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Cerebral flow velocities during daily activities depend on blood pressure in patients with chronic ischemic infarctions

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Abstract

Background—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 (BFV) during daily activities.

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

Results—The mean arterial pressure was similar between the groups (89±15 mmHg). Baseline BFV were lower by ~ 30% in the stroke patients compared to the controls (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 to the control group. Average BFV 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 ~ 30-50% at mean BP > 100 mmHg. 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 BFV are lower in stroke patients and daily activities such as standing could induce hypoperfusion. BFV increase with mean arterial pressure > 100 mmHg. 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.

Keywords

Ischemic stroke; blood flow velocities; head-up tilt; standing; autoregulation; vasoreactivity multimodal pressure flow method

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Introduction

Ischemic stroke affects both cerebral autoregulation [1, 2] and autonomic blood pressure (BP) control[3]. With impaired autoregulation, cerebral blood flow depends on perfusion pressure4. 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 (BFV) 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 (BIDMC). Participants were consecutively recruited and signed informed consent approved by the BIDMC Institutional Review Board. The stroke group consisted of 43 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 NIHSS and Modified Rankin Scales (MRS). The control group consisted of 67 age- and sex-matched controls, with no clinical history of stroke and no focal deficits on neurological examination. Thirty-two of the stroke patients and 35 of the controls 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; controls with carotid stenosis or cases with contralateral stenosis > 50%; 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), BMI >30 (6), no insonation window (7), other causes (10) (i.e. carotid disease, psychiatric, unstable medical condition, MRI etc.) and consent withdrawal (10). Antihypertensive medications were tapered and withdrawn for 3 days prior to 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 3-D positioning probe holder (PMD150 Spencer Technologies, Inc., WA). Heart rate was measured using 3-lead electrocardiogram (SpaceLab Medical, Issaquah, WA). Beat-to-beat BP was continuously recorded with Finapress device (Ohmeda Monitoring Systems, Englewood, CO) and corroborated with Dynamap BP measurements. Respiration and end-tidal CO_2 values were recorded (Capnomac Ultima, Ohmeda Monitoring Systems, Englewood, CO). The protocol conditions were: supine baseline (10 minutes), head-up tilt at 70° (10 minutes), sitting (5

minutes), standing (3 minutes). CO_2 vasoreactivity was measured during hyperventilation (3 minutes) and re-breathing air with of 5% CO_2. (3 minutes). All signals were continuously acquired at 500 Hz using a Labview 6.0, NIDAQ (National Instruments, Inc. Austin, TX). 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, WI). High-resolution anatomical images were used to calculate infarct volume and diameters of intracranial vessels (3D magnetization prepared rapid gradient echo (MP-RAGE), fluid attenuated inversion recovery (FLAIR), magnetic resonance angiography (MRA)).

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 slope closer to 1.0 indicates greater BFV dependence on BP. 3) BP-BFV phase shift was quantified using a multimodal pressure flow method (MMPF).[14] As previously described, MMPF is based on a nonlinear approach that uses empirical signal decomposition and Hilbert Huang transformation to calculate the instantaneous pressure-flow velocity phase relationship from spontaneous BP and BFV fluctuations15،16، 17 or those induced by the Valsalva maneuver. [14]The MMPF 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 ANOVA. Among the stroke group, mean BFV values were compared between the stroke side and non-stroke 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 to the control group randomized side 1 (RND 1), and BFV on the non-stroke side was compared to 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 MANOVA with adjustments for age, sex, infarct side and RND side 1 and 2. Between groups comparisons within each condition were done using ANOVA. The effects of infarct volume, MCA and internal carotid artery (ICA) diameters, CO_2, systolic BP, BMI, hypertension, NIHSS and MRS were assessed using the same approaches. BP-BFV phase shift during baseline and tilt were analyzed using same approach. Data are presented as mean±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 controls (Table 1). Demographic characteristics, BP, MCA

and ICA diameters and laboratory results were similar between the groups. The stroke group had lower total (p=0.0015) and LDL cholesterol (p=0.01), as 30 cases were treated with statins.

Stroke vs. non-stroke group

BFVs in both MCAs were lower in the stroke group compared to the control group at baseline and during postural challenges (Figure 1A): baseline (stroke side: p=<0.0001; non-stroke side: p=<0.0001); tilt (p=0.002, p=0.0005); sitting (p=0.003, p=0.001), and standing (p=0.003 and p=0.01). BFV was not different between the stroke and non-stroke sides (p>0.3). BFV declined by ~13% on the stroke side in upright positions and also declined in the control group (p=0.006). Mean BP increased by ~ 3-6 mm Hg (Figure 1B) and heart rate by ~ 10-16 bpm (p<0.0001) (Figure 1C) 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 BP-BFV relationship during baseline and tilt. Average BFV were positively correlated with BP on the stroke side (or RND 1 in hypertensive controls) 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) (Figure 2 A, B). Mean BP was within the autoregulated range (stroke group: 70-125 mm Hg and control group: 70-150 mm Hg). BP and BFV were not correlated on the non-stroke side, and in normotensive controls. We have identified 11 stroke patients with mean BP < 96 mm Hg (mean+1SD for the control group) and mean BFV < 36 cm/s (mean-1SD for the control group). Based on our regression equation (mean BFV = 2.5+0.46*mean BP), by increasing mean arterial pressure to 100-120 mmHg (systolic BP 120-145 mm Hg and diastolic BP 75-95 mm Hg), mean BFV would increase by ~ 30-55% to 48.5-57.7 cm/s, 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 to the control group (−0.09±0.95 p=0.028), but not on the non-stroke side. Correlation coefficient (R = 0.36-0.54) 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±18.4 vs. 22.2±22.5°, p=0.0006 and non-stroke side: 9.03±22.5 vs. 20.4±18.8°, p=0.01) and borderline during tilt (stroke side 4.64±14.2 vs. 10.4±10.7°, p=0.046; non-stroke side: 4.7±14.1 vs. 7.8±11.5°, NS) compared to controls.

Vasoreactivity to CO_2 challenges was smaller in the stroke group compared to controls (stroke side 0.49±1.2 vs.0.88±0.49%, p=0.03 and non-stroke side 0.59 ± 0.87 vs.0.94±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 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 non-stroke side (p=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 mRS (p=0.001) independent of infarct volume.

Stratification of stroke patients by hypertension status

BFV at similar BP levels, were not significantly different between stroke-normotensive and hypertensive-subjects. BFV were lower in stroke-normotensive subjects compared to normotensive controls during baseline, tilt, sitting and standing (stroke side p=0.02, non-stroke side p=0.002) (Figure 3 A, B). BFV were also lower in stroke-hypertensive patients compared to hypertensive controls during baseline and tilt, but were similar during sitting and standing (stroke-side p=0.001 and non-stroke side, p=0.05) (Figure 3 A, 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.

We showed that BFV were reduced in the stroke patients, and were dependent on perfusion pressure. Baseline BFV were lower by ~30% in the cases compared to the controls and declined further by ~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 mmHg recommended for optimal hypertension control. [12,21]. Concerns remain, whether an 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 120-145 mm Hg and diastolic BP 75-95 mm Hg), mean BFV would increase by ~ 30-55% to 48.5-57.7 cm/s. These BFV values correspond to a normal perfusion in MCA territory (35±10 mL/100g/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 5-18% of the elderly population,[23,24] and identified as an independent predictor of ischemic stroke [9] 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 mRS 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 patient's comorbidities that affect BP profile and responses to daily activities. Furthermore, patients with orthostatic hypotension often have supine hypertension at night. Therefore, antihypertensive therapy needed to lower of supine hypertension at night could be beneficial.

Our study provides information about dynamics of BFV regulation during daily activities, and showed that BP-BFV relationship is altered after stroke. We previously showed that ischemic stroke affects chronically regional perfusion and CO_2 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 stroke [10] 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 of

increased systolic BP.[27] Small vessels in the infarcted hemisphere may be nearly maximally dilatated, 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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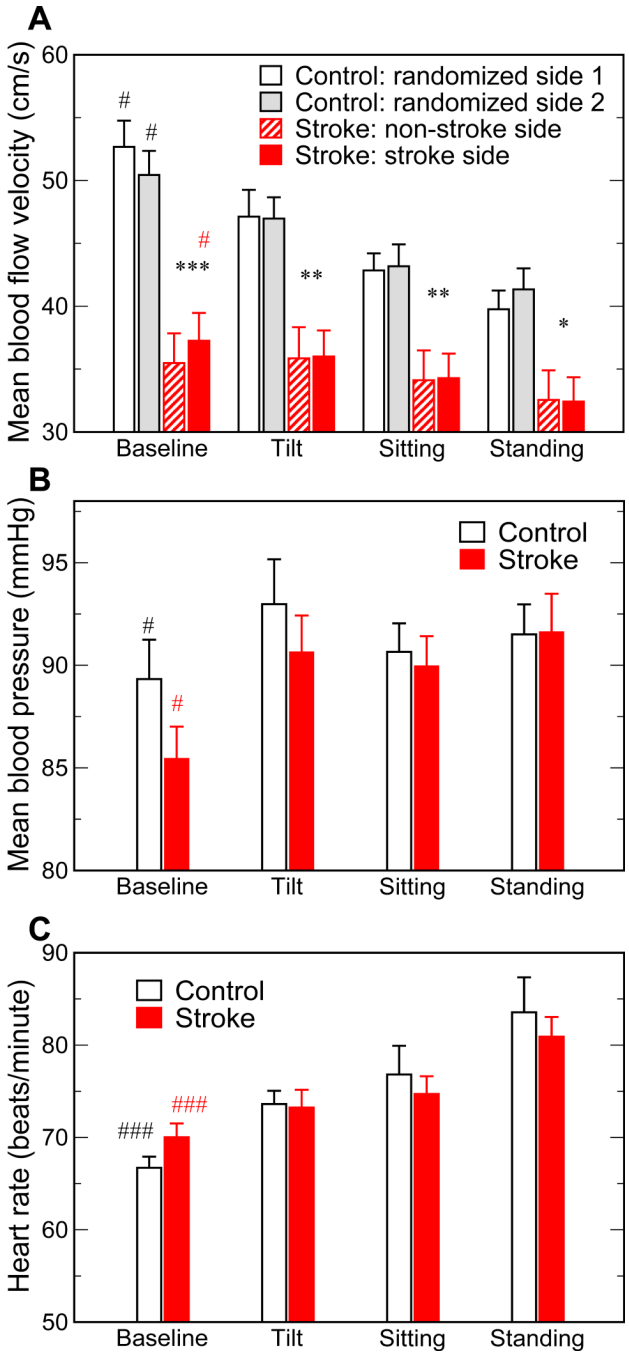

Figure 1.

Mean blood flow velocities (BFV) in middle cerebral arteries (A), mean blood pressure (BP) (B) and heart rate (C) for the control group (randomized side 1 and 2) and for the stroke group (stroke and non-stroke side) during supine baseline, tilt, sitting and standing. * denotes between groups comparisons: *p<0.05, **p<0.001 and ***p<0.0001; and # denotes comparisons between conditions within each group (mean± SE).

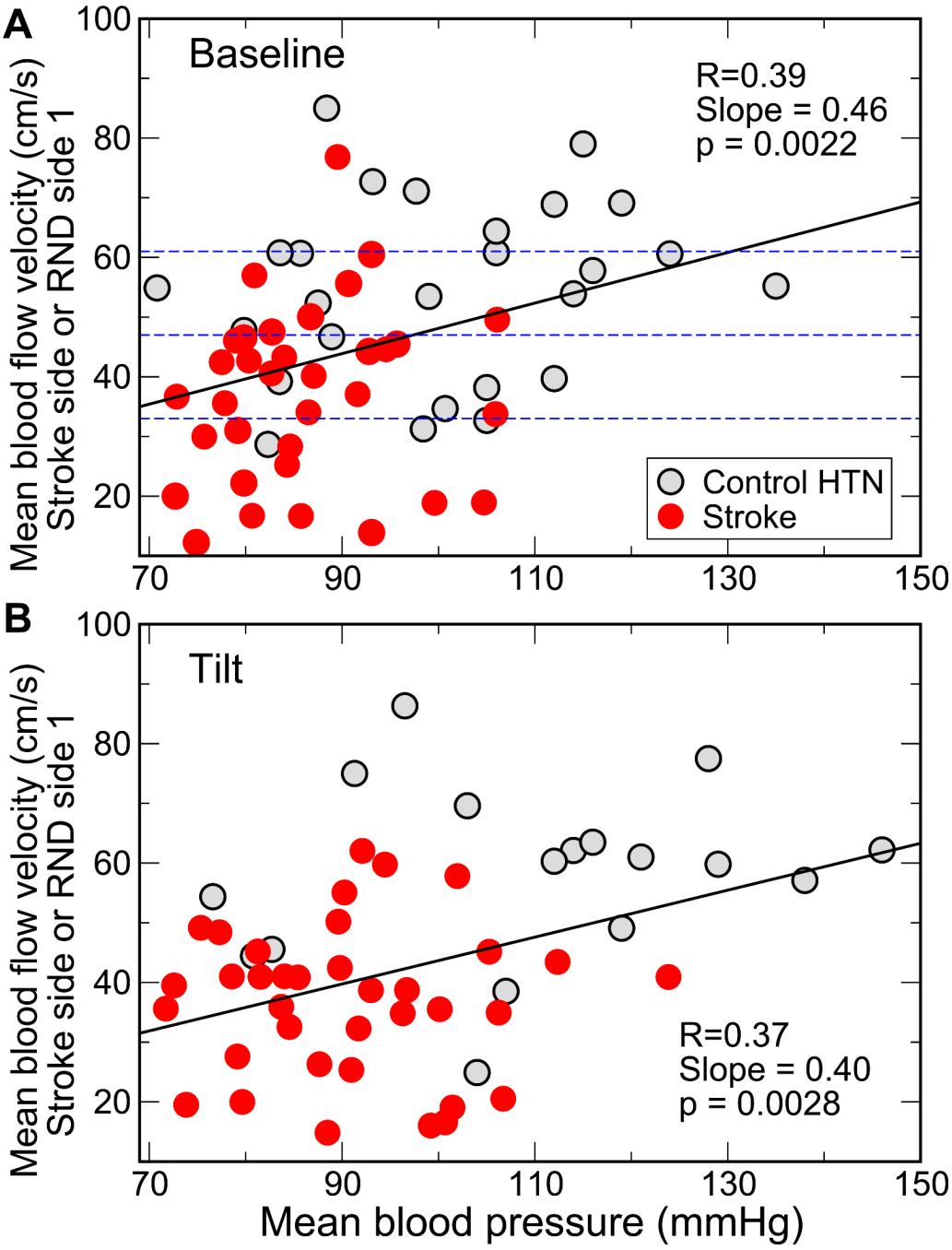

Figure 2.

A linear regression of mean BFV and BP during baseline (A) and tilt (B) in the stroke group (red circles) and hypertensive controls (empty circles). Normotensive controls had no relationship between BP and BFV; not displayed for picture clarity. Blue dotted lines indicate of BFV range in the control group (mean± SD).

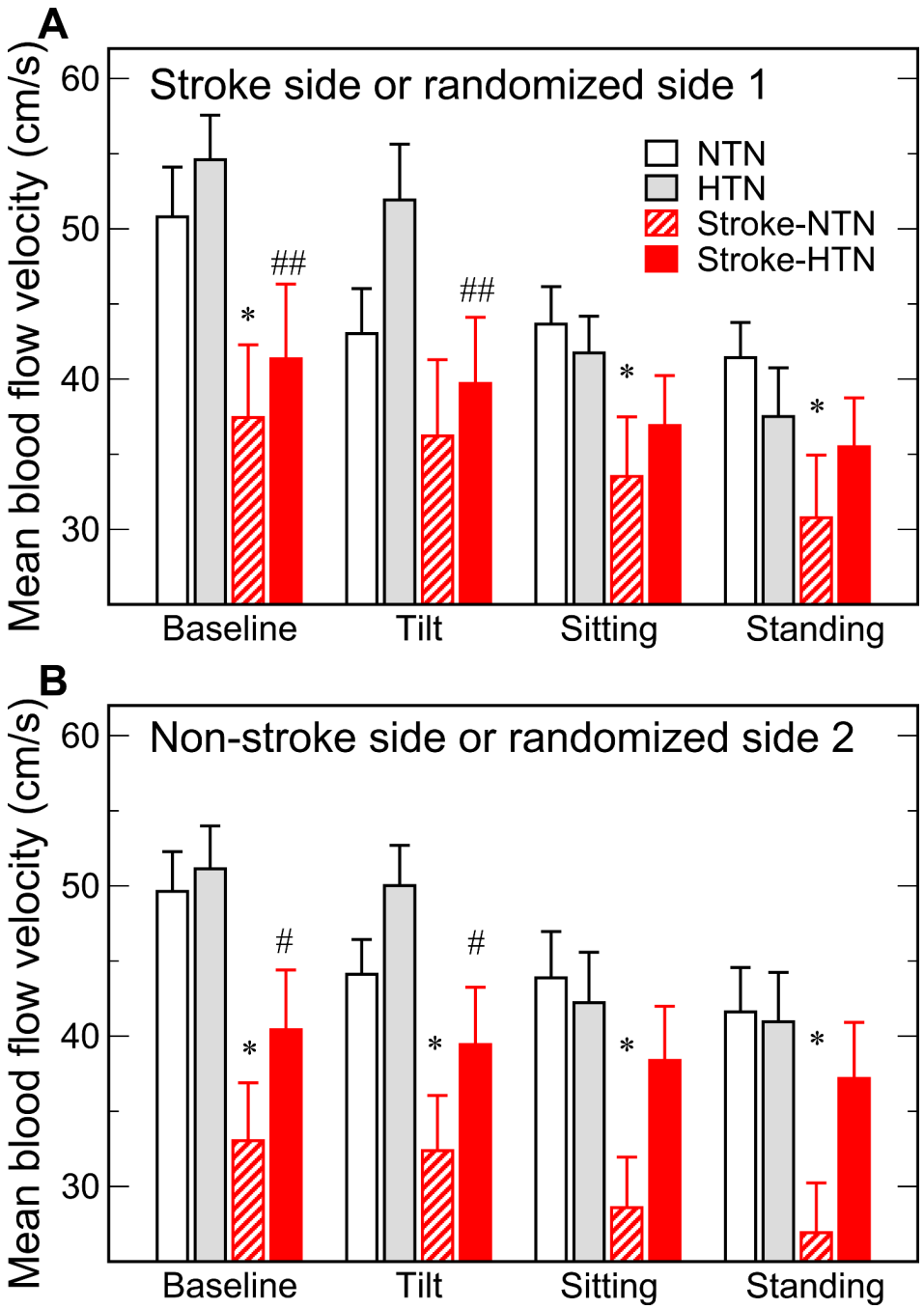

Figure 3.

Comparisons of mean BFV in stroke-normotensive and stroke-hypertensive subjects on the stroke (A) and non-stroke sides (B), and in the non-stroke normotensive and non-stroke-hypertensive groups (randomized side 1 and 2) during supine baseline, tilt, sitting and standing. * denotes comparisons between stroke-normotensive and non-stroke normotensive subjects: *p<0.05 and **p<0.001; and # denotes comparisons between hypertensive and stroke-hypertensive subjects: # p<0.05 and ## p<0.001 (mean± SE).

Table 1

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)	-	-
NIHSS	2.71 (±2.72)	-	-
MRS	1.2 (±1.14)	-	-
Hypertension by 24 hour BP	32	35	
Use of antihypertensives	30	33	
MCAR diameters	2.24 (±0.62)	2.44 (±.26)	0.15
MCAL diameter	2.47 (±0.32)	2.48 (±.28)	0.98
ICAR diameter	5.02 (±0.35)	5.39 (±.46)	0.04
ICAL diameter	5.32 (±0.47)	5.39 (±.47)	0.70
WBC (k/ul)	7.03 (±0.29)	6.56 (±.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
LDL (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
Hx 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 ± SD

Ordinal variables are presented as mean ± SD (range)

Nominal variables are presented as numbers

Comparison is not significantly different if p>0.05

Race: W - White, A - Asian, AI - American Indian, AA - African-American, U - unknown.

LDL - Low density lipoprotein