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Cerebral Flow Velocities During Daily Activities Depend on Blood Pressure in Patients With Chronic Ischemic Infarctions

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Background and Purpose—Target blood pressure (BP) values for optimal cerebral perfusion after an ischemic stroke are still debated. We sought to examine the relationship between BP and cerebral blood flow velocities (BFVs) during daily activities.

Methods—We studied 43 patients with chronic large vessel ischemic infarctions in the middle cerebral artery territory (aged 64.2 ± 8.94 years; at 6.1 ± 4.9 years after stroke) and 67 age-matched control subjects. BFVs in middle cerebral arteries were measured during supine baseline, sitting, standing, and tilt. A regression analysis and a dynamic phase analysis were used to quantify the BP–BFV relationship.

Results—The mean arterial pressure was similar between the groups (89 ± 15 mm Hg). Baseline BFVs were lower by approximately 30% in the patients with stroke compared with the control subjects ($P=0.0001$). BFV declined further with postural changes and remained lower in the stroke group during sitting ($P=0.003$), standing ($P=0.003$), and tilt ($P=0.002$) as compared with the control group. Average BFVs on the stroke side were positively correlated with BP during baseline ($R=0.54$, $P=0.0022$, the slope 0.46 cm/s/mm Hg) and tilt ($R=0.52$, $P=0.0028$, the slope 0.40 cm/s/mm Hg). Regression analysis suggested that BFV may increase approximately 30% to 50% at mean BP >100 mm Hg. Orthostatic hypotension during the first minute of tilt or standing was independently associated with lower BFV on the stroke side ($P=0.0008$). Baseline BP–BFV phase shift derived from the phase analysis was smaller on the stroke side ($P=0.0006$).

Conclusion—We found that BFVs are lower in patients with stroke and daily activities such as standing could induce hypoperfusion. BFVs increase with mean arterial pressure >100 mm Hg. Dependency of BFV on arterial pressure may have implications for BP management after stroke. Further prospective investigations are needed to determine the impact of these findings on functional recovery and strategies to improve perfusion pressure during daily activities after ischemic stroke. (*Stroke*. 2010;41:61–66.)

Key Words: autoregulation ■ blood flow velocities ■ head-up tilt ■ ischemic stroke
■ standing ■ vasoreactivity multimodal pressure flow method

Ischemic stroke affects both cerebral autoregulation^{1,2} and autonomic blood pressure (BP) control.³ With impaired autoregulation, cerebral blood flow depends on perfusion pressure.⁴ Uncontrolled hypertension, labile BP, or hypotension during the acute phase of stroke worsen prognosis in terms of death and disability.^{2,5,6} Long-term hypertension and hypotension also impair autoregulation^{7,8} and increase the risk for recurrent strokes.⁹ Transcranial Doppler studies have shown that blood flow velocities (BFVs) decline on the infarcted side during head-up tilt, and BFV reduction was greater in young women with lower orthostatic BP.¹⁰ We posit that daily activities such as standing up may induce hypotension and increase the risk of hypoperfusion in older adults. This hypothesis has not been formally tested and the therapeutic range for long-term BP management in older patients with ischemic stroke is still debated.

We aimed to determine whether flow velocities are dependent on perfusion pressure after stroke. We investigated the BP and BFV relationships during postural changes in older people with chronic middle cerebral artery (MCA) infarctions. A better understanding of systemic pressure control is needed to achieve optimal perfusion during daily activities in stroke patient management and for future studies of stroke recovery.

Research Design and Methods

Subjects

Studies were conducted in the Syncope and Falls in the Elderly Laboratory at the Clinical Research Center and at the Magnetic Resonance Imaging Center at the Beth Israel Deaconess Medical Center. Participants were consecutively recruited and signed informed consent approved by the Beth Israel Deaconess Medical Center Institutional Review Board. The stroke group consisted of 43

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subjects with chronic hemispheric MCA infarcts documented on MRI or CT during the acute phase. They were studied at an average of 6.1 ± 4.9 years after stroke and were clinically stable. Neurological and functional status of stroke patients was assessed by the National Institutes of Health Stroke Scale and the modified Rankin Scale. The control group consisted of 67 age- and sex-matched control subjects with no clinical history of stroke and no focal deficits on neurological examination. Thirty-two of the patients with stroke and 35 of the control subjects were hypertensive. Hypertension status was defined as use of antihypertensive medications or BP $>140/85$ mm Hg^{11,12} on 24-hour BP monitoring. We excluded subjects with brain hemorrhage on MRI or CT, diabetes mellitus, significant arrhythmias, uncontrolled hypertension (systolic BP >180 and/or diastolic BP >100 mm Hg; or subjects taking ≥ 3 antihypertensives), morbid obesity, control subjects with carotid stenosis, or cases with contralateral stenosis $>50\%$ or any contraindications to MRI. Reasons for exclusion were: uncontrolled hypertension during taper (10), primary care physician did not allow taper (5), different stroke type (21), arrhythmia (2), body mass index >30 kg/m² (6), no insonation window (7), other causes (10; ie, carotid disease, psychiatric, unstable medical condition, MRI, and so on), and consent withdrawal (10). Antihypertensive medications were tapered and withdrawn for 3 days before the study with home BP monitoring.

Transcranial Doppler Studies

Studies were conducted in the morning after an overnight stay at the research center. MCAs were insonated with an ultrasound system equipped with a 3-dimensional positioning probe holder (PMD150; Spencer Technologies, Inc). Heart rate was measured using 3-lead electrocardiogram (SpaceLab Medical, Issaquah, Wash). Beat-to-beat BP was continuously recorded with a Finapres device (Ohmeda Monitoring Systems, Englewood, Colo) and corroborated with Dynamap BP measurements. Respiration and end-tidal CO₂ values were recorded (Capnomac Ultima; Ohmeda Monitoring Systems). The protocol conditions were: supine baseline (10 minutes), head-up tilt at 70° (10 minutes), sitting (5 minutes), and standing (3 minutes). CO₂ vasoreactivity was measured during hyperventilation (3 minutes) and rebreathing air with 5% CO₂ (3 minutes). All signals were continuously acquired at 500 Hz using a Labview 6.0, NIDAQ (National Instruments, Inc, Austin, Texas). Mean BP and BFV were calculated beat-to-beat for each condition and averaged over 30-second intervals.

Magnetic Resonance Imaging

MRI studies were performed on a 3-Tesla GE Signa Vhi or Excite MRI scanner using a quadrature and phase array head coils (GE Medical Systems, Milwaukee, Wis). High-resolution anatomic images were used to calculate infarct volume and diameters of intracranial vessels (3-dimensional magnetization prepared rapid gradient echo, fluid-attenuated inversion recovery, MR angiography).

Pressure–Flow Velocity Analysis

Cerebral autoregulation is assessed by methods that quantify the pressure–flow relationship.¹³ Dependency of blood flow on arterial pressure indicates impairment of autoregulation.⁴ The BP–BFV relationship was analyzed over 3 time periods (minutes, seconds, and beat-to-beat) to capture the dynamics of autoregulation: (1) a regression analysis was used to determine the relationship between BP and BFV averaged over baseline and tilt and (2) using 30-second BP and BFV segments. The slope of regression indicates the change in BFV relative to BP; a larger slope indicates greater BFV dependence on BP; (3) BP–BFV phase shift was quantified using a multimodal pressure flow method.¹⁴ As previously described, this method is based on a nonlinear approach that uses empirical signal decomposition and Hilbert transformation to calculate the instantaneous pressure–flow velocity phase relationship from spontaneous BP and BFV fluctuations^{15–17} or those induced by the Valsalva maneuver.¹⁴ The multimodal pressure flow method has no requirements for signal linearity and stability and thus has greater sensitivity

and specificity for detection of autoregulation impairment than Fourier transform-based methods.¹⁸ The instantaneous BP–BFV phase shift was calculated using spontaneous BP and BFV oscillations and averaged for each condition.

Statistical Analysis

Descriptive statistics were used to summarize all variables. Demographic and laboratory variables were compared between the groups using one-way analysis of variance. Among the stroke group, mean BFV values were compared between the stroke side and nonstroke side. In the control group, mean BFV values were randomized between the right and left hemispheres to match the distribution of infarcts in each hemisphere in the stroke group. BFV on the stroke side was compared with the control group randomized side 1 (RND 1) and BFV on the nonstroke side was compared with the randomized side 2 (RND 2). Between the groups, mean BFV values were compared using the least square models and repeated measures or 2-way multivariate analysis of variance with adjustments for age, sex, infarct side, and RND sides 1 and 2. Between-group comparisons within each condition were done using analysis of variance. The effects of infarct volume, MCA and internal carotid artery diameters, CO₂, systolic BP, body mass index, hypertension, National Institutes of Health Stroke Scale, and modified Rankin Scale were assessed using the same approaches. BP–BFV phase shift during baseline and tilt were analyzed using the same approach. Data are presented as mean \pm SD.

Results

Demographic and Laboratory Measures

The stroke group consisted of 43 subjects with chronic large artery MCA infarctions (24 right; 19 left hemisphere) and 67 matched control subjects (Table). Demographic characteristics, BP, MCA and internal carotid artery diameters, and laboratory results were similar between the groups. The stroke group had lower total ($P=0.0015$) and low-density lipoprotein cholesterol ($P=0.01$), because 30 cases were treated with statins.

Stroke Versus Nonstroke Group

BFVs in both MCAs were lower in the stroke group compared with the control group at baseline and during postural challenges (Figure 1A): baseline (stroke side: $P<0.0001$; nonstroke side: $P<0.0001$), tilt ($P=0.002$, $P=0.0005$), sitting ($P=0.003$, $P=0.001$), and standing ($P=0.003$, $P=0.01$). BFV was not different between the stroke and nonstroke sides ($P>0.3$). BFV declined by approximately 13% on the stroke side in upright positions and also declined in the control group ($P=0.006$). Mean BP increased by approximately 3 to 6 mm Hg (Figure 1B) and heart rate by approximately 10 to 16 beats/min ($P<0.0001$; Figure 1C) in upright positions in both groups. Therefore, for similar BP levels, BFV remained lower in the stroke group in the supine and upright positions.

Pressure–Flow Velocity Relationship

We used a regression analysis to quantify the BP–BFV relationship during baseline and tilt. Average BFVs were positively correlated with BP on the stroke side (or RND 1 in hypertensive control subjects) during baseline ($R=0.39$, $P=0.0022$, the slope 0.46 cm/s/mm Hg) and tilt ($R=0.37$, $P=0.0028$, the slope 0.40 cm/s/mm Hg; Figure 2A–B) in the stroke subjects and control hypertensive subjects. Mean BP was within the autoregulated range (stroke group: 70 to 125 mm Hg and control group: 70 to 150 mm Hg). BP and

Table. Demographic Characteristics and Laboratory Results

Group	Stroke	Control	P
Age, years	64.21 (± 8.94)	64.48 (± 8.07)	0.87
Sex, male, female	23, 20 (43)	23, 44 (67)	N=110
Race, W, A, AI, AA, U	37, 1, 0, 5, 0	54, 2, 1, 9, 1	
Body mass index, kg/m ²	27.53 (± 4.74)	27.59 (± 6.48)	0.95
Systolic BP, mm Hg	129.66 (± 15.28)	129.43 (± 21.18)	0.95
Diastolic BP, mm Hg	61.33 (± 9.68)	67.44 (± 15.48)	0.02
Years after stroke	6.05 (± 4.88)
Stroke side, right, left	24, 19
Infarct volume, cm ³	18.69 (± 34.06)
National Institutes of Health Stroke Scale	2.71 (± 2.72)
Modified Rankin Scale	1.2 (± 1.14)
Hypertension by 24-hour BP	32	35	
Use of antihypertensives	30	33	
MCA right diameters	2.24 (± 0.62)	2.44 (± 0.26)	0.15
MCA left diameter	2.47 (± 0.32)	2.48 (± 0.28)	0.98
Internal carotid artery right diameter	5.02 (± 0.35)	5.39 (± 0.46)	0.04
Internal carotid artery left diameter	5.32 (± 0.47)	5.39 (± 0.47)	0.70
White blood cell count, k/ μ L	7.03 (± 0.29)	6.56 (± 0.27)	0.24
Hemoglobin, g/dL	13.75 (± 1.32)	13.84 (± 1.33)	0.74
Hematocrit, %	40.41 (± 3.73)	40.58 (± 3.30)	0.80
Cholesterol, mg/dL	177.79 (± 40.03)	203.83 (± 35.19)	0.0015
Low-density lipoprotein, mg/dL	92.71 (± 32.77)	110.81 (± 32.86)	0.01
Triglycerides, mg/dL	140.31 (± 87.16)	149.50 (± 68.98)	0.58
History of syncope/OH-min 1	7/10	11/21	0.08
Statins, yes/no	30/13	12/54	0.0001

Continuous variables are presented as mean \pm SD. Ordinal variables are presented as mean \pm SD (range). Nominal variables are presented as numbers. Comparison is not significantly different if $P>0.05$.

W indicates white; A, Asian; AI, American Indian; AA, African American; U, unknown.

BFV were not correlated on the nonstroke side or in normotensive control subjects. We have identified 11 patients with stroke with a mean BP <96 mm Hg (mean+1 SD for the control group) and mean BFV <36 cm/s (mean-1 SD for the control group). Based on our regression equation (mean BFV = $2.5 + 0.46 \times \text{mean BP}$) by increasing mean arterial pressure to 100 to 120 mm Hg (systolic BP 120 to 145 mm Hg and diastolic BP 75 to 95 mm Hg), mean BFV would increase to approximately 48.5 to 57.5 cm/s (ie, 30% to 55% increase), which is a normal range.

We also calculated a regression of 30-second BP and BFV segments between baseline and tilt for each subject. The slope of regression was steeper on the stroke side (0.33 ± 0.10 cm/s/mm Hg) compared with the control group (-0.09 ± 0.95

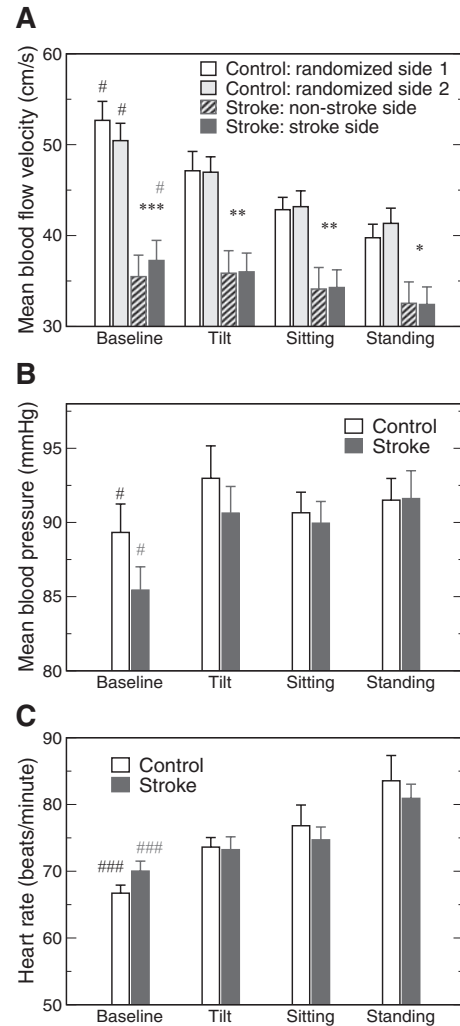


Figure 1. Mean BFVs in MCAs (A), mean BP (B), and heart rate (C) for the control group (RND 1 and 2) and for the stroke group (stroke and nonstroke side) during supine baseline, tilt, sitting, and standing. *Between-group comparisons: * $P<0.05$, ** $P<0.001$, and *** $P<0.0001$. #Comparisons between conditions within each group (mean \pm SE).

$P=0.028$), but not on the nonstroke side. Correlation coefficient ($R=0.36$ to 0.54) was similar between the groups.

We used instantaneous BP-BFV phase shift to assess dynamic autoregulation. A smaller BP-BFV phase shift indicates that BFV follows spontaneous BP fluctuations. In the stroke group, BP-BFV phase was smaller during baseline (stroke side: $4.73^\circ \pm 18.4^\circ$ versus $22.2^\circ \pm 22.5^\circ$, $P=0.0006$ and nonstroke side: $9.03^\circ \pm 22.5^\circ$ versus $20.4^\circ \pm 18.8^\circ$, $P=0.01$) and borderline during tilt (stroke side $4.64^\circ \pm 14.2^\circ$ versus $10.4^\circ \pm 10.7^\circ$, $P=0.046$; nonstroke side: $4.7^\circ \pm 14.1^\circ$ versus $7.8^\circ \pm 11.5^\circ$, nonsignificant) compared with control subjects.

Vasoreactivity to CO_2 challenges was smaller in the stroke group compared with control subjects (stroke side $0.49\% \pm 1.2\%$ versus $0.88\% \pm 0.49\%$, $P=0.03$ and nonstroke side $0.59\% \pm 0.87\%$ versus $0.94\% \pm 0.46\%$, $P=0.023$).

Orthostatic Hypotension

Transient orthostatic hypotension, defined as systolic/diastolic BP reduction $>20/10$ mm Hg during the first minute of

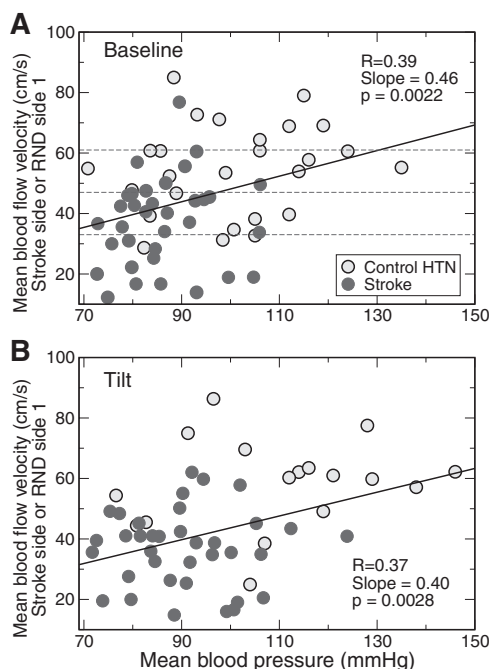


Figure 2. A linear regression of mean BFV and BP during baseline (A) and tilt (B) in the stroke group (dark circles) and hypertensive control subjects (open circles). Normotensive control subjects had no relationship between BP and BFV; not displayed for picture clarity. Dotted lines indicate BFV range in the control group (mean \pm SD).

upright posture, was detected in 23.3% participants in the stroke group (8 stroke hypertensive and 2 stroke normotensive) and 31.3% in the control group. Orthostatic hypotension was independently associated with lower BFV on the stroke side ($P=0.0008$), but not on the nonstroke side ($P=0.58$), after adjustment for age, sex, and condition. Dizziness was not correlated with orthostatic hypotension in the stroke group. Absence of autonomic symptoms was associated with higher modified Rankin Scale ($P=0.001$) independent of infarct volume.

Stratification of Patients With Stroke by Hypertension Status

BFVs at similar BP levels were not significantly different between stroke normotensive and hypertensive subjects. BFVs were lower in stroke normotensive subjects compared with normotensive control subjects during baseline, tilt, sitting, and standing (stroke side $P=0.02$, nonstroke side $P=0.002$; Figure 3A–B). BFVs were also lower in stroke hypertensive patients compared with hypertensive control subjects during baseline and tilt, but were similar during sitting and standing (stroke side $P=0.001$ and nonstroke side, $P=0.05$; Figure 3A–B). BP was higher in participants with hypertension ($P<0.001$). Statins had no significant effects on BFV.

Discussion

This study addressed a clinically important topic on the pressure–flow relationship in older adults with chronic ischemic infarctions.

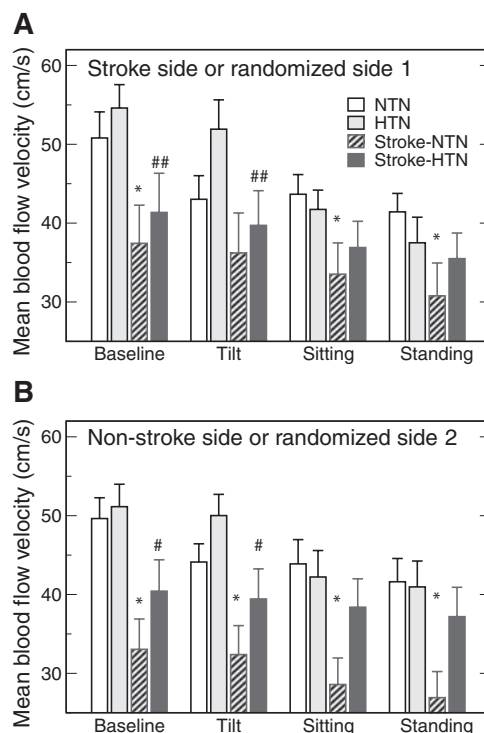


Figure 3. Comparisons of mean BFV in stroke normotensive and stroke hypertensive subjects on the stroke (A) and nonstroke sides (B) and in the nonstroke normotensive and nonstroke hypertensive groups (RND 1 and 2) during supine baseline, tilt, sitting, and standing. *Comparisons between stroke normotensive and nonstroke normotensive subjects: $*P<0.05$ and $**P<0.001$. #Comparisons between hypertensive and stroke hypertensive subjects: $\#P<0.05$ and $##P<0.001$ (mean \pm SE).

We showed that BFVs were reduced in the patients with stroke and were dependent on perfusion pressure. Baseline BFVs were lower by approximately 30% in the cases compared with the control subjects and declined further by approximately 13% on the stroke side in upright positions. Goals for arterial pressure management after stroke are still debated.^{19,20} The unresolved issues are whether BP management should target the levels $<135/85$ mm Hg recommended for optimal hypertension control.^{12,21} Concerns remain whether aggressive BP control would bring benefits or increase the risk of hypotension and hypoperfusion. We found that BFV on the stroke side was dependent on BP and that by increasing mean BP above 100 mm Hg (systolic BP 120 to 145 mm Hg and diastolic BP 75 to 95 mm Hg), mean BFV would increase to approximately 48.5 to 57.5 cm/s. These BFV values correspond to a normal perfusion in the MCA territory (35 ± 10 mL/100 g/min).²² BFV dependency on BP indicates a deficient or exhausted vasomotor reserve. BFV may decline even more for BP below an autoregulated range. Therefore, the range of perfusion pressures that would prevent BFV decline may be narrow.

Transient hypotension was associated with lower BFV on the stroke side. Orthostatic hypotension affects 5% to 18% of the elderly population,^{23,24} and was identified as an independent predictor of ischemic stroke⁹ and all-cause mortality after adjustment for risk factors.²⁵ Therefore, hypotension may contribute to repetitive hypoperfusion during daily

activities, and unawareness of these episodes may contribute to falls and worse outcomes. Establishing a clinical significance of BFV reduction during transient hypotension requires further prospective investigations. Our study was cross-sectional; participants were clinically stable and were studied off antihypertensive therapy. However, it is of interest that the absence of autonomic symptoms in our study was associated with higher modified Rankin Scale score independent of infarct volume. Our findings do not necessarily conflict with the benefits shown in clinical trials from using antihypertensives after stroke. It is possible that the benefit-harm ratio of BP-lowering and its impact on BFV depends on a combination of factors, including the patient's comorbidities that affect the BP profile and responses to daily activities. Furthermore, patients with orthostatic hypotension often have supine hypertension at night. Therefore, antihypertensive therapy needed to lower supine hypertension at night could be beneficial.

Our study provides information about dynamics of BFV regulation during daily activities and showed that the BP-BFV relationship is altered after stroke. We previously showed that ischemic stroke affects chronically regional perfusion and CO₂ vasoreactivity in main vascular territories.²² Vasodilation responses to hypercapnia were markedly reduced, but vasoconstriction responses to hypocapnia were preserved or even exaggerated. Supporting this notion are findings of lower BFV, higher cerebrovascular resistance, and exaggerated vasoconstriction responses to hypocapnia in younger patients with stroke¹⁰ and orthostatic intolerance during tilt.²⁶ Cerebral oxygenation and blood volume in the frontal lobes, measured by near infrared spectroscopy, diminished during active standing in elderly people despite increased systolic BP.²⁷ Small vessels in the infarcted hemisphere may be nearly maximally dilated and so be unable to respond adequately and to further augment perfusion during BP challenges. Our study has other limitations. We studied selected patients with large vessel MCA territory infarcts. Thus, it is unclear if these findings can be generalized to larger population, other stroke subtypes, and vascular territories. Similarly, we excluded stroke subjects with uncontrolled hypertension and high BP during taper, which limits the applicability of our findings to this population. A prospective study is needed to establish a cause-effect relationship between BP levels, autoregulation, and functional outcomes in other stroke subtypes and patients treated with antihypertensive therapy.

In conclusion, we showed that cerebral flow velocities are dependent on systemic pressure in older people with chronic ischemic infarctions; that activities of daily living may induce hypotension and transient hypoperfusion; and that increasing BP may increase flow velocities and improve perfusion pressure. Our study indicates that Doppler-based assessment of vasomotor responses, which can be done in the office setting, can be potentially used to guide the management of systemic pressure after stroke and to develop therapies to improve perfusion after stroke.

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Disclosures

None.

References

1. Immink RV, van Montfals GA, Stam J, Karemaker JM, Diamant M, van Lieshout JJ. Dynamic cerebral autoregulation in acute lacunar and middle cerebral artery territory ischemic stroke. *Stroke*. 2005;36:2595–2600.
2. Eames PJ, Blake MJ, Dawson SL, Panerai RB, Potter J. Dynamic cerebral autoregulation and beat-to-beat blood pressure control are impaired in acute ischaemic stroke. *J Neurol Neurosurg Psychiatry*. 2002;72:467–473.
3. Dawson SL, Evans SN, Manktelow BN, Fotherby MD, Robinson TG, Potter JF. Diurnal blood pressure change varies with stroke subtype in the acute phase. *Stroke*. 1998;29:1519–1524.
4. Aaslid R. Cerebral hemodynamics. In: Newell DW, Aaslid R, eds. *Transcranial Doppler*. New York: Raven Press; 1992:49–55.
5. Dawson SL, Bradley TD, Manktelow BN, Robinson TG, Panerai RB, Potter JF. Which parameters of beat-to-beat blood pressure and variability best predict early outcome after acute ischemic stroke? *Stroke*. 2000;31:463–468.
6. Schwarz S, Georgiades A, Aschoff A, Schwab S. Effects of induced hypertension on intracranial pressure and flow velocities of the middle cerebral arteries in patients with large hemispheric stroke. *Stroke*. 2002;33:998–1004.
7. Novak V, Novak P, Spies JM, Low PA. Autoregulation of cerebral blood flow in orthostatic hypotension. *Stroke*. 1998;29:104–111.
8. Lipsitz LA, Gagnon M, Vyas M, Iloputaife I, Kiely DK, Sorond F, Serrador J, Cheng DM, Babikian V, Cuppler LA. Antihypertensive therapy increases cerebral blood flow and carotid distensibility in hypertensive elderly subjects. *Hypertension*. 2005;45:216–221.
9. Eigenbrodt ML, Rose KM, Couper DJ, Arnett DK, Smith R, Jones D. Orthostatic hypotension as a risk factor for stroke. The Atherosclerosis Risk in Communities (ARIC) Study, 1987–1996. *Stroke*. 2000;31:2307–2313.
10. Novak V, Chowdhary A, Farrar B, Nagaraja H, Braun J, Kanard R, Novak P, Slivka A. Altered cerebral vasoregulation in hypertension and stroke. *Neurology*. 2003;60:1657–1663.
11. O'Brien E, O'Malley K. Evaluation of blood pressure measuring devices with special reference to ambulatory systems. *J Hypertens Suppl*. 1990;8:S133–S139.
12. O'Brien E, Asmar R, Beilin L, Imai Y, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *J Hypertens*. 2005;23:697–701.
13. Aaslid R, Newell DW, Stooss R, Sorteberg W, Lindegaard K. Assessment of cerebral autoregulation dynamics from simultaneous arterial and venous transcranial Doppler recordings in humans. *Stroke*. 1991;22:1148–1154.
14. Novak V, Yang ACC, Lepicovsky L, Goldberger AL, Lipsitz LA, Peng CK. Multimodal pressure-flow method to assess dynamics of cerebral autoregulation in stroke and hypertension. *BioMedical Engineering Online*. 2004;3:39. Available at <http://www.biomedical-engineering-online.com/>. Accessed on November 18, 2009.

15. Hu K, Peng CK, Czosnyka M, Zhao P, Novak V. Nonlinear assessment of cerebral autoregulation from spontaneous blood pressure and cerebral blood flow fluctuations. *Cardiovasc Eng*. 2008;8:60–71.
16. Hu K, Lo M-T, Peng CK, Novak V, Schmidt EA, Kumar A, Czosnyka M. Nonlinear pressure–flow relationship is able to detect asymmetry of brain blood circulation associated with midline shift. *J Neurotrauma*. 2009;26:227–233.
17. Lo MT, Hu K, Liu Y, Peng CK, Novak V. Multimodal pressure flow analysis: application of Hilbert Huang transform in cerebral blood flow regulation. *EURASIP J Appl Signal Processing*. 2008;2008:785243.
18. Lo MT, Novak V, Peng CK, Liu Y, Hu K. Nonlinear phase interaction between nonstationary signals: a comparison study of methods based on Hilbert-Huang and Fourier transforms. *Phys Rev E Stat Nonlin Soft Matter Phys*. 2009;79:061924.
19. Voko Z, Bots ML, Hofman A, Koudstaal PJ, Witteman JCM, Breteler MMB. J-shaped relation between blood pressure and stroke in treated hypertensives. *Hypertension*. 1999;34:1181–1185.
20. Sleight P, Redon J, Verdecchia P, Mancia G, Gao P, Fagard R, Schumacher H, Weber M, Bohm M, Williams B, Pogue J, Koon T, Yusuf S. Prognostic value of blood pressure in patients with high vascular risk in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial study. *J Hypertens* 2009 June 5 [Epub ahead of print].
21. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens*. 2003;21:821–848.
22. Zhao P, Alsop D, Abduljalil A, Selim M, Lipsitz L, Novak P, Caplan L, Hu K, Novak V. Altered vasoreactivity and peri-infarct hyperintensities affect multiple territories in stroke. *Neurology*. 2009;72:643–649.
23. Rutan GH, Hermanson B, Bild DE, Kittner SJ, LaBaw F, Tell GS. Orthostatic hypotension in older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. *Hypertension*. 1992;19:508–519.
24. Chokroverty S, Barron KD, Katz FH, Del Greco F, Sharp JT. The syndrome of primary orthostatic hypotension. *Brain*. 1969;92:743–768.
25. Rose KM, Eigenbrodt ML, Biga RL, Couper DJ, Light KC, Sharrett AR, Heiss G. Orthostatic hypotension predicts mortality in middle-aged adults: the Atherosclerosis Risk In Communities (ARIC) Study. *Circulation*. 2006;114:630–636.
26. Novak V, Spies JM, Novak P, McPhee BR, Rummans TA, Low PA. Hypocapnia and cerebral hypoperfusion in orthostatic intolerance. *Stroke*. 1998;29:1876–1881.
27. Mehagnoul-Schipper DJ, Colier WN, Jansen RW. Reproducibility of orthostatic changes in cerebral oxygenation in healthy subjects aged 70 years and older. *Clin Physiol*. 2001;21:77–84.