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Ⅳ. 研究成果の刊行物・別刷

Right-to-Left Shunt Evaluated at the Aortic Arch by Contrast-Enhanced Transesophageal Echocardiography

Masahiro Yasaka, MD, Koichi Ikeno, MD, Ryoichi Otsubo, MD, Hiroshi Oe, MD, Keiko Nagano, MD, Kazuo Minematsu, MD

Objective. The right-to-left shunt (RLS) is diagnosed by contrast-enhanced transesophageal echocardiographic monitoring of the bilateral atria (cTEE-BA). However, the procedure is often disturbed by nonsmoke spontaneous individual contrast (NSSIC) with fast motion, which appears in the left atrium after respiratory maneuvers without administration of a contrast medium and moves past in several seconds. We attempted to perform cTEE monitoring of the aortic arch (cTEE-AA) for evaluation of the RLS and compared the findings with those of cTEE-BA. ***Methods.*** Both cTEE-BA and cTEE-AA were performed in 168 patients with ischemic stroke (133 men and 35 women; mean age ± SD, 62.0 ± 14.4 years). The frequency of NSSIC in the left atrium was compared with that in the aortic arch during the respiratory maneuver. When contrast much brighter than the NSSIC was visualized in the left atrium and the aortic arch during the respiratory maneuver with administration of the contrast medium, we considered the RLS to be positive in the cTEE-BA and cTEE-AA, respectively. Findings were then compared between the 2 examinations. ***Results.*** Nonsmoke spontaneous individual contrast was more frequently observed in the left atrium than the aortic arch (61.3% versus 14.9%; χ^2 test, $P <$ .0001). The RLS was positive in 34 patients in the cTEE-BA and in 39 patients in the cTEE-AA. The sensitivity and specificity of the cTEE-AA for the cTEE-BA were 100% and 97.0%, respectively. ***Conclusions.*** *The cTEE-AA may be an alternative method for detection of an RLS, especially in patients with a large amount of NSSIC in the left atrium.* ***Key words:*** *aortic arch; patent foramen ovale; respiratory maneuver; right-to-left shunt; transesophageal echocardiography.*

Abbreviations
cTEE-AA, contrast-enhanced transesophageal echocardiographic monitoring of the aortic arch; cTEE-BA, contrast-enhanced transesophageal echocardiographic monitoring of the bilateral atria; NSSIC, nonsmoke spontaneous individual contrast; PAVF, pulmonary arteriovenous fistula; PFO, patent foramen ovale; RLS, right-to-left shunt

Received August 20, 2004, from the Cerebrovascular Division, Department of Medicine, National Cardiovascular Center, Suita, Osaka, Japan. Revision requested August 31, 2004. Revised manuscript accepted for publication November 12, 2004.

This study was supported in part by research grants for cardiovascular diseases 12A-2 and 15C-1 from the Ministry of Health, Labor, and Welfare of Japan.

Address correspondence and reprint requests to Masahiro Yasaka, MD, Cerebrovascular Division, Department of Medicine, National Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan.
E-mail: yasakam@hsp.ncvc.go.jp

The right-to-left shunt (RLS) represented by the patent foramen ovale (PFO) and pulmonary arteriovenous fistula (PAVF) can be a cause of paradoxical embolism. The PFO is found in about 30% of autopsies.[1] The prevalence of the PFO in patients with stroke is higher than in healthy individuals, and the PFO is more frequently detected in cryptogenic stroke than in stroke of known etiology.[2-4]

Contrast-enhanced transesophageal echocardiographic monitoring of the bilateral atria (cTEE-BA) has enabled us to detect the PFO with a higher degree of sensitivity, contributing to the diagnosis of paradoxical brain embolism.[5] However, in the cTEE-BA examination, respiratory maneuvers frequently induce the transient appearance of mild to moderate contrast in the left atrium, that is, nonsmoke spontaneous individual contrast (NSSIC), independently of venous injections of contrast medium.[6] The NSSIC may lead to false-positive or -negative findings in

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the diagnosis of the RLS. The NSSIC is thought to be rouleaux formation caused by blood flow stasis at the pulmonary vein at the respiratory maneuver.[6]

Conversely, the RLS can be evaluated by cTEE monitoring of the aortic arch (cTEE-AA). We previously reported in 2001 that, after release of the respiratory maneuver, flow of a contrast medium into the left atrium through the PFO could be clearly visualized at the aortic arch.[7] Thereafter, when cTEE has been required, we have performed both cTEE-BA and cTEE-AA routinely. In the current study, we retrospectively investigated the sensitivity and specificity of cTEE-AA for cTEE-BA and compared the frequency of NSSIC between the left atrium and the aortic arch.

Materials and Methods

From October 2001 to September 2002, we performed both cTEE-BA and cTEE-AA in 168 patients with ischemic stroke of unknown origin (133 men and 35 women; mean age ± SD, 62.0 ± 14.4 years).

We performed cTEE using a commercially available real-time 2-dimensional echocardiography system (SSD-2200; Aloka Co, Ltd, Tokyo, Japan) equipped with a 5.0-MHz (variable from 3.5 to 7.5 MHz) phased array omniplane transesophageal transducer after informed consent was obtained from the patient or the patient's family. The frequency of probe transmission and depth of the focal zone were changed according to the depths of the objectives. First, we investigated the left atrium and the aortic arch for smokelike swirling contrast echo at rest, which was observed independently of the respiratory maneuver. Then, without any contrast medium, we inspected the left atrium and the aortic arch NSSIC, which came from the upper part of the left atrium, not from the interatrial septum, and was visualized as individual intense contrast with fast motion after the release of the Valsalva maneuver. The NSSIC had a weaker echo density than microbubbles in the right atrium after contrast medium injection. Then, without any contrast medium, we inspected the left atrium and the aortic arch NSSIC. Subsequently, the contrast medium, a mixture of 9 mL of saline and 1 mL of air, was infused into the right antecubital vein during the Valsalva maneuver. When the right atrium was opacified by the contrast medium, as shown on the monitor, we asked the patient to release the Valsalva maneuver in the cTEE-BA. In the cTEE-AA examination, we asked the patient to release the Valsalva maneuver 3 or 4 seconds after the contrast medium was administered. We regarded individual contrast in the left atrium as coming from the interatrial septum and as bright as the contrast medium in the right atrium as contrast medium in the left atrium. We also regarded individual contrast in the aortic arch that was much brighter than the NSSIC as contrast medium in the aortic arch. When the contrast medium was found in the left atrium within 3 cardiac cycles after release of the Valsalva maneuver, we diagnosed PFO. When contrast medium was found in the left atrium after 3 cardiac cycles, we suspected the presence of PAVF,[5–8] and when found in the aortic arch within 10 cardiac cycles after the release of the Valsalva maneuver, we diagnosed RLS. Assessment of the smokelike echo, the NSSIC, and contrast medium in the left atrium or the aortic arch was performed by agreement of 3 physicians operating the echo machine and probe and injecting the contrast medium. When the PFO in the cTEE-BA or the RLS in the cTEE-AA was positive, we measured the size of the PFO and categorized it into less than 2, 2 to 10, and greater than 10 mm.

We compared the frequencies of the smokelike echo at rest, the NSSIC during the respiratory maneuver without administration of the contrast medium, and the contrast medium during the respiratory maneuver with administration of the contrast medium in the left atrium with those in the aortic arch. We also compared the age, sex, and presence of atrial fibrillation between patients with PFO or PAVF as shown by cTEE-BA and those without and between patients with RLS as shown by cTEE-AA and those without.

Continuous data were expressed as mean ± SD. We used the χ^2 test for analysis of discrete variables and the unpaired t test for analysis of continuous variables. In cases of low cell counts (<5), the Fisher exact test was used instead of the χ^2 test.

Results

Nonsmoke spontaneous individual contrast was more frequently noted in the left atrium than in the aortic arch (61.3% versus 14.9%; χ^2 test, $P < .0001$; Figures 1–3 and Table 1), although a significant difference in the frequency of the smokelike echo and contrast medium was not shown

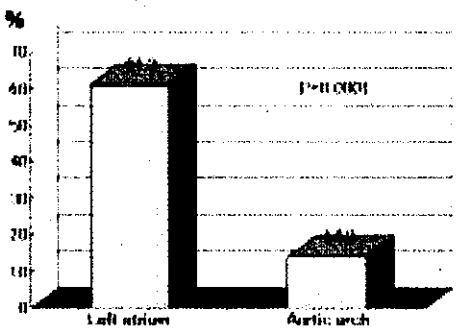

Figure 1. Frequency of NSSIC in the left atrium and the aortic arch.

Figure 2. Contrast in the left atrium (LA). **A**, Smokelike echo in the left atrium. **B**, Typical NSSIC in the left atrium intensified by a respiratory maneuver. Arrows indicate NSSIC. **C**, Contrast medium appearing in the left atrium during the respiratory maneuver.

Figure 3. Contrast in the aortic arch (Ao). **A**, Smokelike echo in the aortic arch. **B**, Typical NSSIC in the aortic arch intensified by a respiratory maneuver. Arrows indicates NSSIC. **C**, Contrast medium appearing in the aortic arch during the respiratory maneuver.

between the left atrium and the aortic arch. The NSSIC in the aortic arch was frequently accompanied by that in the left atrium (20 [83.3%] of 24).

Patients with NSSIC in the left atrium were younger than those without but not significantly ($P = .12$; Figure 2 and Table 2). The frequency of men was higher in patients with NSSIC in the left atrium than in those without (84.8% versus 69.8%; $P = .0336$). No differences in the frequency of atrial fibrillation and smokelike echo in the left atrium and the aortic arch were observed between patients with NSSIC and those without.

Patients with NSSIC in the aortic arch were significantly younger than those without ($P = .0030$; Figure 3 and Table 3). Men were more prevalent among patients with NSSIC in the aortic arch than those without (87.5% versus 77.8%; $P = .028$), but this difference was not significant. No differences in the frequency of atrial fibrillation and smokelike echo in the left atrium and the aortic arch were observed between patients with NSSIC in the aortic arch and those without.

In cTEE-BA, RLS was shown in 34 patients; PFO was shown in 30 patients; and PAVF was shown in the other 4. In the 30 patients with the diagnosis of PFO, the size of the PFO was less than 2.0 mm in all.

In cTEE-AA, 39 patients had RLS-positive findings. A comparison of the results of cTEE-AA with those of cTEE-BA revealed 2 positive findings in 34 patients and 2 negative findings in 129. The other 5 patients had RLS-positive findings in cTEE-AA but negative findings in cTEE-BA. Of these 5 patients, NSSIC in the left atrium and the aortic arch was positive in both evaluations in 1 patient, positive and negative in 2 patients, negative and positive in 1 patient, and negative in both in 1 patient.

The sensitivity, specificity, and accuracy of cTEE-AA for cTEE-BA were 100%, 96.3%, and 97.0%, respectively (Table 4).

Discussion

The NSSIC that appears in the left atrium transiently with fast echo motion by the respiratory maneuver is clearly different from the spontaneous swirling smoke contrast and is called the snowstorm aspect, multiple scattered echoes, or contrast with fast motion.[6,8,9] Although the echo density of the NSSIC is lower than that of the contrast medium appearing in the left atrium in the cTEE-BA examination in patients with PFO, the NSSIC may be a cause of pseudopositive diagnoses for RLS.[6,9] Therefore, it was recommended that a respiratory maneuver should always be performed before contrast medium injections to allow better distinction between NSSIC and true RLS.[6] However, accurate distinction may still be difficult in patients with a small amount of shunting and a large amount of NSSIC or with poor imaging of the bilateral atria.

Table 1. Frequency of the Smokelike Echo, NSSIC, and Contrast Medium in the Left Atrium and the Aortic Arch

Finding	Condition			Frequency, n (%)		P
	At Rest	Respiratory Maneuver	Administration of Contrast Medium	Left Atrium	Aortic Arch	
Smokelike echo	Yes	No	No	26 (15.5)	38 (22.6)	.0955
NSSIC	No	Yes	No	103 (61.3)	25 (14.9)	<.0001
Contrast medium	No	Yes	Yes	35 (20.8)	39 (23.2)	.6014

Conversely, this current study showed that cTEE-AA had high sensitivity and specificity in diagnosing RLS. The frequency of NSSIC appearing in the aorta was much lower than that in the left atrium, and most patients with NSSIC in the aortic arch had NSSIC in the left atrium as well. This result may be consistent with the cause of NSSIC in the left atrium. Van Camp et al[6] reported that the NSSIC they observed in the left atrium came from the pulmonary vein and disappeared within 3 or 4 cardiac cycles. They then surmised that the NSSIC in the left atrium represented rouleaux formation of red blood cells in the pulmonary vein during the respiratory maneuver, which caused abrupt stasis of blood in the pulmonary vein, and found that the NSSIC disappeared in the bloodstream after release of the respiratory maneuver. This may explain why, in the present study, the frequency of NSSIC in the aortic arch was significantly lower than that in the left atrium, why the NSSIC in the left atrium was common in patients with NSSIC in the aortic arch, and why NSSIC in the left atrium and the aortic arch was related to men and younger age (a stronger respiratory maneuver resulted in greater rouleaux formation).

Five cases had RLS-positive findings by cTEE-AA but negative findings by cTEE-BA. This inconsistency may have been the result of underestimation of cTEE-BA. The NSSIC found in the left atrium in 3 of these cases (60%) may have concealed the true RLS. A small amount of contrast coming through the PFO or PAVF might not have been noticed because it might not have gone through the cross section of the left atrium set by the cTEE-BA. Conversely, the inconsistency may have been due to overestimation of cTEE-AA. The NSSIC in the aortic arch could have been confused with the true contrast of the RLS. However, the detection rate of the true contrast in the cross section of the aortic arch monitored by cTEE-AA would logically be higher than that monitored by cTEE-BA because most particles of the contrast medium pass the aortic arch cross section perpendicular to the bloodstream, except those flowing into the branches of the aortic arch. All the particles of the contrast medium in the left atrium do not go through the cross section of cTEE-BA because it is not always placed perpendicularly to the blood flow in the left atrium.

Table 2. Nonsmoke Spontaneous Individual Contrast in the Left Atrium and Demographics

Demographic	NSSIC		P
	Positive (n = 103)	Negative (n = 65)	
Age, y, mean ± SD	60.6 ± 13.6	64.2 ± 15.0	.12
Men, n (5)	89 (84.8)	44 (69.8)	.036
Atrial fibrillation, n (%)	12 (11.4)	6 (9.5)	.62
Smokelike echo in left atrium, n (%)	17 (16.2)	9 (14.3)	.64
Smokelike echo in aortic arch, n (%)	26 (24.8)	12 (19.0)	.31

Table 3. Nonsmoke Spontaneous Individual Contrast in the Aortic Arch and Demographics

Demographic	NSSIC		P
	Positive (n = 24)	Negative (n = 144)	
Age, y, mean ± SD	54.0 ± 13.5	63.3 ± 14.1	.0029
Men, n (5)	21 (87.5)	112 (77.8)	.28
Atrial fibrillation, n (%)	3 (12.5)	15 (10.4)	.76
Smokelike echo in left atrium, n (%)	2 (8.3)	24 (16.7)	.30
Smokelike echo in aortic arch, n (%)	4 (16.7)	34 (23.6)	.45

Table 4. Findings of cTEE-BA and cTEE-AA

cTEE-AA	cTEE-BA		
	Positive	Negative	Total
Positive	34	0	34
Negative	5	129	134
Total	39	129	168

When compared with cTEE-BA, cTEE-AA is not as useful in distinction of PFO from PAVF, which can be differentiated by cTEE-BA. This current study was a retrospective study; thus, a prospective study is required to determine the algorithm that will effectively show RLS, PFO, and PAVF.

In conclusion, because the sensitivity, specificity, and accuracy of cTEE-AA for cTEE-BA are very high, cTEE-AA may be an alternative technique with which to evaluate RLS.

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AJNR Am J Neuroradiol 25:428–430, March 2004

Case Report

A Small Pulmonary Arteriovenous Malformation as a Cause of Recurrent Brain Embolism

Kenichi Todo, Hiroshi Moriwaki, Masahiro Higashi, Kohji Kimura, and Hiroaki Naritomi

Summary: We report a case of recurrent paradoxical brain embolism mediated through a small pulmonary arteriovenous malformation (PAVM) with a 1.8-mm-diameter feeding artery. In this case, the further recurrent stroke was prevented successfully by PAVM embolization. Although embolization therapy is currently recommended only for PAVMs with feeding arteries greater than 3 mm in diameter, the therapy may be needed also in the smaller PAVMs.

Pulmonary arteriovenous malformation (PAVM) is well recognized as a cause of paradoxical brain embolism. Brain infarction associated with PAVMs most likely occurs in patients with feeding arteries of more than 3-mm diameter and not in those of smaller size (1–5). We report the case of a PAVM patient with a 1.8-mm-diameter feeding artery who had recurrent paradoxical brain embolism and was successfully treated with embolotherapy.

Case Report

A 67-year-old right-handed woman was admitted in February 2002 after suddenly developing dizziness, nausea, and speech disturbance. She was admitted to our hospital 7 hours after the onset of symptoms. At the time of admission, her blood pressure was 140/80 mm Hg. She had a regular heart rate of 60 beats per minute and a respiratory rate of 16 breaths per minute. Neither pathologic breath sounds nor heart murmurs were auscultated. No edema was present in her extremities. No cutaneous vascular malformations were observed. She had no episodes of hemoptysis or dyspnea. In neurologic examinations, she had dysarthria and left limb ataxia. Laboratory findings showed normal blood cell counts, normal liver and renal functions, and normal serum cholesterol and blood glucose levels. Plasma protein C, protein S, and antithrombin III levels were within normal ranges. Arterial blood gas analysis showed mild hypoxemia, with PaO_2 84.6 mm Hg and $PaCO_2$ 43.2 mm Hg in room air. Chest radiographic and electrocardiographic findings were normal. Carotid ultrasonography failed to detect atherosclerotic changes and showed normal blood flow velocities in the common carotid arteries and vertebral arteries. Transthoracic echocardiography failed to find any embolic sources, including valvular pathology, dilated cardiomyopathy, akinetic left ventricular segment, and intracardiac thrombus. Cranial CT demonstrated an equivocal hypoattenuated area in the left cerebellar hemisphere but no abnormality in other areas. Diffusion-weighted MR images disclosed a high-signal-intensity area in the left cerebellar hemisphere (Fig 1A). Twelve hours after the onset of stroke, intraarterial digital subtraction cerebral angiography revealed no stenotic lesion in the extra- or intracranial vertebral arteries or basilar artery. With suspicion of embolic brain infarction, anticoagulation therapy with 10,000 U/day heparin was started 18 hours after the onset of symptoms, although the embolic source could not be identified.

On day 3, the patient also developed right limb ataxia. Activated partial thromboplastin time was 28.0 seconds on admission and was prolonged to 43.1 second on day 3. The second CT scan showed only a hypoattenuated area in the left cerebellar hemisphere. Diffusion-weighted imaging on day 5 confirmed the development of new ischemic lesion in the right cerebellar hemisphere (Fig 1B). On day 6, transcranial Doppler sonography with saline contrast material injection (C-TCD) was performed to examine the presence of the right-to-left shunt. The C-TCD study was performed by using a mixture of saline solution (9 mL) and air (1 mL) agitated between two 10-mL syringes connected by a three-way stopcock. The solution was injected into the left antecubital vein within 2–3 seconds. C-TCD depicted multiple high-intensity transient signals (HITS) at the basilar artery during normal respiration (Fig 2A), which suggested the presence of continuous right-to-left shunt (6). Transesophageal echocardiography with saline contrast material injection into the antecubital vein confirmed a significant entry of microbubbles into the left atrium. Transesophageal echocardiography failed to show any embolic sources, including valvular pathology, intracardiac thrombus, atrial myxoma, spontaneous echo contrast of the left atrium, and complex atheroma of the aortic arch. Holter electrocardiographic monitoring failed to find atrial fibrillation or flutter. Radioisotope venography of the lower extremities displayed a filling defect with collateral pathways in the left popliteal vein, indicating the association of deep vein thrombosis. A contrast-enhanced CT scan of the patient's chest revealed a small nodular lesion connected with the pulmonary artery and vein branches in the left pulmonary lower lobe. Selective pulmonary angiography on day 13 demonstrated a single PAVM with a 1.8-mm-diamter feeding artery at the corresponding area (Fig 3). The diagnosis of paradoxical brain embolism mediated through the PAVM was, thus, established. Subsequently, the PAVM was obstructed by using an embolization coil (Cook, Bloomington, IN). Following the embolization therapy, C-TCD detected no more HITS (Fig 2B), and the hypoxemia was slightly improved (PaO_2 92.4 mm Hg in room air). On day 22, she was discharged without neurologic deficits. C-TCD never detected HITS on day 105. MR imaging on day 126 showed only old brain infarction equivalent to that on day 5. The patient had no recurrent attacks for the following 12 months.

Discussion

PAVMs are commonly associated in hereditary hemorrhagic telangiectasia (HHT): approximately

Received June 5, 2003; accepted after revision June 11.

From the Departments of Cerebrovascular Medicine (K.T., H.M., H.N.) and Radiology (M.H., K.K.), National Cardiovascular Center, Osaka, Japan.

Supported in part by the Research Grants for Cardiovascular Diseases (14–1) from the Ministry of the Health and Welfare of Japan.

Address reprint requests to Kenichi Todo, MD, Department of Cerebrovascular Medicine, National Cardiovascular Center, 5–7-1, Fjishirodai, Suita, Osaka, 565-8565, Japan.

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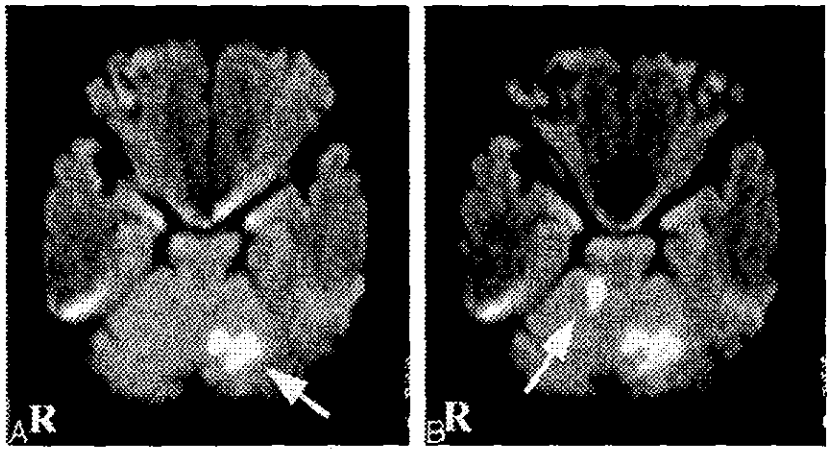

FIG 1. Diffusion-weighted MR images. *A*, Diffusion-weighted image on day 1 shows a high-signal-intensity area in the left cerebellar hemisphere (*arrow*). *B*, Diffusion-weighted image on day 5 shows a new ischemic lesion in the right cerebellar hemisphere (*arrow*).

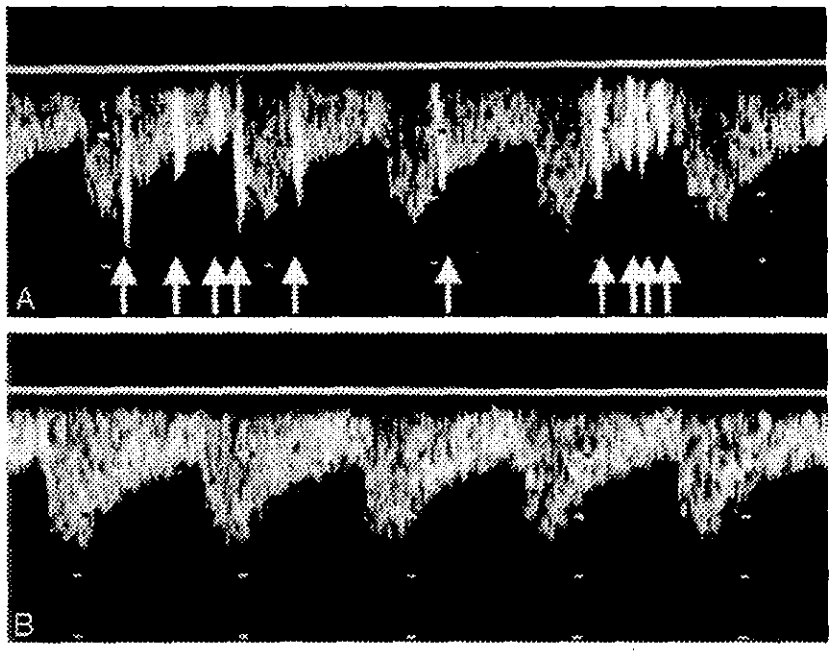

FIG 2. C-TCD findings before and after the embolization therapy. *A*, C-TCD shows many HITS (*arrows*) from the basilar artery before the embolization therapy. *B*, C-TCD failed to depict any HITS after the embolization therapy.

15–35% of HHT patients have PAVMs, and 50–85% of PAVMs patients have HHT (1). The present patient, however, had no clinical signs suggestive of HHT. PAVMs increase the risk of paradoxical embolism because of continuous right-to-left shunt. Brain infarction is one of the most important complications that may occur in PAVM patients (1, 2). Stroke is often the first manifestation of PAVM and even of HHT (7).

Moussouttas et al (1) documented that brain infarction most likely occurs in PAVM patients with feeding arteries more than 3 mm in diameter and not in those with smaller size. Accordingly, they recommended embolization therapy for all PAVMs with feeding artery diameters exceeding 3 mm. To the best of our knowledge, the occurrence of brain infarction in PAVMs with less than 3 mm in feeding artery diameter has not been previously reported. The present patient had a small-sized PAVM, the diameter of which was 1.8 mm. In the present patient, the other embolic sources—including atrial fibrillation or flutter, bacterial endocarditis, valvular pathology, myocardial infarction, dilated cardiomyopathy, akinetic left ventricular segment, intracardiac thrombus, atrial myxoma, spontaneous echo contrast of the left atrium, or complex atheroma of the aortic arch—were ruled out, and other causes of stroke—such as atherosclerotic arterial changes, nonatherosclerotic arteriopathies, coagulopathies, hematologic or systemic disorders, or migranous infarction—were found to be negative (8, 9). The patient had deep vein thrombosis, which may cause arterial embolism under the presence of right-to-left shunt. Thus, paradoxical embolism is only one possible mechanism that can explain recurrent strokes in this patient. After the embolization therapy, this patient had no more recurrent stroke, and C-TCD never detected HITS, indicating successful obstruction of right-to-left shunt (10).

A recent study reported that the stroke recurrence rate in patients with patent foramen ovale (PFO) was unaltered regardless of whether the diameter was more than 2 mm or less (11). Paradoxically, PAVMs

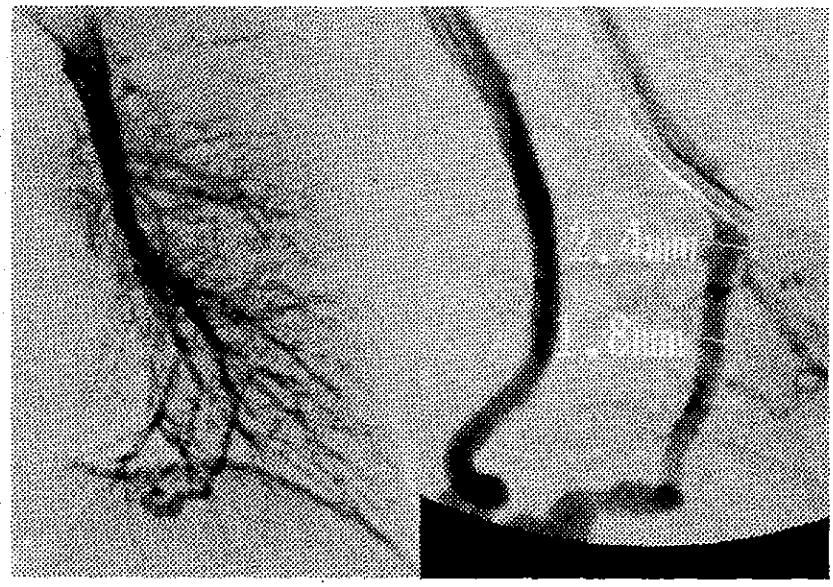

FIG 3. Selective pulmonary angiogram shows a single PAVM with a feeding artery diameter of 1.8 mm.

and PFO share the similar mechanisms in the development of brain infarction through the right-to-left shunt. The shunt flow goes through PAVMs continuously, whereas it can pass though PFO only intermittently at the time of right atrial pressure increase. In this context, PAVM is regarded to be more risky than PFO as a route of paradoxical embolism. The size of right-to-left shunt may not be a critical factor for stroke occurrence. Embolization therapy appears to be useful for preventing recurrent attacks in stroke patients with a small PAVM in whom other causes of cerebral infarction are definitely ruled out. A randomized controlled study may be necessary to elucidate the requirement of embolization therapy in small-sized PAVMs.

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Journal of Human Hypertension (2004) 18, 693–699
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www.nature.com/jhh

ORIGINAL ARTICLE

Losartan, an angiotensin II (AT_1) receptor antagonist, preserves cerebral blood flow in hypertensive patients with a history of stroke

H Moriwaki[1], H Uno[1], Y Nagakane[1], K Hayashida[2], K Miyashita[1] and H Naritomi[1]
[1]*Department of Cerebrovascular Medicine, National Cardiovascular Center, Suita, Osaka, Japan;*
[2]*Department of Radiology, National Cardiovascular Center, Suita, Osaka, Japan*

In patients with severe hypertension, chronic heart failure or a history of stroke, the lower limit of autoregulation of cerebral blood flow (CBF) is shifted to higher levels of blood pressure (BP) than those observed in healthy subjects. The aim of pharmacotherapy for hypertensive patients with an impaired autoregulation of CBF should be to reduce BP while preserving an appropriate CBF. In the present study, 16 hypertensive patients who had had an episode of stroke more than 4 weeks previously were administered the angiotensin II (AT_1) receptor antagonist losartan at daily doses of 25–100 mg for 4 weeks. Systolic and diastolic blood pressures were recorded for 24 h using an ambulatory BP monitoring system. CBF in both hemispheres of the cerebrum and cerebellum was quantified using single photon emission tomography with *N*-isopropyl-*p*-[^{123}I]iodoamphetamine. At baseline, CBF was 29.7±6.7 ml/min/100 g in the cerebrum and 31.5±7.5 ml/min/100 g in the cerebellum. At the end of treatment, BP was lower, while CBF increased by 7.7% in the cerebrum, and remained at the baseline level in the cerebellum. Thus, CBF was preserved despite the reduction in BP. We consider the use of losartan is advantageous for hypertensive patients with a history of stroke in whom autoregulation of CBF is potentially impaired.
Journal of Human Hypertension (2004) **18**, 693–699. doi:10.1038/sj.jhh.1001735
Published online 6 May 2004

Keywords: stroke; cerebral blood flow; angiotensin; losartan; hypertension

Introduction

It is well known that cerebral blood flow (CBF) in healthy subjects is autoregulated to maintain a stable flow rate within a wide range of changes in blood pressure (BP), with the lower limit of mean BP being as low as 50–60 mmHg. However, in patients with severe hypertension, CBF is affected when the mean BP decreases below 100 mmHg.[1] Furthermore, in patients with a cerebrovascular disease, the autoregulation of CBF may be disturbed so that the lower limit necessary to maintain a constant CBF is shifted to a BP level higher than that seen in healthy subjects.[2,3] This impaired autoregulation is considered to be mostly a consequence of structural damage of small arteries in the brain, accompanying with higher susceptibility to vasoactive substances.

Correspondence: Dr H Moriwaki, Department of Cerebrovascular Medicine, National Cardiovascular Center, 5-7-1, Fujishirodai, Suita, Osaka 565-8565, Japan. E-mail: hmoriwa@hsp.ncvc.go.jp
Received 26 May 2003; revised 11 November 2003; accepted 17 November 2003; published online 6 May 2004

On the basis of knowledge of the actions of angiotensin II on vascular beds in organs including the brain, therapeutic benefits of intervention of the renin–angiotensin system has been considered to normalize the lower limit of CBF autoregulation in patients with an impaired cerebral circulation. The ACE inhibitor captopril was the first drug to maintain CBF while BP was reduced beyond lower limit of autoregulation in hypertensive rats.[4,5] Similar results were obtained in patients with chronic heart failure.[6,7] In 1992, Kuriyama *et al*[8] reported that the ACE inhibitor enalapril preserved CBF in hypertensive patients with an old history of stroke with effectively reducing BP, indicating successful shifting of the lower limit of CBF autoregulation to lower BP levels. These findings led us to postulate that a direct blockade of angiotensin II receptors may result in a reduction of BP while maintaining an appropriate CBF in patients whose autoregulation is impaired.

In the present study, we assessed the effect of the angiotensin II (AT_1) receptor antagonist (AIIA) losartan on CBF in hypertensive patients with a

history of stroke. We used an ambulatory BP monitoring (ABPM) system to measure BP, and single photon emission computed tomography (SPECT) with the tracer *N*-isopropyl-*p*-[^{123}I]iodoamphetamine to measure the blood flow in both hemispheres of the cerebrum and cerebellum.

Patients and methods

Study patients

In-patients and outpatients of either gender, $\geqslant$20–$<$75 years old, who had hypertension and a history of stroke were eligible for the study, provided they satisfied the following criteria during a pretreatment screening period of 2 days–one week.

(a) Hypertensive patients. That is, their systolic BP (SBP) and diastolic BP (DBP) in the supine position measured using a mercury sphygmomanometer, at least twice on their visits to the hospital, were $\geqslant$140 or $\geqslant$90 mmHg, respectively, and average 24 h ambulatory SBP (24-h SBP) during the screening period was $\geqslant$135 mmHg or their average 24 h DBP (24-h DBP) was $\geqslant$85 mmHg.
(b) Patients with a chronic cerebrovascular disease. That is, the patients who had had an episode of stroke (cerebral infarction, defined by X-ray computed tomography or magnetic resonance imaging), more than 4 weeks, previously.

The principal investigator decided the eligibility of the patients. Exclusion criteria were as follows:

(a) Severe hypertension (DBP$\geqslant$110 mmHg).
(b) Secondary hypertension.
(c) Patients who could not discontinue antihypertensive drug therapy.
(d) A serum creatinine concentration of $\geqslant$2.5 mg/dl.
(e) Patients with a severe cerebrovascular lesion.
(f) Patients showing hypersensitivity to the test drug.
(g) Patients of pregnancy, possibility of pregnancy, and in a period of lactation.
(h) Patients suffering from a severe hepatic disease.

Study design

The overview of the study design is shown in Figure 1. This study was designed as a self-control study by comparing values of BP and CBF on weeks 2 and 4 of treatment to those observed during the screening period (baseline) in each patient. Before the screening period, a washout period of at least 2 weeks was required for the patients who had been treated with antihypertensive drugs. Following the screening period, the patients were administered losartan once daily at the starting dose of 25 mg. However, in cases in which a patient's compliance was judged by investigator(s) to be sufficiently good for the administration of a higher dose, a starting dose of 50 mg was applied. Thus, in the first 2 weeks the dose of losartan was 25 or 50 mg. In the following 2 weeks, however, the dose was escalated if the 24-h SBP/DBP of $<$135/85 mmHg was not achieved, or if reductions in 24-h SBP of $\geqslant$10 mmHg and 24-h DBP of $\geqslant$5 mmHg were not satisfied.

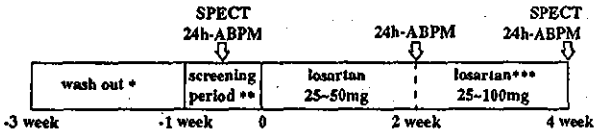

Figure 1 Study design for treatment of hypertensive patients with a history of stroke. *Patients who had been treated with any antihypertensive drug were entered after a washout period of at least 2 weeks. **Two-day to 1-week screening period was followed by the treatment period of 4 weeks. CBF was measured by SPECT and mean 24-h BP by ABPM during the screening period, and the last days of weeks 2 and 4. ***When BP control was inadequate within the first 2 weeks (see Study design), the dose of losartan was escalated.

BP was recorded by ABPM and CBF was measured by SPECT during the screening period, and at weeks 2 and 4 of treatment. To measure 24-h BP, the patients were fitted with an ABPM and the pressure was recorded every 30 min from 0600 to 2200 (daytime) and every 60 min from 2200 to 0600 (nighttime). For measurements of the 24-h BP, the ABPM device Type TM-2421(A&D Co. Ltd., Tokyo, Japan) was used. CBF was evaluated using the *N*-isopropyl-*p*-[^{123}I]iodoamphetamine (^{123}I-IMP) autoradiographic method based on a two-compartment kinetic model in which the input function is determined by arterial counting 10 min after the injection of ^{123}I-IMP instead of frequent blood sampling. The absolute value was obtained by the table look-up method after the arterial count was converted to the scale of the SPECT count using a cross calibration factor that was determined *a priori* in a phantom study.[9,10]

SPECT was performed using a ring-type gamma camera (Headtome SET-070; Shimadzu, Kyoto, Japan) with an 8-mm FWHM obtained. Patients were immobilized with eyes covered, and 4.5 mCi (166.5 MBq) of ^{123}I-IMP was injected intravenously. Data collection began 15 min after injection of the tracer. Image data over 30-min were collected onto a 128 × 128 matrix using a general all-purpose collimator. All data were corrected for an attenuation of 0.1/cm and tomographic data were reconstructed using a filtered back-projection algorithm. The regions of interest (ROIs) were drawn on the both sides of middle cerebral artery territories and cerebellar hemispheres according to our previous report.[11] These ROIs were defined with reference to the atlas of Kretschmann and Weinrich.[12] If an infarct was included within a standard ROI, the size of the ROI was reduced to avoid the area of infarct.

The study protocol was in accordance with the declaration of Helsinki and was reviewed and approved by the Institutional Review Board of the

National Cardiovascular Center. Written informed consent was obtained from all enrolled patients.

Statistics

All values are expressed as the mean ± s.d. Differences of values on weeks 2 and 4 from the respective baseline values were analysed by one-sample *t*-test. Differences with a *P*-value of <0.05 were considered statistically significant.

Results

Patient characteristics at baseline and at week 4

We enrolled 16 patients in the study. One patient showed increases in AST (GOT) and γ-GTP at the week-2 determination point and the principal investigator considered it was desirable for this patient to discontinue the treatment. Changes of CBF were therefore assessed in 15 patients. Table 1 summarizes baseline characteristics of the 15 patients and their CBF measured at baseline, and CBF measured at week 4 as the result. Averaged values are, age: 63.8 ± 6.2-year-old, office SBP/DBP: 158.7 ± 11.4/84.9 ± 9.5 mmHg, 24-h SBP/DBP: 154.1 ± 14.1/90.2 ± 9.8 mmHg, CBF at baseline (cerebrum/cerebellum): 29.7 ± 6.7/31.5 ± 7.5 ml/min/100 g.

Blood pressure

Figure 2 shows changes in BP measured using the ABPM system during treatment with losartan. Both 24-h SBP and 24-h DBP decreased significantly during treatment (SBP: from 154.1 ± 14.1 at baseline to 140.3 ± 19.6 on week 4 ($P<0.05$); DBP: from 90.2 ± 9.8 at baseline to 82.1 ± 12.2 on week 4 ($P<0.05$)). The difference in BP between daytime and nighttime increased but it did not reach statistical significance during the study period (day/night; SBP: 157.3 ± 13.5/147.8 ± 18.0 mmHg, DBP: 91.8 ± 9.8/87.3 ± 11.2 mmHg at baseline; SBP: 145.7 ± 19.7/129.5 ± 20.8 mmHg, DBP: 84.5 ± 12.2/77.3 ± 13.3 mmHg on week 4), suggesting that the diurnal BP change tended to be restored to some extent during the treatment (Figure 2). In stratified analyses of the effect of losartan in 15 patients, a successful reduction in 24-h SBP and 24-h DBP (SBP: from 150.4 ± 16.8 at baseline to 126.5 ± 13.7 mmHg, on week 4, DBP: from 86.8 ± 9.2 at baseline to 73.3 ± 5.1 mmHg, on week 4) was observed in eight patients, while in seven patients, 24-h SBP and 24-h DBP decreased only slightly without statistical significance (SBP: from 158.3 ± 9.9 at baseline to 156.1 ± 11.3 mmHg, on week 4, DBP: from 94.1 ± 9.7 at baseline to 92.1 ± 9.7 mmHg, on week 4).

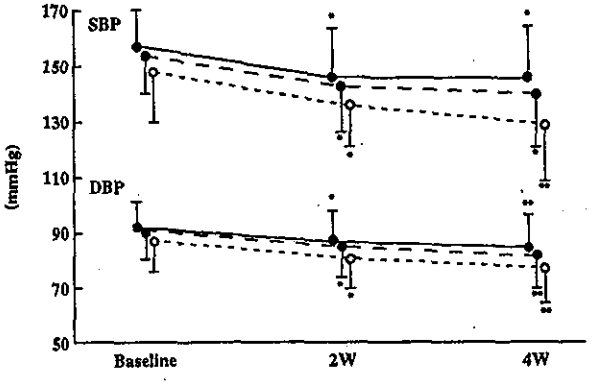

Figure 2 Changes in BP in hypertensive patients with a history of stroke. Patients were treated with losartan at doses of 25–100 mg/day during 4 weeks. A circle with a bar represents the mean value ± s.d ($n=15$). *$P<0.05$, **$P<0.01$ *vs* baseline. –●–, daytime average; ···○···, nighttime average; ----●----, 24-h average.

Cerebral blood flow

Types of cerebrovascular disease (CVD) of our patients were atherothrombotic brain infarction (ATBI), lacunar infarction (LA), cardioembolic infarction (CE), and aortogenic infarction (Aorta). There were three patients who had periventricular hyperintensity (PVH). There was no specific trend in response to losartan in relation to CVD types. CBF values of individual patients measured at week 4 are summarized in Table 1.

Figure 3 shows global blood flow in the cerebrum and cerebellum, at baseline and after 4 weeks of treatment with losartan. The average blood flow in the cerebrum increased by 7.7% (from 29.7 ± 6.7 to 32.0 ± 8.0 ml/min/100 g) with statistical significance ($P<0.05$), while in the cerebellum the blood flow remained unchanged (from 31.5 ± 7.5 to 33.4 ± 8.7 ml/min/100 g; NS).

We next divided the patients into two subgroups based on their responsiveness of BP to losartan. The upper panels of Figure 4 show the change in CBF in the cerebellum and cerebrum of the eight patients who showed an effective decrease of 24-h SBP and 24-h DBP (subgroup A). In this subgroup the increase in CBF in the cerebrum was statistically significant. The lower panels of Figure 4 show the CBF in the cerebellum and cerebrum of the seven patients in whom no decrease of 24-h SBP and 24-h DBP was observed (subgroup B). CBF did not increase and remained unchanged, although two patients in this subgroup showed prominent increases; one from 35.8 to 43.1 (20.4%) and the other from 40.0 to 50.5 ml/min/100 g (26.3%) in the cerebellum, and from 34.4 to 42.4 (23.3%) and 38.2 to 49.9 (30.6%) in the cerebrum, respectively.

Serum uric acid and safety evaluation

Laboratory measurements revealed a statistically significant decrease in serum uric acid in all

Table 1 Patient characteristics and CBF at baseline and at week 4

Patient number	*Gender*	*Age (years)*	*Weeks after the event of stroke*	*Previous anti-hypertensive therapy*	*BP (mmHg) systolic/diastolic*		*Dipper (D), Extreme dipper (ED) or Non dipper (N)*	*CVD*					*CBF (ml/min/100 g) cerebrum/cerebellum*	
					Office BP	*24-h BP*		*CVD type*	*MRA findings*	*Lesion location*	*Lesion size (cm^3)*	*Modified Rankin scale*	*Baseline*	*Week 4*
1	M	71	140.6	Yes	158/77	142/93	N	ATBI	Lt SCA.O Rt MCA. 70% St	Lt Cerebellum	3.0	1	21.7/22.5	22.5/24.4
2	M	66	53.1	Yes	177/85	169/79	N	ATBI	Rt PCA. wall irregular	Rt Occipital	12.0	1	29.9/28.6	29.0/27.6
3	M	72	5.0	Yes	151/74	139/75	D	ATBI	Lt ICA 70% St	Lt frontal	1.0	0	24.6/25.4	28.4/28.8
4	M	64	4.1	Yes	169/103	157/90	N	LA	n.p.	Lt corona radiata	1.4	0	24.5/28.4	26.2/29.8
5	M	53	4.4	Yes	148/87	132/91	N	CE	n.p.	Rt MCA area	71.7	2	21.7/22.5	22.3/22.4
6	M	70	671.3	No	162/82	177/105	N	ATBI	Rt MCA. branch.O	Rt MCA area	30.0	2	20.6/22.0	26.3/26.4
7	F	60	254.9	Yes	152/82	162/87	N	ATBI	Lt MCA 50% St	Lt corona radiata	1.6	0	34.4/35.8	42.4/43.1
8	M	71	5.3	Yes	161/85	157/84	N	ATBI	BA. 90% St	Lt pons	1.5	3	26.8/25.2	25.9/24.4
9	M	69	69.6	No	143/86	129/87	N	LA	n.p.	Rt corona radiata	1.2	1	37.0/43.7	39.1/42.0
10	M	62	5.7	Yes	156/80	148/90	D	LA	n.p.	Lt thalamus	0.8	0	34.8/36.2	32.6/36.0
11	F	53	5.9	Yes	161/91	169/90	N	Aorta	Rt VA 50% St	Rt pons	0.5	0	42.4/42.4	39.6/39.3
12	M	58	6.7	No	164/79	129/81	ED	Aorta	n.p.	Lt frontal	13.9	1	31.4/34.0	35.1/38.9
13	M	61	5.0	Yes	158/93	149/105	N	LA	n.p.	Lt corona radiata	0.8	0	32.3/38.2	35.1/41.6
14	M	65	4.6	Yes	140/68	155/86	D	ATBI	BA. 70% St	Lt Cerebellum	3.0	1	25.5/27.3	25.9/26.3
15	F	61	5.3	Yes	181/102	171/110	N	LA	n.p.	Lt corona radiata	0.5	0	38.2/40.0	49.9/50.5

Abbreviations: ATBI = atherothrombotic brain infarction; LA = lacunar infarction; CE = cardioembolic infarction; Aorta = aortogenic embolic infarction; Lt = left; Rt = right; ICA = internal carotid artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; SCA = superior cerebellar artery; O = occlusion; St = stenosis; BA = basilar artery; VA = vertebral artery; n.p. = no particular.

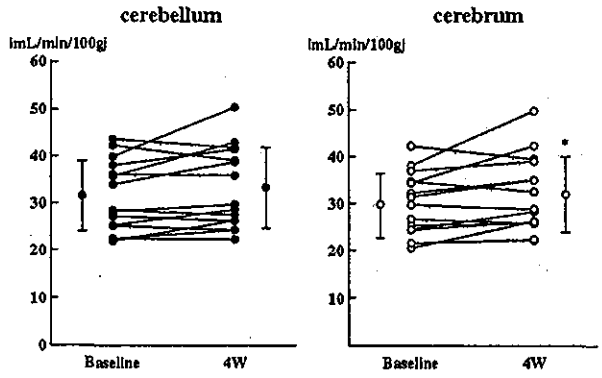

Figure 3 Changes in individual CBF in the cerebrum and cerebellum in hypertensive patients with a history of stroke. The blood flow is expressed as ml/min/100 g brain ($n=15$). A circle with a bar represents the mean value ±s.d. The increase in CBF observed in the cerebrum was statistically significant (*$P<0.05$ *vs* baseline).

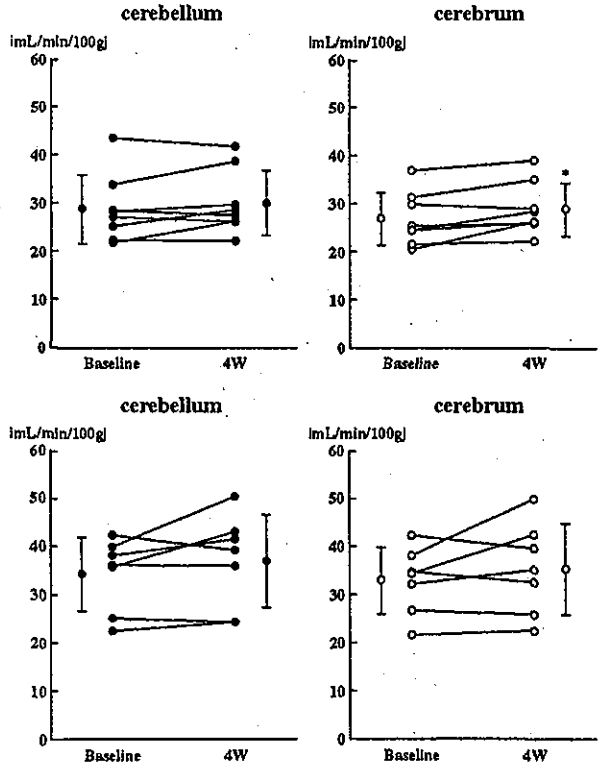

Figure 4 Changes in CBF in patients divided according to the response of BPs to losartan during the 4-week treatment. Upper panels correspond to subgroup A (BP was reduced; $n=8$) and the lower panels to subgroup B (BP was not reduced; $n=7$). A circle with a bar represents the mean value ±s.d. In subgroup A, the increase in CBF was statistically significant in the cerebrum (*$P<0.05$ *vs* baseline).

patients: the average concentration of serum uric acid was 356.9±49.2 μmol/l at baseline and 312.5±56.5 μmol/l at week 4 (12% reduction, $P<0.01$). As for adverse effects, six patients reported experiences that were considered by the investigator to be possibly or probably related to the study treatment. The patient who was dropped out of the study showed an increase in AST (GOT) from 51 to 72 IU/l and of γ-GTP from 296 to 380 IU/l and vomiting in the first 2-weeks of losartan treatment. In another patient, slight increases in AST (GOT) from 30 to 65 IU/l and ALT (GPT) from 24 to 69 IU/l and γ-GTP from 215 to 348 IU/l were observed. In four other patients, dizziness, transient loss of consciousness, diarrhea and swelling and tenderness of the right hand were reported. No severe or fatal adverse events were observed during the 4 weeks of treatment with losartan.

Discussion

In our present study, treatment of hypertensive patients with a history of stroke for 4 weeks with losartan resulted in an effective average reduction of 13.7 mmHg in 24-h SBP and of 8.1 mmHg in 24-h DBP, as measured using an ABPM system. Whereas the average blood flow in the cerebrum showed a statistically significant increase. The average blood flow in the cerebellum tended to increase, but the increase did not reach statistical significance. Thus, the blood flow in both cerebrum and cerebellum was well preserved, despite the decrease of BP. However, there were seven patients who showed only a 2.1 mmHg decrease in 24-h SBP and a 2.0 mmHg decrease in 24-h DBP. As a result, of a total of 15 patients, eight were well responded and seven were poorly responded to losartan. Although there was no statistical correlation between the change in BP and the change in CBF, in patients whose BPs were reduced, only one had a reduced flow in the cerebrum, while in patients whose BPs were poorly reduced, three had the reduced flow (Figure 4). These results led us to postulate that the more effectively losartan reduces BP, the more favourably CBF is preserved.

In our patients the average baseline CBF, excluding the area of infarct, was 29.7±6.7 ml/min/100 g in the cerebrum and 31.5±7.5 ml/min/100 g in the cerebellum. Kuriyama *et al*[8] reported that global CBF in patients with a history of stroke and impaired autoregulation was 42.3±6.1 ml/min/100 g. Iida *et al*[10] reported CBF was 39.0±2.9 ml/min/100 g in the cerebellum of healthy volunteers. By comparison, the CBF of our patients was low, indicating an impaired cerebral circulation.

The beneficial effect of ACE inhibition on CBF was first reported by Barry *et al*[4] and Jarden *et al*[5] in hypertensive rats, using captopril. They demonstrated that although BP fell below the previously established lower limit of autoregulation, CBF remained unchanged. Clinical evidences of this

effect of ACE inhibitors was obtained in patients with chronic heart failure,[6,7] and then in hypertensive patients with a history of stroke.[8] Our present results are consistent with such previous findings, thereby the effect of ACE inhibitors to preserve CBF is probably attributed to the interference of angiotensin II AT_1 receptor mediated actions, since losartan is a selective angiotensin II AT_1 receptor antagonist (AIIA). The important role of angotensin II AT1 receptors to affect CBF is also supported by the results reported by Nishimura *et al*,[13] who demonstrated the effect of the AIIA candesartan to preserve CBF in spontaneously hypertensive rats with cerebral ischaemia. Furthermore, the effect of repeated administration of losartan may differ from that of ACE inhibitors. Recent advances in interventional pharmacology of the renin–angiotensin system have revealed clear differences between the properties of AIIAs and those of ACE inhibitors. First, AIIAs inhibit angiotensin II AT_1 receptors, but not AT_2 receptors which may counteract the actions of AT_1 receptors.[14] The actions of AT_2 are considered to include vasodilation, induction of apoptosis, interference of vascular remodeling, all which may contribute to preserve the vascular structure.[15] However, ACE inhibitors cannot block the production of angiotensin II via a non-ACE enzyme, such as chymase, which is known to exist in the vascular tissue.[16,17]

Taken together, the beneficial effect of losartan in hypertensive patients with a history of stroke may be explained by its acute effect that is similar to that of ACE inhibitors, as well as by its chronic effect on vascular tissue, through which it ameliorates its structure and function. If the latter were the case, it is considered that the effects of a blockade of angiotensin II AT_1 receptors by losartan are amelioration of the damaged vascular structure and restoration of a physiologically normal tone in resistant arteries; thereby the lower limit of autoregulation would be reset to a level of BP lower than that established as a consequence of stroke. These assumptions must be substantially demonstrated in the future in both experimental and clinical studies.

Recently, an interesting clinical study involving hypertensive patients with left ventricular hypertrophy, named LIFE study, was reported.[18] In this study, 4588 patients were treated with the beta-blocker atenolol and 4605 patients with the AIIA losartan, for more than 60 months. The efficacy of these drugs regarding BP reduction was similar. However, the proportion of patients with first event of stroke was significantly lower in the losartan group than in the atenolol group. The investigators of this mega-trial did not state the reason for this difference, but it may be possible that losartan reduced the risk of infarction by protecting cerebral vessels from structural changes. If this were the case, the result of our present study would be compatible with the result of the LIFE study in terms of protection of function and structure of vascular beds in the brain.

In conclusion, administration of losartan to hypertensive patients with a history of stroke for four consecutive weeks resulted in a decrease of BP with a preserved blood flow in both the cerebrum and cerebellum. The blockade of angiotensin II AT_1 receptors by losartan is considered to be safe in such patients, because it preserves the function of autoregulation of cerebral blood flow in therapy of BP control.

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