Impact of Acute and Chronic Hypertension on Changes in Pial Collateral Tone In Vivo During Transient Ischemia

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Abstract—We investigated vasoconstrictive responses of pial collaterals in vivo at baseline and during transient middle cerebral artery occlusion during chronic hypertension. A cranial window was used to measure diameter of leptomeningeal anastomoses (pial collaterals) in male Wistar (n=8) and spontaneously hypertensive rats (SHRs; n=8) using video dimensional analysis. Middle cerebral artery occlusion was induced by remote filament for 2 hours with 2 hours reperfusion. Phenylephrine was infused during ischemia as a pressor therapy. Active diameters of pial collaterals were significantly smaller in SHRs versus Wistar (14.1±1.5 versus 21.6±2.8 µm; $P<0.01$); however, passive diameters were similar (25.0±2.9 versus 25.0±2.6 µm; $P>0.05$). Basal tone of pial collaterals before occlusion was 42±5% in SHRs versus 15±4% in Wistar ($P<0.01$). Tone decreased in both Wistar and SHRs during occlusion but remained higher in SHRs (9±2% versus 29±4%; $P<0.05$). Phenylephrine increased blood pressure in both groups but had little effect on leptomeningeal anastomoses diameters. Reperfusion caused vasoconstriction of pial collaterals, increasing tone from 8±1% to 20±5% in Wistar and 29±5% to 44±5% in SHRs ($P<0.01$). Higher tone in pial collaterals from SHRs basally and during occlusion/reperfusion could limit flow to the penumbra and promote evolution of infarction. Sustained elevated tone of pial collaterals from SHRs with phenylephrine suggests pressor therapy may not be appropriate during chronic hypertension. **(*Hypertension*. 2020;76:1019-1026. DOI: 10.1161/HYPERTENSIONAHA.120.15356.)**

Key Words: acute stroke ■ cerebrovascular circulation ■ hemodynamics ■ phenylephrine ■ reperfusion

The leptomeningeal anastomoses (LMAs), also known as pial collaterals, are distal connections between major arterial territories in the brain that maintain perfusion to the penumbra.[1,2] Pial collaterals have been shown to have a critical role in stroke progression and outcome from large vessel occlusion (LVO).[1–5] Several studies have shown that patients with good collateral status on imaging have more salvageable tissue, smaller ischemic cores, and better neurological outcome after LVO.[3–5] Collateral status is also important for clinical decision-making. Patients with good collaterals have recently been shown to be eligible for endovascular therapy without a time window.[6–8] Although this recent development has revolutionized endovascular therapy for LVO treatment, therapeutics are still needed for patients with large ischemic cores and small amounts of salvageable tissue that would otherwise not be good candidates for endovascular therapy.

Therapies for improving collateral flow are currently being tested in a number of clinical trials. As retrograde flow through the pial collaterals is dependent on the pressure gradient between the anterior or posterior cerebral arteries and the middle cerebral artery (MCA), one approach has been to increase blood pressure to facilitate collateral perfusion, that is, pressor therapy. This approach assumes that pial collaterals are pressure-passive and will increase diameter, and therefore flow, with increased blood pressure. However, we previously demonstrated that pial collaterals isolated from spontaneously hypertensive rats (SHRs) were highly vasoconstricted, but not structurally smaller, compared with normotensive Wistar Kyoto rats.[9] In addition, pial collaterals from SHR constricted in response to increased intravascular pressure and displayed a robust myogenic response. This vasoconstrictive response to pressure was essentially absent from LMAs taken from normotensive Wistar Kyoto rats. These findings suggest that pressor therapy may not be beneficial to all patients, especially those with chronic hypertension. In fact, this type of therapy may actually be detrimental under certain conditions by inducing vasoconstriction of LMAs and restricting flow to the penumbra. However, the functional response of LMAs to pressure in vivo is largely unknown, but important to understand if collateral therapy is to be successful.

In the current study, we used a cranial window combined with video microscopy and dimensional analysis to investigate changes in LMA diameter and tone in vivo in normotensive Wistar and chronically hypertensive rats (SHR). We determined basal tone and changes in diameter and tone in response to an infusion of phenylephrine to acutely raise blood pressure during MCA occlusion (MCAO) to mimic pressor therapy. We hypothesized that LMAs from SHR would have increased basal tone compared with Wistar. We further hypothesized that pressor therapy during an occlusion would increase tone in LMAs in SHR, but not Wistar rats.

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Materials and Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Animals

Male Wistar (n=8) and SHRs (n=8; Envigo, Dublin, VA), aged 15 to 25 weeks old, were used in this study. Rats were randomly assigned by an online randomization tool and housed in the Animal Care Facility at the University of Vermont, an Association for Assessment and Accreditation of Laboratory Animal Care-accredited facility. Rats were maintained on a 12-hour light/dark cycle and allowed food and water ad libitum. All animal procedures were approved by the Institutional Animal Care and Use Committee at the University of Vermont and complied with the National Institutes of Health guidelines for care and use of laboratory animals.

Visualization of LMAs In Vivo Through Craniotomy

An open cranial window (6×5 mm) was made with animals in a prone position by craniotomy (Figure 1A, left). The position of the cranial window was between +3 mm and −3 mm of Bregma and 0 and +5 mm lateral (ipsilateral to the occlusion) from the midline. LMAs were identified as connections between distal branches of the MCA and anterior cerebral artery (ACA). The dura remained intact but carefully thinned using fine tweezers to improve LMA diameter measurements. This maintained intracranial pressure and minimized brain swelling. LMA diameter was continuously measured by a Video Dimension Analyzer (Living Systems Instrumentation, St Albans, VT) before and during ischemia and during recanalization (Figure 1A, right). At the end of the experiment, LMAs were exposed to ethylenediaminetetraacetic acid (EDTA, 67 mmol/L in physiological saline) to obtain maximally dilated diameters and for calculation of % tone of LMAs. EDTA is a calcium chelator and potent vasodilator.[10]

Model of Remote Transient Focal Ischemia

Animals were anesthetized with isoflurane in oxygen (1.5%–2%) and laid on a heating pad in supine position. Rats were mechanically ventilated through tracheotomy to maintain blood gases within physiological ranges. A femoral artery catheter was placed for obtaining blood samples for blood gas analysis that was also connected to a pressure transducer and servo system for monitoring blood pressure (Living Systems Instrumentation, St Albans, VT). A femoral vein catheter was inserted for pentobarbital infusion. After instrumentation, pentobarbital (20 mg/kg/h, IV) anesthesia was used in place of isoflurane because isoflurane has a potent vasodilator effect of the cerebral circulation. The use of pentobarbital over previously used chloral hydrate was to reduce the blood pressure-lowering effect of chloral hydrate.

The right common carotid artery was exposed and occluded with a 4-O suture. The external carotid artery was isolated and cauterized for insertion of a custom-made filament for remote MCAO (rMCAO, Figure 1B). A custom filament for rMCAO was made with a 15 cm 5-O mono-nylon nonabsorbable suture (Surgical Specialties Corporation, Reading, PA). The tip of the filament was coated with polysiloxane impression material (Haraeus Kulzer, Hanau, Germany). The filament was inserted into a 12 cm polyethylene tubing (OD:0.61 mm; ID:0.28 mm, Warner Instrument, Hamden, CT), and the tubing was secured on the external carotid artery. The filament was initially inserted through an incision in the external carotid artery and advanced through the internal carotid artery into the circle of Willis without occluding the MCA. Transient focal ischemia was induced by further advancing the filament to occlude the MCA. To confirm focal ischemia, a laser Doppler probe was placed above the cranial window at the MCA core territory to measure perfusion (Figure 1C). After 2 hours of ischemia, the filament was retracted to allow for reperfusion for 2 hours.

Induction of Pressor Therapy

After 30 minutes of ischemia, with the filament still in place, phenylephrine (10 mg/mL, 4–30 µL/min, and 10 minutes) was infused through a catheter connected to the femoral vein. Blood pressure and changes in diameter of LMAs were measured. Phenylephrine was used for several reasons: (1) Phenylephrine is used clinically to maintain blood pressure during endovascular therapy.[11] (2) Cerebral pial and parenchymal vessels have few adrenergic receptors and respond little to phenylephrine.[12] (3) Phenylephrine does not readily cross the

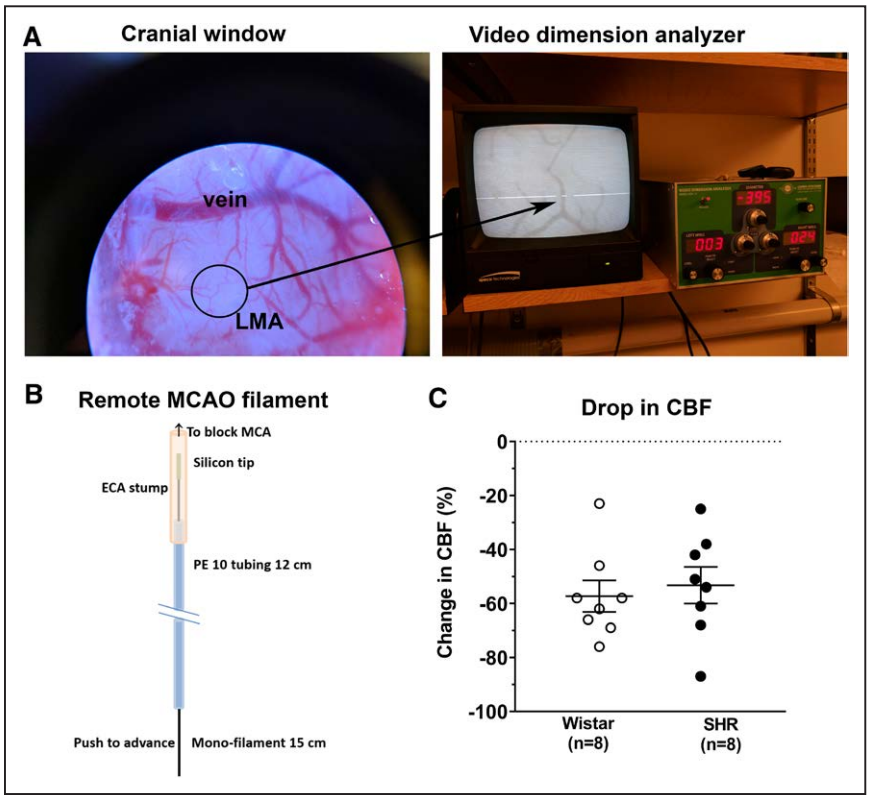

Figure 1. Visualization and measurement of leptomeningeal anastomoses (LMA) diameters and remote middle cerebral artery occlusion (MCAO). **A**, Photomicrograph showing a cranial window (**left**) that was used to visualize LMAs, defined as distal branches connecting middle and anterior cerebral arteries. Video microscopy (**right**) combined with video dimensional analysis was used to measure changes in diameter of LMAs continuously during the experiment. **B**, Diagram of the remote MCAO filament that was used to induce ischemia and reperfusion while animals were in the prone position. **C**, Graph showing the drop in cerebral blood flow (CBF) was similar during remote MCAO in spontaneously hypertensive rats (SHRs) and Wistar rats, measured using laser Doppler. MCA indicates middle cerebral artery.

blood-brain barrier and, therefore, changes in diameter most likely reflect the response to a change in blood pressure and not a direct vasosconstrictor effect.

Inclusion/Exclusion of Animals

A total of 7 animals were excluded from the study, making N=21 total. Exclusion was due to excessive bleeding and death (n=4), inability to place remote filament (n=1), or poor visualization through cranial window (n=2).

Data Calculations and Statistical Analysis

LMA diameters were measured first without EDTA buffer and were considered to be active diameters and tone. Addition of EDTA to fully relax LMA smooth muscle was considered passive diameters. This allowed for calculation of % tone. Myogenic tone was calculated as a percent decrease in maximally dilated (passive) LMA diameter in the presence of EDTA by the equation: $(1-(\phi_{tone}/\phi_{passive}))\times 100\%$; where ϕ_{tone} is the inner diameter of LMA with tone and $\phi_{passive}$ is the passive inner diameter. Data are presented as mean±SEM. One LMA per animal was measured over the course of the rMCAO experiment. A Mann-Whitney test was used to determine differences between the 2 groups using GraphPad Prism 7 (La Jolla, CA). Repeated measures ANOVA was used to determine differences within groups compared to baseline. Differences were considered significant at $P<0.05$.

Results

Baseline LMA Diameters and Basal Tone

Baseline diameters of LMAs were measured through the cranial window in Wistar and SHR before advancing the filament to induce rMCAO. In Wistar rats, active diameters of LMAs were not significantly different compared with their own passive diameters (Figure 2A). In SHR, however, active diameters of LMA were significantly smaller than that of the Wistar and were significantly smaller than their own passive diameters. The smaller lumen diameters of LMAs from SHR was not due to structurally smaller vessels (compared to fully passive in the presence of EDTA) but increased basal tone. Figure 2B shows that LMAs from SHR had significantly greater basal tone in vivo at baseline when compared with that of Wistar rats. Baseline blood pressures were also higher in SHR versus Wistar, as expected (136±4 versus 105±4; $P<0.01$). Arterial blood gases were in physiological ranges and not different between Wistar rats and SHR at baseline: pH: 7.41±0.01 and 7.44±0.02; P_{CO_2}: 40.04±1.11 and 38.76±2.24 mm Hg; P_{O_2}: 98.43±8.45 and 87.60±6.68 mm Hg, respectively.

Changes in LMA Tone During Transient Ischemia

The remote filament was advanced to initiate rMCAO, which was confirmed by a significant decrease in perfusion in the MCA territory measured by laser Doppler. Active diameters of LMAs were significantly smaller in SHR versus Wistar rats throughout rMCAO and recanalization to allow for reperfusion (Figure 3A). When percent tone was calculated, it showed that tone of LMA was also significantly higher in SHR compared with that of Wistar rats throughout rMCAO and reperfusion (Figure 3B). It is interesting to note that passive diameters of LMAs (in EDTA) in SHR were similar to that of Wistar rats (Figure 3A), suggesting inward remodeling did not occur in LMAs from SHR. Blood pressure was higher in SHR versus Wistar rats throughout the 2 hours of ischemia and 2 hours of reperfusion period (Figure 3C).

Figure 4A shows the percent tone during the first 15 minutes of ischemia (during filament occlusion) in both strains of rats. Notice that filament insertion caused a decrease in tone in LMAs from both Wistar and SHR that remained decreased from baseline during this period (Figure 4A). However, although LMA tone decreased in SHR, it remained considerably higher than that of Wistar rats. In fact, tone in LMAs from SHR remained at ≈30%. Interestingly, and in contrast to ischemia, reperfusion caused an increase in tone (vasoconstriction) in LMAs from both SHR and Wistar rats (Figure 4B). Again, tone was significantly increased in LMAs from SHR during reperfusion compared with Wistar. Figure 4C compares the percent tone in LMAs from Wistar and SHR at baseline, after 4 and 110 minutes of ischemia and after 10 minutes of reperfusion. After 4 and 110 minutes of ischemia, tone was decreased from baseline that was significant only in LMAs from SHR. However, reperfusion caused an increase in tone in both groups that was significant from baseline in LMAs from both Wistar and similar to baseline in SHR. Last, tone was increased in LMAs from SHR versus Wistar at all points analyzed.

Effect of Pressor Therapy on LMA Diameters and Tone

Acute hypertension was induced by phenylephrine infusion after 30 minutes of ischemia to investigate the response to pressor therapy and evaluate myogenic reactivity of LMAs in Wistar rats and SHR. Phenylephrine infusion increased

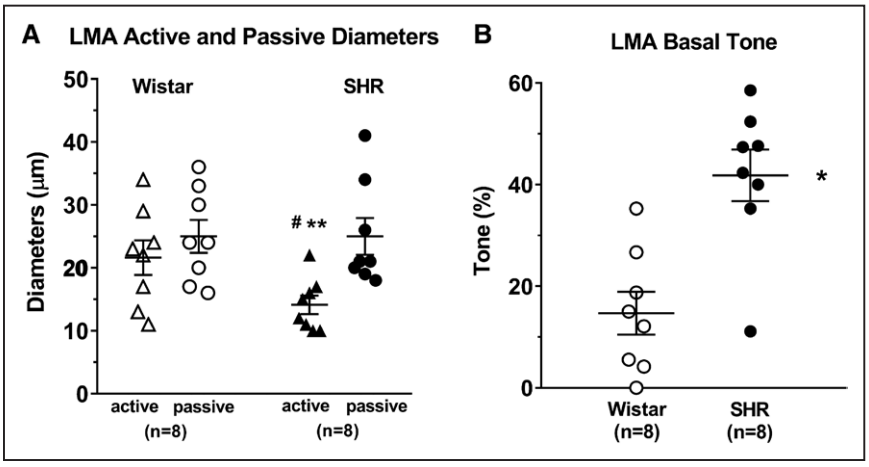

Figure 2. Baseline diameters and tone of leptomeningeal anastomoses (LMAs) from Wistar and spontaneously hypertensive rats (SHRs). **A**, Graphs showing active (basal conditions) and passive (in presence of ethylenediaminetetraacetic acid; EDTA) diameters of LMAs from Wistar and SHR. LMAs from SHR were considerably smaller compared with Wistar under active baseline conditions. There was no difference in LMA diameters between Wistar and SHR under passive conditions, suggesting a lack of inward remodeling in SHR. **$P<0.01$ vs SHR passive; #$P<0.05$ vs Wistar active. **B**, Percent tone of LMAs under baseline conditions calculated from passive diameters in EDTA. Under basal conditions, SHR had significantly increased tone compared with Wistar. *$P<0.05$ vs Wistar.

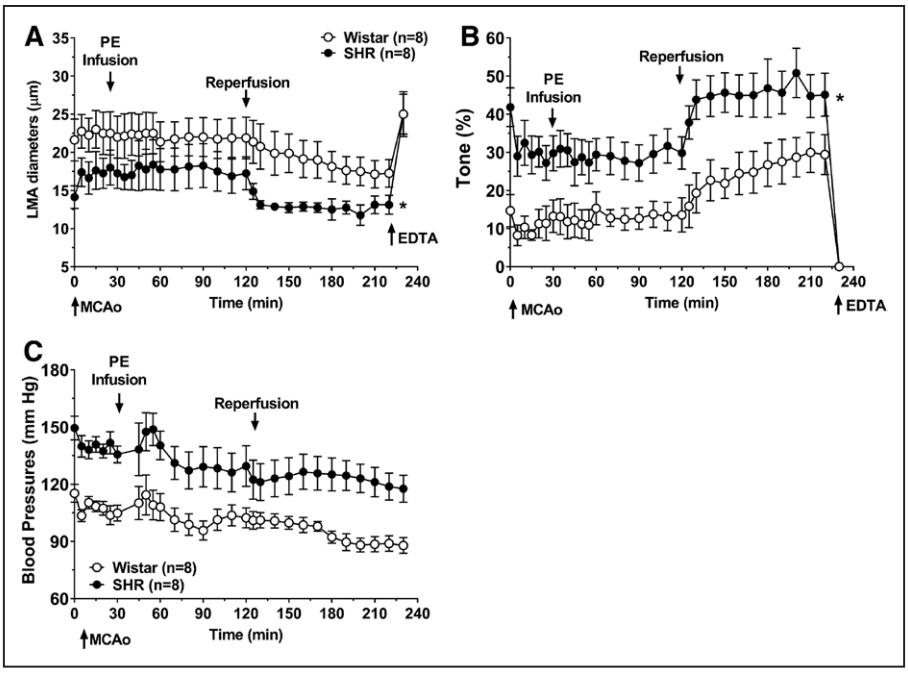

Figure 3. Changes in blood pressures, leptomeningeal anastomoses (LMA) diameters and tone during remote middle cerebral artery occlusion (MCAO). **A**, Graph showing LMA diameters measured via video microscopy during the entire experiment. Notice that LMAs from spontaneously hypertensive rats (SHRs) were considerably smaller throughout ischemia and reperfusion compared with Wistar. Addition of ethylenediaminetetraacetic acid (EDTA) to the cranial window caused vasodilation of LMAs from both groups. Ischemia caused modest vasodilation of LMAs in both groups that was not affected by phenylephrine (PE) infusion. However, reperfusion caused significant vasoconstriction of LMAs from both groups of animals. Diameters of LMAs were not different in EDTA suggesting hypertension did not cause inward remodeling. **B**, Percent tone of LMAs from Wistar and SHR during the entire experiment. Tone was considerably increased in LMAs from SHR during ischemia and reperfusion compared with Wistar rats. Filament insertion caused vasodilation and decreased tone in LMAs from both groups. PE infusion did not appreciably change tone in LMAs from either group. However, reperfusion caused an increase in tone in both SHR and Wistar rats, demonstrating active vasoconstriction. EDTA to inactivate smooth muscle decreased tone, as expected. **C**, Changes in blood pressure measured via femoral artery catheter over the course of the experiment. SHR had increased blood pressure compared with Wistar during the entire experiment. Filament insertion modestly decreased blood pressure in both strains, however, blood pressure in SHR remained high. PE infusion increased blood pressure in both SHR and Wistar that peaked after 30 min then declined. Reperfusion decreased blood pressure in both strains compared to baseline.

systemic blood pressure in both Wistar rats and SHR, with a more substantial increase in SHR that peaked at about 6 minutes of infusion (Figure 5A). Despite acute hypertension, LMA diameters remained relatively unchanged during phenylephrine infusion in both Wistar rats and SHR (Figure 5B). Similarly, the percent tone of LMAs remained relatively constant during acute hypertension in both groups (Figure 5C).

Discussion

Chronic hypertension has a profound effect on the cerebral circulation, including pial collaterals.[9] In the present study, LMAs from SHR had increased basal tone before rMCAO compared with normotensive Wistar rats that was maintained during ischemia and reperfusion. Although tone decreased in both strains of rats during filament occlusion, tone remained considerably higher in SHR compared with Wistar rats (Figure 4C). In fact, tone in LMAs from SHR did not decrease below ≈30% for the entire duration of ischemia. Infusion of phenylephrine to induce pressor therapy did not change diameters or tone in either strain, suggesting autoregulation may have been intact in this vascular territory. Last, reperfusion increased tone in both Wistar and SHR that was unrelated to changes in blood pressure (Figure 4).

The increased basal tone of LMAs from SHR is in agreement with our previous study using isolated LMAs and likely contributes to the poor stroke outcome in patients and animal models with chronic hypertension. Although relatively young animals (15–25 weeks old) were used in the current study that may not reflect the majority of hypertensive stroke patients, our previous study found no difference in LMA function between young and aged SHR.[9] Models of chronic hypertension, including SHR, stroke-prone SHR, and renal hypertension, have been shown to have larger core infarction and smaller amounts of salvageable tissue.[13–18] In addition, SHR and stroke-prone SHR have rapid evolution of infarction that encompasses the penumbra and poor recruitment of collaterals during LVO.[14,19,20] Vasoconstriction of LMAs before and during MCAO would likely be a primary contributor to the establishment and fate of the penumbra during MCAO. Although prior studies in mice and rats have shown no change in diameter of LMAs during MCAO, despite large increases in flow and shear stress, these studies used normotensive animals.[21,22] Vasoconstriction of LMAs during hypertension correlates well with animal studies showing poor collaterals and limited penumbra.[13–18] Clinical studies have also shown an association between history of hypertension and poor collateral status.[23–26] For example, chronic hypertension was significantly associated with poor collateral status in the acute phase of LVO, regardless of admission blood pressure.[26] In this study, 78% of patients without chronic hypertension had excellent

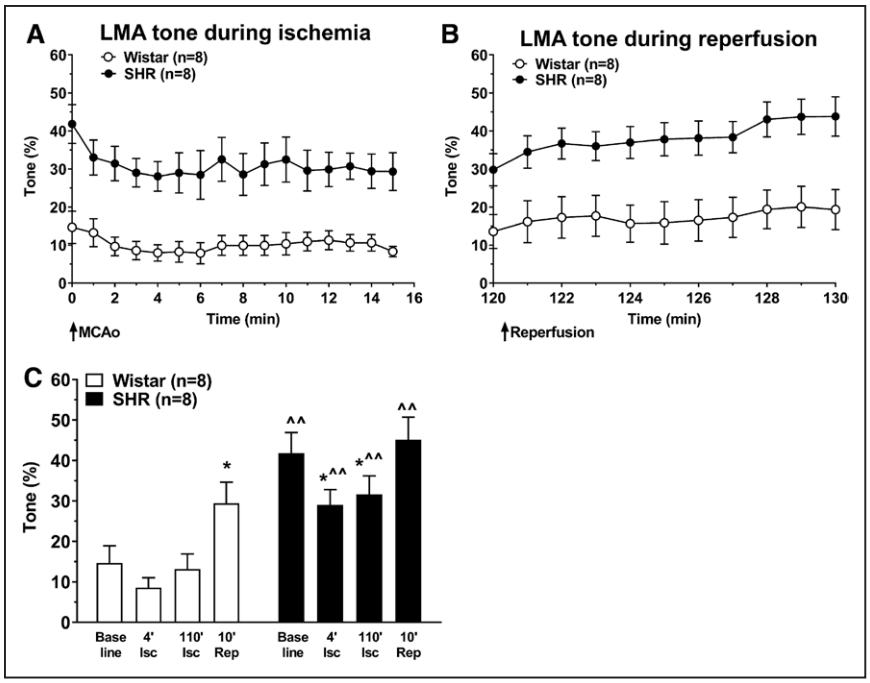

Figure 4. Changes in tone during acute middle cerebral artery occlusion (MCAO) and reperfusion. **A**, Percent tone of leptomeningeal anastomoses (LMAs) during the first 15 min of MCAO. Notice that while tone in LMAs decreased in both strains during acute ischemia, tone remained considerably higher (≈30%) in LMAs from spontaneously hypertensive rats (SHRs). **B**, Percent tone of LMAs during the first 10 min of reperfusion. Notice the tone increased in LMAs from both SHR and Wistar rats. **C**, Summary graph showing percent tone at baseline, after acute ischemia (4 min), after 110 min of ischemia and after 10 min of reperfusion. Tone decreased in LMAs during ischemia that was only significant in SHR. There was no difference in LMA tone after 4 min of ischemia compared with baseline in LMAs from Wistar rats. Reperfusion increased tone in LMAs from both strains such that both were similar to the level of tone in LMAs from SHR as baseline. *P<0.05 vs baseline; ^^P<0.01 vs Wistar.

collateral status, whereas only 20% of patients with chronic hypertension had excellent collateral status. Importantly, there was a graded effect of antihypertensive medication such that 55% of chronic hypertensive patients had excellent collateral status if on pharmacological antihypertensive medication. Excellent collateral status is generally defined as the majority of LMAs in LVO patients that are visible during angiography and, therefore, dilated to allow more blood flow. These findings demonstrate that chronic hypertension may adversely affect the function of LMAs in humans and that antihypertensive medication may improve that function. In that regard, a recent study showed that treatment of SHR with an ACE (angiotensin-converting enzyme) inhibitor, but not hydralazine, reversed LMA vasoconstriction in SHR.[27]

Augmenting collateral flow with induced or permissive hypertension is an attractive approach to salvaging tissue, but its efficacy has been difficult to prove clinically. In fact, there is no consensus on the optimal target for baseline blood pressure in acute stroke patients, adding to the difficulty of defining blood pressure parameters for poststroke therapy. Studies of the association between acute blood pressure and clinical outcomes are contradictory, with positive, negative,

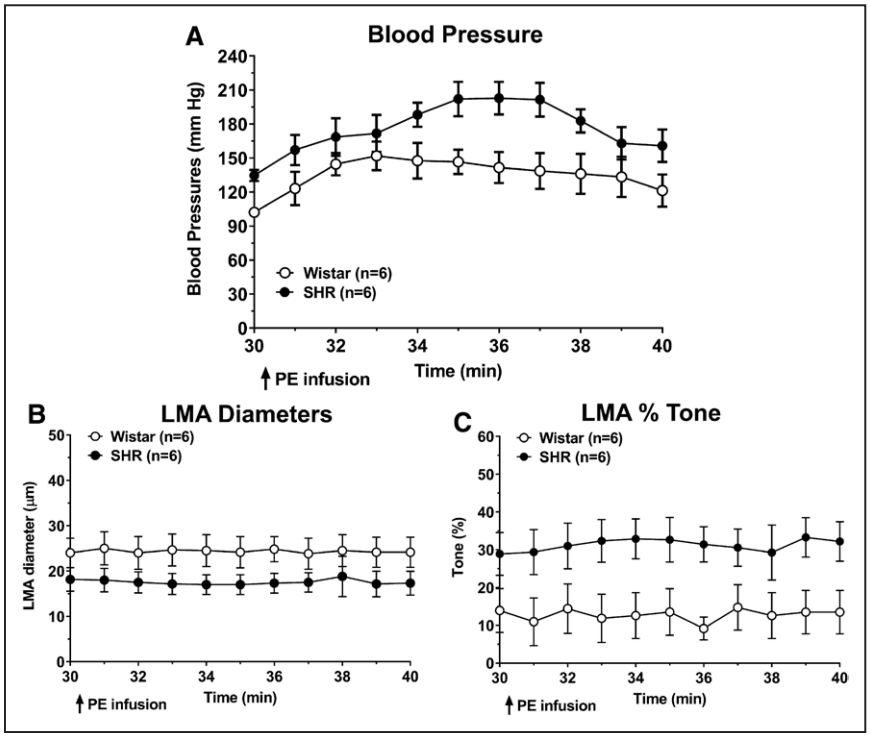

Figure 5. Changes in blood pressure, leptomeningeal anastomoses (LMA) diameters and tone during phenylephrine (PE) infusion. **A**, PE was infused after 30 min of middle cerebral artery occlusion (MCAO) and increased blood pressure in both Wistar and spontaneously hypertensive rats (SHRs). The pressor response appeared greater in SHRs. **B**, Diameter of LMAs from Wistar and SHRs in response to PE infusion. There was little change in diameter despite increased blood pressure in both groups. **C**, Percent tone of LMAs from Wistar and SHRs in response to PE infusion. There was little change in tone of LMAs from both groups.

and U-shaped correlations found, as well as a dependence on reperfusion status.[28–30] Comorbidities such as hypertension further confound this issue. An acute increase in blood pressure (≈35–45 mm Hg) has been shown to occur in patients with stroke, a response recapitulated in both normotensive and hypertensive rats.[31–33] This hypertensive response is thought to be due to sympathetic activation that may serve to increase cerebral perfusion.[32] This is supported by studies showing normalizing blood pressure is detrimental to stroke outcome in SHR.[31] In addition, increasing blood pressure as a means of augmenting flow to the ischemic region has been shown in animal studies to decrease infarction and improve neurological deficit.[34,35]

The results of the current study found that LMAs from SHR have highly vasoconstricted LMAs in vivo that remained constricted during phenylephrine infusion. While one interpretation of this finding is that pressure increased in these vessels during phenylephrine infusion, inducing a myogenic response in LMAs that was greater in SHR versus Wistar. However, we did not measure pressure or flow within these vessels and, therefore, cannot be certain that was the case. Alternatively, transmural pressure may not have increased if the pressure in distal MCA arterioles was low and the pressure drop across the distal ACA arteriole network sufficiently increased. If the former was the case, then pressor therapy may not be appropriate for patients with chronic hypertension since vasoconstriction of LMAs would limit collateral flow and possibly hasten collateral failure. Other therapies that selectively target LMA vasodilation may work better under conditions of chronic hypertension, as has been previously shown.[36,37] Further work is needed to understand the hemodynamic shift during occlusion and phenylephrine infusion and whether transmural pressure is increased that can induce myogenic responses.

An interesting finding was that filament withdraw to allow for reperfusion caused vasoconstriction of LMAs from both SHR and Wistar rats. The decrease in diameter was associated with modestly decreased blood pressure in both strains. Although this could be interpreted as a lack of autoregulation, that is, a passive response to decreased pressure, the myogenic tone in the vessels increased (calculated as a percent decrease in diameter from passive in EDTA) suggesting vasoconstriction. This finding suggests that reperfusion is associated with decreased penumbral flow and may relate to the evolution of infarction to encompass the penumbra even with reperfusion. We previously demonstrated that parenchymal arterioles had increased myogenic tone in vitro after 2 hours of ischemia and 30 minutes of reperfusion that was due to smooth muscle calcium sensitization.[38] The response of LMAs to reperfusion may be similar and that vasoconstriction could severely limit perfusion of distal tissues and contribute to impaired reperfusion, that is, no reflow as well as infarct expansion. The vasoconstrictive response of LMAs to reperfusion may reflect a myogenic response as reperfusion causes an increase in local pressure in LMAs as well as flow. This may serve to redistribute flow to the ischemic territory to recover function that may be limited by LMA vasoconstriction. This finding also highlights that recanalization does not always lead to complete reperfusion of distal tissue. In support of this interpretation, a previous study found that reperfusion cerebral blood flow decreased over time, both in the MCA and collateral territories.[37]

An interesting consideration is the stimulus that causes vasoconstriction of LMAs in response to reperfusion. LMAs experience unique hemodynamics—they exist under conditions of low flow and low shear stress during normal physiological conditions but are pressurized almost equally from ACA and MCA.[21,22] During occlusion, a large pressure differential is created in favor of increasing flow and shear stress from ACA to MCA.[21,22] During reperfusion, flow and shear stress drop due to the pressure gradients normalizing, restoring flow and shear stress to low levels.[21] Thus, there is potential for a large increase in pressure in LMAs during reperfusion that may cause a myogenic vasoconstriction. Another possibility is that shear stress changes rapidly from low and bidirectional to high and unidirectional during occlusion that is reversed during reperfusion. This change in shear stress may stimulate the endothelium to produce vasoactive factors. However, the vasoconstrictive response of LMAs to reperfusion was sustained and at a time when shear stress would return to low levels. Thus, it is more likely that the increase in intravascular pressure in LMAs underlies reperfusion-induced vasoconstriction.

There are several limitations to this study. First, we only measured changes in diameter and tone and not intravascular pressure within LMAs and therefore could not determine cerebrovascular resistance or flow. Although diameter is the most powerful determinant of flow, understanding the pressure gradients during ischemia and reperfusion is important to understand how LMA vasoconstriction influences hemodynamics. Other studies have used magnetic resonance imaging and laser-speckle contrast imaging in stroke-prone SHR and found poor collateral recruitment and flow during permanent MCAO that would support these findings.[14,20] Second, we measured only one LMA in each animal connecting ACA and MCA, where there were ≈10 of them in each rat.[39] Because of the complex hemodynamic relationship of LMAs being interconnected branches of ACA and MCA, we were unable to determine simultaneous diameter and tone changes in other related LMAs that may or may not be similar to the one studied. Third, although the current study investigated changes in tone, the in vivo approach precluded more detailed mechanistic studies on the function of LMAs. Our previous study using isolated and pressurized LMAs characterized a number of vascular parameters of these vessels from normotensive and hypertensive, young and aged animals; however, that study was done under nonischemic conditions and further studies are needed to investigate how pial collateral function may be altered during ischemia and reperfusion. Last, we studied the acute phase of stroke and, therefore, could not assess final brain injury or neurological deficit.

Perspectives

Chronic hypertension increased tone of pial collaterals both basally and in response to ischemia induced by filament occlusion. Phenylephrine infusion during ischemia did not alter baseline diameters in either strain, although tone was significantly higher in SHR. Reperfusion caused significant

vasoconstriction of LMAs from both SHR and Wistar rats, suggesting a functional response of these vessels that could contribute to collateral failure and poor outcome despite recanalization. Taken together, the effect of chronic hypertension on pial collaterals is one of vasoconstriction before and during ischemia and reperfusion. Understanding the underlying mechanisms by which hypertension and other comorbidities influence vascular function of LMAs could provide for appropriate therapies that target pial collaterals during ischemic stroke.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This study demonstrates that pial collaterals are vasoconstricted in spontaneously hypertensive rats basally and during ischemia and reperfusion. In addition, reperfusion caused vasoconstriction of pial collaterals from both Wistar and spontaneously hypertensive rats.

What Is Relevant?

- Increased tone of pial collaterals in spontaneously hypertensive rats may contribute to collateral failure during large vessel occlusion. Vasoconstriction of pial collaterals during reperfusion could contribute to infarct expansion in both normotensive and hypertensive animals and patients even when recanalization is achieved.

Summary

Pial collaterals are highly vasoconstricted in hypertensive rats before and during occlusion and reperfusion. Phenylephrine infusion during ischemia did not appreciably change diameter of pial collaterals that were vasoconstricted in spontaneously hypertensive rats, suggesting pressor therapy may not be appropriate for all patients.