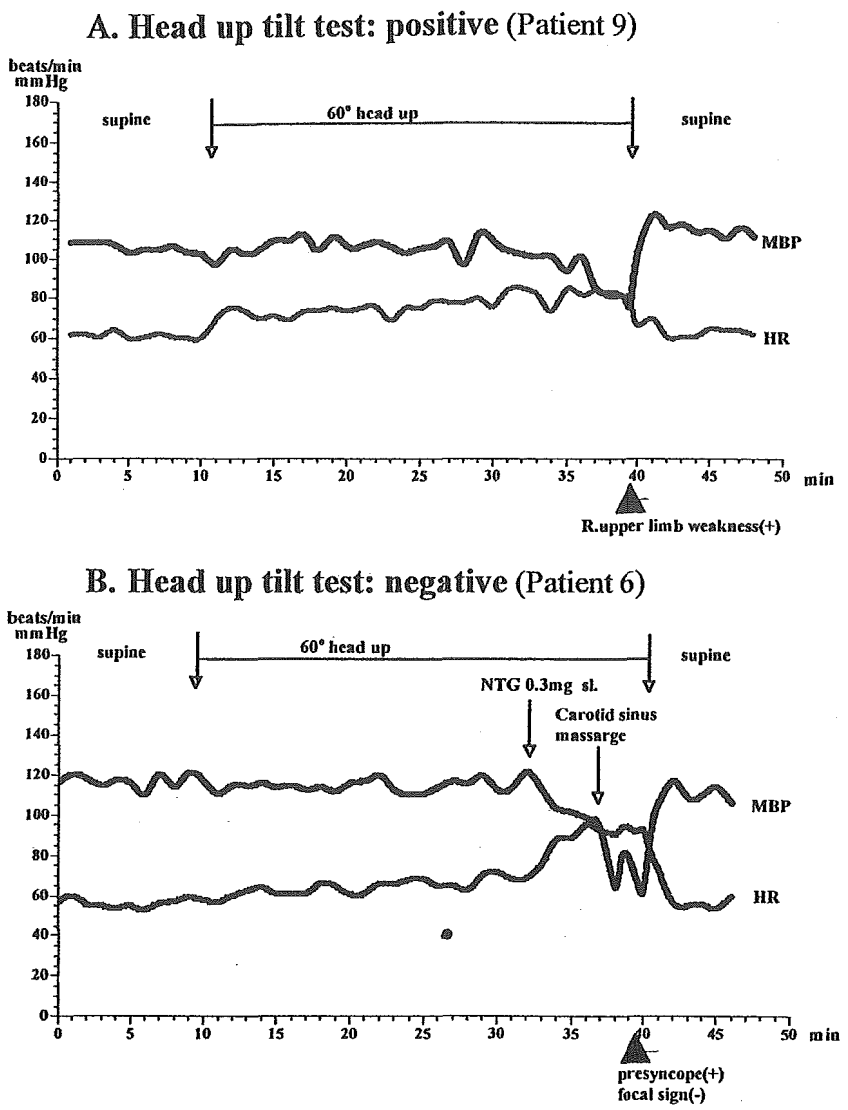

Fig 1. Time course of mean blood pressure (MBP) and heart rate (HR) in head-up-tilt test. (A) Head-up-tilt test: positive (patient 9 in Table 1). A 63-year-old man who complained of weakness of the right lower extremity during walking. MBP started to decline from 104 mmHg during tilting for 28 min. He complained of weakness of the right upper limb when MBP was 72 mmHg. After returning to the supine position, MBP returned to 102 mmHg promptly and his symptoms disappeared within 30 s. (B) Head-up-tilt test: negative (patient 6 in Table 1). After head-up, administration with nitroglycerin (NGT) and carotid sinus massage, MBP declined from 120 mmHg to 65 mmHg at which stage he had presyncopal sensation without focal symptoms.

Results

In 1 of 14 patients, blood pressure did not fall despite orthostatic stress, nitroglycerin administration and carotid sinus massage, and so the patient was excluded from this study.

The clinical characteristics of the 13 patients included in this study are summarized in Table 1. Infarction was found with MRI in 7. In the HUT tests, 3 of the 13 patients showed a transient event such as limb-shaking and hemiparesis (Table 1). Change in blood pressure and heart rate, and clinical symptoms during the HUT test and after return to the sipine position in cases 6 and 9 are shown in Fig 1. Four patients had presyncopal sensation without an event comparable to a previous TIA. Focal symptoms in 3 patients (cases 7, 9 and 13 in Table 1) that appeared during the HUT tests disappeared completely within 60 s after returning to the supine position.

CBF, $CMRO_2$, OEF and CBV values were obtained in the MCA territory of the affected hemisphere of 13 patients (Fig 2). All 3 patients who were HUT positive had OEF >53% (ie, misery perfusion) (Fig 3). In contrast, only 2 of 10 patients without focal symptoms during the HUT test had OEF >53.3%. Therefore, the sensitivity and specificity of the HUT test for predicting patients with misery perfusion were 60% and 100%, respectively. By contrast, no clear cut-off point was found for the CBF, CBV and $CMRO_2$ values between the HUT-positive and -negative groups (Fig 2).

Discussion

In patients with major cerebral arterial occlusive disease, the mechanisms of stroke ipsilateral to the occlusive vessel include embolism from the atherosclerotic plaque and hemodynamic insufficiency[3] Since a large international clinical trial failed to show the efficacy of the EC-IC bypass procedure in preventing stroke,[20] it has been abandoned in most parts of the world. However, this procedure has been shown to be successful, at least, in eliminating repetitive symptoms in patients with hemodynamic TIA[9–11] Identification of hemodynamic CVD is important for management of carotid occlusion because patients may benefit from therapeutic interventions that improve blood flow to the brain. Because the degree of stenosis or the presence of arterial occlusion does not predict the hemodynamic status

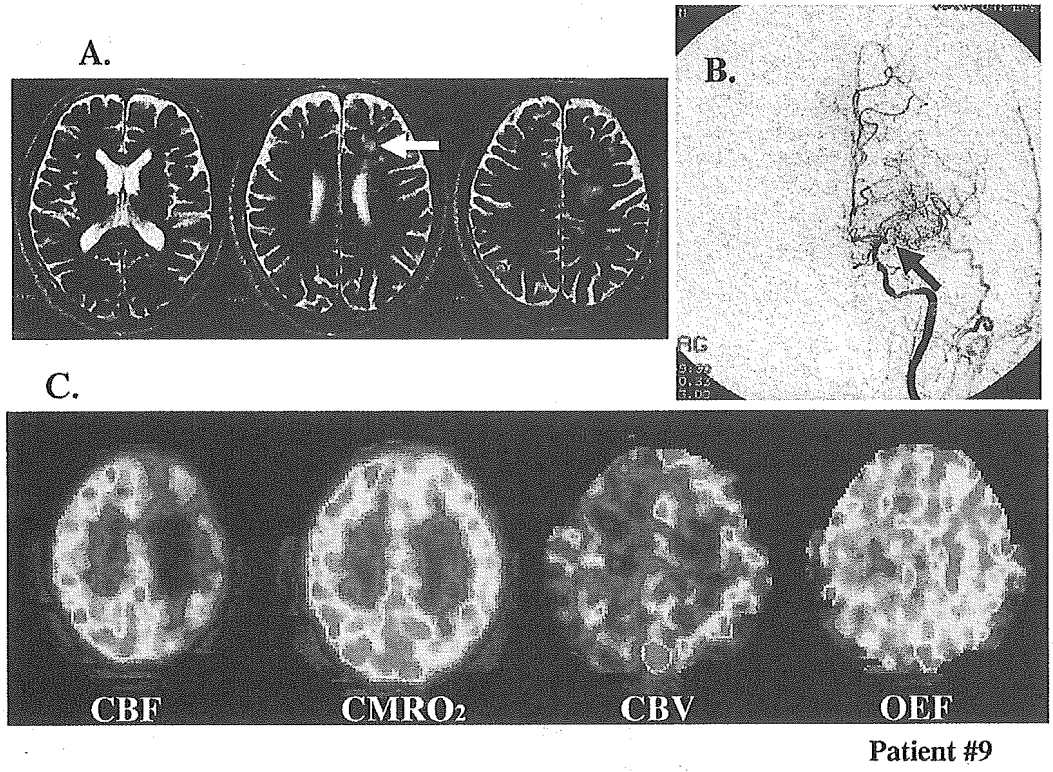

Fig 2. Representative MRI (A), angiography (B) and positron emission tomography (PET) images (C) in a patient with limb weakness during head-up tilt tests and misery perfusion (patient 9 in Table). (A) MRI shows ischemic lesions (white arrow) in the subcortical watershed territory of the left frontal cortex. (B) Carotid angiography shows occlusion of the left middle cerebral artery (arrow). (C) PET images demonstrate decreased cerebral blood flow (CBF), increased cerebral blood volume (CBV) and elevated oxygen extraction fraction (OEF) in the left cerebral hemisphere (OEF=58%).

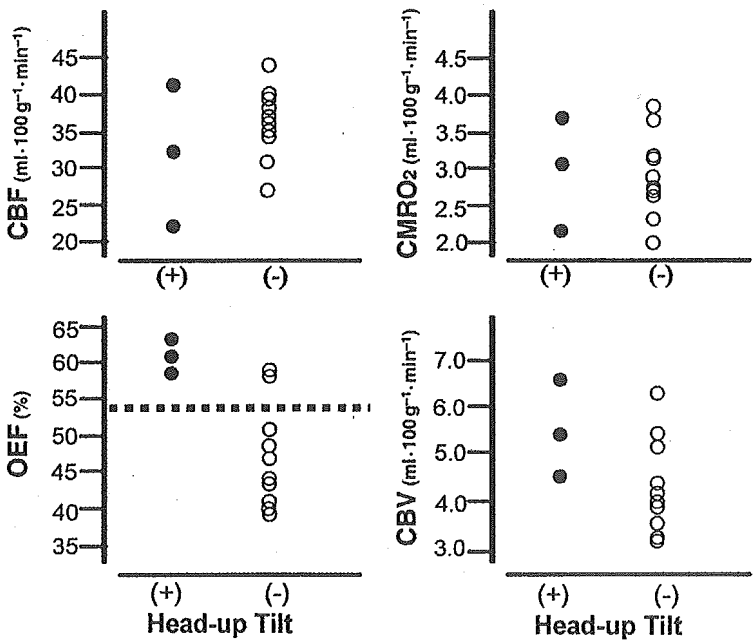

Fig 3. Positron emission tomography (PET) parameters of the territory of the affected middle cerebral artery (MCA) in patients with and without focal symptoms during head-up tilt tests. Closed circles indicate patients who showed focal symptoms during head-up-tilt tests; broken line indicates the OEF cutoff value of 53.3.

of the distal circulation[2] measurement of cerebral hemodynamics by single-photon emission computed tomography;[21–23] PET[5,6,24] or transcranial Doppler (TCD)[25] have been used to detect hemodynamic insufficiency. Among several hemodynamic parameters, the OEF obtained in PET is believed to be the most reliable predictor of future stroke in carotid occlusion.[1,2] Stage 2, in which CBF is reduced and OEF is increased to maintain $CMRO_2$, has been called "misery perfusion"[4] and represents an inadequate blood supply relative to metabolic demand. It has been dem-