Effects of Poststroke Losartan Versus Captopril Treatment on Myogenic and Endothelial Function in the Cerebrovasculature of SHRsp

John S. Smeda, PhD; John J. McGuire, PhD

Background and Purpose—We assessed the ability of poststroke captopril and losartan treatment to reverse myogenic and endothelial dysfunction in the middle cerebral arteries of Kyoto-Wistar stroke-prone spontaneously hypertensive rats (SHRsp) that developed intracerebral hemorrhagic stroke.

Methods—SHRsp were sampled before and after stroke development and after up to 37 days of captopril (50 mg/kg per day) or losartan (35 mg/kg per day) treatment initiated after stroke. Pressure-dependent constriction to a 100-mm Hg pressure step, constriction to nitric oxide synthase inhibition (100 μmol/L Nω-nitro-l-arginine methyl ester), and endothelium-dependent vasodilation to bradykinin (1.6 μmol/L), 2-f-LIGRLO-NH₂ (1 μmol/L, a protease-activated receptor-2 agonist), and A23187 (2 μmol/L) were evaluated in middle cerebral arteries at 100 mm Hg with a pressure myograph.

Results—Middle cerebral arteries from SHRsp with stroke could not constrict to pressure or nitric oxide synthase inhibition, lacked the ability to vasodilate to bradykinin, and exhibited attenuated dilation and vasomotion in response to A23187. Vasodilation to 2-f-LIGRLO-NH₂ was unaltered. The aforementioned cerebrovascular alterations were reversed after 31 days of poststroke losartan but not of captopril treatment in the absence of an antihypertensive effect. Captopril treatment restored middle cerebral artery constriction to pressure, NOS inhibition, and bradykinin vasodilation temporarily after 7 to 18 days of treatment, after which function deteriorated to a level observed in SHRsp at stroke.

Conclusions—Aspects of poststroke cerebrovascular dysfunction, which likely play an important role in altering and modulating cerebral blood flow autoregulation, can be reversed in SHRsp more effectively after stroke development by blocking angiotensin II type 1 receptors as opposed to lowering angiotensin II levels. (Stroke. 2007;38:1590-1596.)

Key Words: captopril ■ endothelium ■ intracerebral hemorrhage ■ myogenic response ■ SHRsp

Hemorrhagic stroke development in Kyoto-Wistar stroke-prone spontaneously hypertensive rats (SHRsp) is associated with the presence of an overactive renin–angiotensin II (AII)–aldosterone system and rapid death. Treatment of SHRsp with captopril after stroke increases the lifespan of SHRsp from 2 to 35 weeks in the absence of an antihypertensive effect. SHRsp with stroke also lose their ability to autoregulate cerebral blood flow (CBF) and develop cerebrovascular myogenic dysfunction. The current study tested the hypothesis that the inhibition of AII formation or action after stroke development restores cerebrovascular myogenic and endothelial function in the middle cerebral arteries (MCAs) of SHRsp. The effects of captopril, an angiotensin-converting enzyme inhibitor that inhibits AII formation, were compared with those of losartan, an angiotensin II type 1 (AT-1) receptor blocker. An equal ability to restore cerebrovascular function after stroke would indicate that the benefits of treatment were mediated through AII stimulation of AT-1 receptors.

Studies involving the MCAs of prestroke SHRsp (J. Smeda et al, unpublished results) indicated that A23187 (a Ca²⁺ ionophore), 2-f-LIGRLO-NH₂ (2-Fly; a protease-activated receptor-2 agonist), and bradykinin elicited endothelium-dependent vasodilation by the activation of endothelial Ca²⁺-activated K⁺ channels. These responses are marginally affected by nitric oxide synthase (NOS) inhibition with Nω-nitro-l-arginine methyl ester (l-NAME), are unaffected by cyclooxygenase inhibition (indomethacin at 10 μmol/L), and are inhibited by [K⁺]o depolarization (44.6 mmol/L), characteristics consistent with vasodilation produced by endothelium-dependent hyperpolarizing factor (EDHF). In the presence of NOS inhibition, vasodilation in response to A23187 differed from that produced by 2-Fly or bradykinin, in that it was inhibited by Ba²⁺ (30 μmol/L) plus ouabain (10 μmol/L). This suggested that A23187 mediates vasodilation through an EDHF mechanism that involves the activation of smooth muscle cell inward rectifying K⁺ channels and Na⁺/K⁺-ATPase. By using the aforementioned vasodilators...
as tools, a global assessment of endothelial function and recovery was undertaken involving the evaluation of dilation produced by the spontaneous release of NO and by vasodilators using different signaling pathways and alternative EDHF mechanisms. We attempted to determine whether cerebrovascular dysfunction associated with stroke and recovery in response to treatment was ubiquitous or limited to specific myogenic and/or endothelial mechanisms. Myogenic and endothelial function was evaluated in MCAs sampled from SHRsp before and after stroke and in animals treated with either losartan or captopril for a period of up to 37 days after stroke.

**Materials and Methods**

Experiments complied with the Canadian Council on Animal Care. Rats were fed a Japanese-style diet (Zeigler Bros, Gardners, Pa) containing 4% NaCl. SHRsp were sampled at 10 weeks of age, 3 weeks before stroke development. Littermates were allowed to mature and develop stroke. Stroke was associated with the development of seizures, consisting of repetitive forelimb and/or head flexion that was followed by a period of lethargy and immobility. Previous studies indicated that death occurred in 1.7±0.2 weeks.1,2 Detailed descriptions of the behavioral characteristics of stroke and the cerebrovascular lesions present in our SHRsp are presented in a previous publication.2 After stroke, SHRsp were randomly either sampled or given captopril (150 mg/L) or losartan (100 mg/L) in the drinking water (≈50 mg·kg⁻¹·d⁻¹ captopril or 35 mg·kg⁻¹·d⁻¹ losartan ingestion) for 30 to 37 days and sampled. Both of the latter treatments suppressed the high levels of plasma aldosterone (≈5 nmol/L) observed in SHRsp with stroke equally and effectively (to <0.5 nmol/L) during the treatment period (J. Smeda and S. Vasdev, unpublished results), indicating continuous effective suppression of the AT₁ receptor response. Systolic blood pressures (SBPs) were measured with a tail-cuff compression method.1,4 Rats were anesthetized with 65 mg/kg IP sodium pentobarbital. A segment of the right or left MCA that crossed over the rhinalis fissure was mounted in a pressure myograph. MCAs were pressurized to 100 mm Hg for 30 minutes at 37°C, allowing pressure-dependent constriction (PDC) to develop. Subsequently, the pressure was decreased to 0 mm Hg for 6 minutes to inactivate PDC and then repressurized to 100 mm Hg. The reduction in lumen diameter between 1 second and 4 minutes after pressurization to 100 mm Hg was used as a measure of PDC.

Detailed descriptions of the methodology used and the rationale for using this protocol to measure myogenic constriction have been previously discussed.1,4 Lumen diameter changes were measured at ×322 magnification. 2-Fly was purchased from Peptides International. All other chemicals were purchased from Sigma Chemical Co. An ANOVA followed by Fisher’s post hoc test was used to determine subgroup differences. The mean±SE values are shown, and results were considered significant at \( P<0.05 \).

**Results**

**Characteristics of the SHRsp in the Study**

SHRsp were mated at the same time, producing offspring born within 1 week of each other. Male SHRsp at 10 weeks of age (9.8±0.15 weeks; \( n=7 \), SBP, 216.5±2.6 mm Hg), 3 weeks before stroke development, were sampled (referred to as “prestroke SHRsp”). SHRsp exhibited behavioral alterations consistent with stroke development (ie, seizures1,2) between 13 and 17 weeks of age. The onset of these symptoms was often associated with the development of intracerebral hemorrhage. The infusion of Evans blue dye (30 mg/kg IV, 20 minutes), which binds to albumin,5 also showed sites of plasma extravasation and edema in areas where intracerebral hemorrhage was absent (Figure 1).

SHRsp that exhibited stroke behavior were randomly either sampled or orally treated with captopril (50 mg·kg⁻¹·d⁻¹) or losartan (35 mg·kg⁻¹·d⁻¹) for 31 days. Both treatments prevented death during the treatment period. The characteristics of the SHRsp sampled are as follows: SHRsp at stroke (subsequently referred to as “poststroke SHRsp”; \( n=10 \)) were 15.0±0.3 weeks old and had an SBP of 256±11 mm Hg. Poststroke losartan-treated SHRsp (\( n=6 \)) were 19.1±0.5 weeks old and had an SBP of 244±9 mm Hg, with 32±0.8 days on losartan treatment. Poststroke captopril-treated SHRsp (\( n=5 \)) were 19.7±0.6 weeks old and had an SBP of 258±8 mm Hg, with 31±0.5 days on captopril treatment. The SBPs of untreated, losartan, and captopril poststroke SHRsp were not significantly different (ANOVA). The SBP of each of the latter groups was higher (\( P<0.05 \)) than that of each of the latter groups.
present in prestroke SHRsp, which had not developed full established hypertension.

Alterations in PDC in the MCAs of SHRsp

The MCAs of SHRsp sampled at stroke lost their ability to elicit PDC in response to a 100-mm Hg pressure step (Figure 2A and 2B). Equilibration of the MCAs to 0 mm Hg for 6 minutes deactivates PDC. At 1 second after the abrupt application of the 100-mm Hg pressure step, the lumen diameter will expand to a size that would be present at 100 mm Hg in the absence of PDC. Full reconstriction to a smaller lumen diameter occurs in 4 minutes after pressure is applied. These characteristics were exhibited by all of the MCAs from prestroke SHRsp (Figure 2A). MCAs from SHRsp with stroke exhibited significant basal tone 1 second after the application of 100 mm Hg pressure (compare the lumen diameter 1 second after 100 mm Hg versus that at maximal relaxation with nifedipine) and did not have further significantly altered lumen diameters during the next 4 minutes (Figure 2A).

Losartan treatment for 31 days after stroke reduced the level of basal constriction observed in MCAs 1 second after the application of 100 mm Hg pressure (compare the lumen diameter 1 second after 100 mm Hg versus that at maximal relaxation with nifedipine) and did not have further significantly altered lumen diameters during the next 4 minutes (Figure 2A).

Alterations in Constriction Induced by NOS Inhibition

The MCAs of prestroke SHRsp pressurized to 100 mm Hg constricted in response to the NOS inhibitor l-NAME. This response was attenuated in the MCAs of SHRsp with stroke (Figure 3A, a versus b). Poststroke losartan treatment for 31 days increased MCA constriction to l-NAME (Figure 3A, c), whereas captopril treatment did not (Figure 3A, d). This suggested that losartan treatment enhanced basal NO release or influence in the MCAs of poststroke SHRsp.

Contralateral MCAs from SHRsp used in Figure 3A were dilated by A23187 (2 μmol/L), and the ability of l-NAME to elicit constriction was tested (Figure 3B). l-NAME only constricted MCAs sampled from prestroke and poststroke losartan-treated SHRsp under conditions where the endothelium was made permeable to Ca2+ (an environment conducive to maximal NOS stimulation). MCAs from poststroke SHRsp and those subjected to poststroke captopril treatment did not respond to l-NAME (Figure 3B).

Bradykinin-, Protease-Activated Receptor Agonist-, and A23187-Mediated Vasodilation

Previous experiments with MCAs from prestroke SHRsp indicated that maximal vasodilation to bradykinin and 2-Fly was achieved at 1.6 and 1 μmol/L, respectively. Both of these peptides produced endothelium-dependent vasodilation (percent change in lumen diameter, endothelial damage [air bubbles through the lumen] versus no damage; bradykinin, 12 ± 7% constriction versus 48 ± 5% vasodilation; 2-Fly, 3 ± 3% constriction versus 83.4% vasodilation; left versus right MCAs; 5 prestroke SHRsp).

MCAs from SHRsp with stroke did not vasodilate in response to bradykinin (Figure 4A). This ability was regained with losartan but not captopril treatment for 31 days. The responses in captopril-treated SHRsp were comparable to those of untreated poststroke SHRsp (Figure 4A, d versus b).

MCAs from the various groups of SHRsp exhibited comparable vasodilation in response to the protease-activated

Figure 2. Alterations in MCA lumen diameter in response to a 100-mm Hg pressure step in SHRsp subjected to losartan or captopril treatment. A and B show the absolute and percent changes, respectively, in diameter that occurred in the MCAs between 1 second and 4 minutes after application of pressure. Nifedipine (3 μmol/L) maximally diluted the MCAs. MCAs from poststroke SHRsp developed a constant level of elevated tone and did not further constrict to pressure. Losartan but not captopril treatment for 31 days after stroke allowed the MCAs to regain the characteristics of PDC present in prestroke SHRsp. Statistics used were ANOVA and Fisher post hoc test: in A at 1 second, a vs b and d, c vs d, P < 0.05; at 4 minutes c vs b and d, a vs d, P < 0.05; with nifedipine, a vs d, P < 0.05. In B a and c vs b or d, P < 0.05. n values are for MCA/SHRsp in A and B: a = 7/7, b = 10/10, c = 6/6, d = 5/5.
receptor-2 agonist 2-Fly in the presence or absence of NOS inhibition (Figure 4B). NOS inhibition (L-NAME) plus NO scavenging (vitamin B12a) reduced vasodilation in response to 2-Fly in MCAs from prestroke, poststroke, and losartan-treated SHRsp (Figure 4B). A23187 also produced endothelium-dependent dilation (percent change in lumen diameter, endothelial damage [air bubbles through the lumen] versus no damage; 9.3±6.2% constriction versus 70±9% vasodilation; left versus right MCA; 5 prestroke SHRsp). MCAs sampled from SHRsp with stroke exhibited attenuated responses to A23187 when compared with prestroke SHRsp (Figure 5A, a, versus b1). Losartan treatment of poststroke SHRsp enhanced the responses to A23187 (Figure 5A, c1 versus b1). Poststroke SHRsp treated with captopril had MCAs that exhibited higher (but not statistically different) average vasodilator responses to A23187 than those of poststroke SHRsp (Figure 5A, d1 versus b1). NOS inhibition and the presence of an NO scavenger did not significantly suppress A23187-mediated MCA vasodilator responses within the SHRsp groups (ie, Figure 5A, a1 versus a2, b1 versus b2, etc). It did, however, slightly suppress responses in MCAs sampled from prestroke SHRsp and poststroke SHRsp treated with captopril, which altered the statistical differences between the groups in a manner wherein the presence of NOS inhibition, responses to A23187 were not different in pre- vs poststroke SHRsp (Figure 5A, a1 versus b1) and were different in losartan- versus captopril-treated poststroke SHRsp (Figure 5A, c1 versus d1).

Figure 3. Alterations in MCA constriction in response to NOS inhibition in the absence (A) or presence (B) of A23187 (2 μmol/L) in SHRsp subjected to poststroke losartan or captopril treatment. Maximal constriction to L-NAME was measured at 100 mm Hg pressure. MCAs from poststroke SHRsp exhibited an attenuated (A) or absent (B) ability to constrict in response to NOS inhibition, suggesting that the basal influence of NO on MCA tone was altered. Treatment with losartan but not captopril after stroke (31 days) enhanced the ability of MCAs to constrict to L-NAME. Statistics used were ANOVA plus Fisher post hoc test: in A, $P<0.05$ for all comparisons; in B, a vs b or d, $P<0.05$. n values are for MCA/SHRsp in A or B (separate MCA segments) a=7/7, b=10/10, c=6/6, d=5/5.

Figure 4. Alterations in bradykinin- and 2-Fly–mediated vasodilation in MCAs sampled from SHRsp subjected to poststroke losartan or captopril treatment. The MCAs were at 100 mm Hg pressure. A, MCAs sampled from SHRsp with stroke lost the ability to vasodilate in response to bradykinin (1.6 μmol/L). Poststroke losartan, but not captopril, treatment (31 days) restored this ability. B, MCA vasodilation in response to PAR2 stimulation by 2-Fly (1 μmol/L) was not altered between SHRsp groups in the absence of NOS inhibition. Statistics used were ANOVA plus Fisher post hoc test: in A, a and c vs b or d, $P<0.05$; in B, for ANOVA group analysis of a1 to d1, $P=0.267$, a1 to d2, $P=0.091$. Paired t test of a1 vs a2, b1 vs b2, c1 vs c2, $P<0.05$. n values in A and B are for MCA/SHRsp a=7/7, b=10/10, c=6/6, d=5/5.
A23187-Induced Oscillations in Lumen Diameter in the MCAs of Prestroke SHRsp

The MCAs of poststroke SHRsp vasodilated to A23187 without subsequent spontaneous vasomotion (Figure 5B). The treatment of poststroke SHRsp with losartan but not captopril allowed the MCAs of poststroke SHRsp to regain their oscillation characteristics. The presence or absence of an NOS inhibitor plus NO scavenger did not significantly alter the oscillation characteristics of MCAs (Figure 5B).

Chronological Variations in the Effects of Poststroke Captopril Treatment

In other studies (Davis L, Smeda J, unpublished results), we observed that poststroke captopril treatment produced a temporary restoration of CBF autoregulation, which was followed by a deterioration of this function. We therefore suspected that the effectiveness of poststroke captopril treatment in restoring cerebrovascular function in isolated MCAs may vary with treatment duration, and therefore, we assessed this possibility.

The characteristics of the SHRsp used were as follows: prestroke SHRsp (n=7) were 10.3±0.6 weeks old and had an SBP of 192±7 mm Hg; poststroke SHRsp with no treatment (n=7) were 15.8±0.6 weeks old and had an SBP of 252±10 mm Hg; poststroke SHRsp with 7 days (7±0.2 days; n=5) of captopril treatment had an SBP of 233±10 mm Hg; poststroke SHRsp with 18 days (18±0.3 days; n=7) of captopril treatment did not have their SBP measured; and poststroke SHRsp with 37 days (37±0.6 days; n=5) of captopril treatment had an SBP of 268±12 mm Hg. The SBPs in poststroke SHRsp receiving 0, 7, or 37 days of captopril treatment did not differ significantly (ANOVA, P=0.08). As in the previous group of SHRsp studied (Figures 2 through 5), prestroke SHRsp were not fully mature and exhibited lower SBPs than the other groups of SHRsp.

The ability of MCAs to constrict to a 100-mm Hg pressure step (Figure 6A, c versus d) or to respond to NOS inhibition (Figure 6B) and to vasodilate in response to bradykinin (Figure 6C) followed the same pattern. These functions were very robust in the MCAs of prestroke SHRsp (a in each figure) and were attenuated in SHRsp that developed stroke (b in each figure). MCAs from SHRsp that received 7 days of poststroke captopril treatment regained the aforementioned cerebrovascular functions (c in each figure).

The levels of constriction in response to pressure (Figure 6A, c versus d) or vasodilation in response to bradykinin (Figure 6C, c versus d) were similar in SHRsp receiving 18 versus 7 days of poststroke captopril treatment. We did not have a suitable number of MCA segments to adequately assess constriction in response to NOS inhibition in the 18-day poststroke captopril-treated SHRsp (Figure 6B). We did, however, carry out such experiments in 2 MCAs from 2 SHRsp. These produced a mean level of 20% constriction (individual values of 30% and 11%), which spanned the levels of constriction observed in SHRsp treated with captopril for 7 days. Therefore, it would appear that this latter function is also continuously maintained to 18 days of treatment. After 37 days of poststroke captopril treatment, the MCAs of SHRsp lacked the ability to constrict to pressure (Figure 6A, e) or to respond to NOS inhibition (Figure 6B, d).
and could not vasodilate to bradykinin (Figure 6C, e). Thus, captopril treatment allowed poststroke SHRsp to regain the cerebrovascular functional parameters discussed earlier, but unlike with losartan treatment, such benefits were temporary.

**Discussion**

The most remarkable observations of the study were related to the comparative effects of poststroke losartan versus captopril treatment. After 31 days of losartan treatment, the MCAs of SHRsp regained the ability to constrict in response to pressure and NOS inhibition. Such treatment also restored vasodilator function in response to bradykinin, established prestroke oscillatory characteristics, and enhanced vasodilation in response to A23187. Captopril treatment did not duplicate these effects. A short (7 day) duration of captopril treatment allowed the MCAs of SHRsp to temporarily regain the cerebrovascular functions discussed earlier, but unlike with losartan treatment, such benefits were temporary.

PDC is thought to be the primary mechanism that promotes CBF autoregulation. Consistent with this belief, the loss of CBF autoregulation in the perfusion domain of the MCA coincides with the loss of PDC in isolated MCAs sampled from SHRsp. In view of this, one would predict that the temporary ability of poststroke captopril treatment of SHRsp to restore PDC in the MCAs might also lead to only a temporary restoration of CBF autoregulation. Consistent with this hypothesis, our recently completed studies (Davis L, Smeda J, unpublished results) indicate that 10 days of poststroke captopril treatment of SHRsp allows SHRsp to regain CBF autoregulation, whereas continued treatment up to 25 days results in the subsequent loss of this function. Current studies in our laboratory have indicated that the benefit of poststroke captopril treatment with respect to the duration of its ability to restore PDC and bradykinin relaxation in the MCAs of poststroke SHRsp can vary between different generations of SHRsp, and we have seen these functions maintained in some SHRsp for up to 30 days and then decline after 45 days. Losartan is also capable of restoring both PDC and bradykinin vasodilation in the MCAs of SHRsp after as little as 7 days of poststroke treatment (respectively, 42.0±2.5% constriction to a 100-mm Hg pressure step and 91.2±5.5% maximal relaxation to 1.6 μmol/L bradykinin; n=5 SHRsp); however, unlike captopril treatment, we have never observed the loss of these functions in any poststroke losartan-treated SHRsp. We have studied a limited number of SHRsp (n=3) with up to 109 days of poststroke losartan treatment and have found that they maintained robust constriction to pressure (>40%, to a 100-mm Hg pressure step) and vasodilation to bradykinin (>75% maximal vasodilation to 1.6 μmol/L; J. Smeda, unpublished results).

l-NAME, A23187, bradykinin, and 2-Fly were used as tools to assess alterations in endothelial function in relation to stroke in SHRsp. Our ongoing studies (J.S. et al, unpublished results) indicate that the vasodilation sensitivity and responsiveness of MCAs to sodium nitroprusside are not altered with stroke. Our confocal microscopy studies have indicated
that endothelial NOS is highly prevalent in the MCA endothelium after stroke, suggesting that the stroke-related reduction in 1-NAME constriction observed in the current study was most likely attributable to altered NO release or influence as opposed to altered endothelial levels of endothelial NOS or smooth muscle cell NO reactivity. MCAs from prestroke SHRsp vasodilated in response to A23187, bradykinin, and 2-Fly through mechanisms primarily not involving NO. Our other studies have indicated that the characteristics of vasodilation are consistent with the actions of EDHF (ie, mediated through endothelial Ca^{2+}-activated K⁺ channels, inhibited by depolarization, and not involving a cyclooxygenase product or a cytochrome P450 metabolite) and likely involve at least 2 different EDHF systems. Dilation to A23187 but not bradykinin or 2-Fly can be inhibited by Ba^{2+} (30 μmol/L) plus ouabain (10 μmol/L; Smeda J, McGuire J, unpublished results). The observation of differing alterations in response to bradykinin (complete inhibition), 2-Fly (no inhibition), and A23187 (partial inhibition) after stroke in the current study suggests that a generalized defect in the mechanisms promoting EDHF vasodilation is not present. Because bradykinin and 2-Fly share common characteristics of EDHF vasodilation, the attenuation of vasodilation in response to bradykinin can best be explained by alterations relating to the bradykinin B2 receptor as opposed to the postreceptor signaling cascade, which is shared with 2-Fly. Reduced vasodilation and absent vasoconstriction in response to A23187 after stroke suggested that alternate EDHF mechanisms, possibly involving K⁺ activation of smooth muscle cell inward rectifying K⁺ channels plus Na⁺/K⁺-ATPase, are affected by stroke development. The observation that both cerebrovascular myogenic and vasodilator functions exhibited a similar pattern of deterioration in relation to stroke development and restoration in response to poststroke losartan or captopril treatment suggests that common physiologic mechanisms may be involved in promoting and restoring these functions.

SHRsp capable of developing stroke have an overactive renin-angiotensin system and high blood aldosterone levels. Captopril treatment suppresses plasma AI in SHR. Plasma AI levels are not suppressed and could become elevated during AT-1 receptor blockade. The enhanced AT-2 receptor stimulation by AI under the latter conditions may be beneficial. AT-2 receptor stimulation has been suggested to accelerate neuronal tissue repair after stroke. In renal-wrap forms of high-AII hypertension, AT-2 receptor antagonists aggravated hypertension and prevented losartan from exerting an antihypertensive effect. Studies have indicated that AT-2 receptor upregulation and stimulation may promote a protective effect against renal glomerular injury and proteinuria during nephrectomy. Therefore, it may be of greater benefit to maintain AT-1 receptor blockade, thus allowing high levels of AI to stimulate the AT-2 receptor (losartan action), than to decrease AI production (captopril action). Both captopril and losartan can retard the onset of death after stroke; therefore, counteracting AI stimulation of AT-1 receptors must promote this effect. Because SHRsp treated with captopril were spared death under conditions where their MCAs eventually lost their ability to elicit PDC and maintain vasodilator function, it would appear that the ability to regain these functions is not a prerequisite for preventing death. There could, however, be more subtle benefits to losartan treatment. For example, the restoration of PDC could dampen downstream microvascular pressures, which would reduce the risk of further vascular damage and neurodegeneration resulting from such damage. By slowing such damage, aspects of motor coordination, memory, and cognitive function that contribute to well-being may be improved and overlooked by judging outcome only in terms of an extension of lifespan after stroke.

**Summary**

There are few useful interventions that can prevent death and disability after hemorrhagic stroke. Our previous studies have indicated that the onset of death can be retarded by treating SHRsp with captopril after stroke. The current study expands these findings to suggest that poststroke losartan treatment may be more effective than captopril in restoring cerebrovascular myogenic and endothelial functions. The importance of the study resides in the demonstration that cerebrovascular defects associated with hemorrhagic stroke have a capacity to be reversed in SHRsp by altering renin-angiotensin pharmacology.

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**Disclosures**

None.

**References**


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