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*Hypertension* published online Mar 12, 2007;

DOI: 10.1161/HYPERTENSIONAHA.106.084939

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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# Cerebral Hemodynamics After Short- and Long-Term Reduction in Blood Pressure in Mild and Moderate Hypertension

Rong Zhang, Sarah Witkowski, Qi Fu, Jurgen A.H.R. Claassen, Benjamin D. Levine

**Abstract**—This study tested the hypothesis that acute reduction in blood pressure (BP) at the initial stage of antihypertensive therapy compromises brain perfusion and dynamic cerebral autoregulation in patients with hypertension. Cerebral blood flow velocity and BP were measured in patients with mild and moderate hypertension and in healthy volunteers at baseline upon reduction of BP within 1 to 2 weeks of administration of losartan/hydrochlorothiazide and after 3 to 4 months of treatment. The transfer function between beat-to-beat changes in BP and cerebral blood flow velocity was estimated to assess dynamic autoregulation. After 1 to 2 weeks of treatment, BP was reduced in mild ( $143\pm 7/88\pm 4$  versus  $126\pm 12/77\pm 6$  mm Hg) and moderate hypertension ( $163\pm 11/101\pm 9$  versus  $134\pm 17/84\pm 9$  mm Hg;  $P<0.05$ ). These reductions in BP were well maintained over the 3 to 4 month period. Cerebral blood flow velocity did not change, whereas cerebrovascular resistance index was reduced by 17% ( $P<0.05$ ) after reduction in BP. Responses of cerebral blood flow velocity to head-up tilt remained unchanged. Baseline transfer function gain at the low frequencies (0.07 to 0.20 Hz) was reduced in moderate hypertension, consistent with cerebral vasoconstriction and/or enhanced dynamic autoregulation. However, this reduced transfer function gain was restored to the level of control subjects after reduction in BP. These findings, contrary to our hypothesis, demonstrate that there is a rapid adaptation of the cerebral vasculature to protect the brain from hypoperfusion even at the initial stage of antihypertensive therapy in patients with mild and moderate hypertension. (*Hypertension*. 2007;49:1-7.)

**Key Words:** hemodynamics ■ brain ■ hypertension ■ cerebral blood flow ■ angiotensin AT1 receptor ■ transcranial Doppler

The relationship between high blood pressure (BP) and the risk of stroke and other cerebral and cardiovascular diseases has been well established. Recent studies and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure also suggest the significant benefits of control of systolic BP  $<120$  mm Hg and diastolic BP  $<80$  mm Hg in the general population.<sup>1</sup>

However, despite these widely accepted guidelines, reduction in BP acutely and aggressively in patients with hypertension still is an important concern in clinical practice.<sup>2</sup> For the most part, these concerns are derived from the prevailing concept that cerebral autoregulation is impaired in patients with hypertension (ie, there is a rightward shift of the steady-state cerebral autoregulatory curve to higher BPs). Thus, brain hypoperfusion and ischemic damage may occur associated with an acute and aggressive reduction in BP.<sup>3</sup>

In addition, accumulating evidence indicates that regulation of cerebral blood flow (CBF) under steady-state conditions may be related to, but not necessarily equivalent to, that

under dynamic conditions.<sup>4-6</sup> In contrast to static autoregulation, which describes CBF responses to steady-state changes in BP, dynamic autoregulation examines CBF responses to transient changes in BP in time scales of seconds to minutes, which may be critical in preserving CBF during rapid perturbations in BP presented in daily life.<sup>4,6</sup>

Recently, several studies have shown that dynamic autoregulation is likely to be preserved in patients with mild to moderate hypertension<sup>5,7,8</sup> but becomes less effective in severe hypertension.<sup>9</sup> However, one important question yet to be answered is whether dynamic autoregulation is altered at the initial stages of lowering of BP consequent to effective antihypertensive treatment.

This study tested the hypothesis that, in contrast to the salutary effects of long-term antihypertensive treatment through vascular remodeling, brain perfusion and dynamic autoregulation are compromised in patients with hypertension after acute reduction in BP. For this purpose, changes in CBF velocity in the middle cerebral artery, presumably reflective of CBF, were measured before and after short- and long-term

Received November 21, 2006; first decision December 5, 2006; revision accepted February 14, 2007.

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*Hypertension* is available at <http://www.hypertensionaha.org>

DOI: 10.1161/HYPERTENSIONAHA.106.084939

reduction in BP. Hypertension was treated with administration of a combination of angiotensin II type 1 (AT<sub>1</sub>) receptor antagonist losartan with hydrochlorothiazide.<sup>10</sup> Tests were performed in the supine position and during head-up tilt (HUT), because regulation of CBF is likely to be challenged substantially under orthostatic stress.

## Methods

### Subjects

Twelve patients with mild hypertension (3 women; racial makeup: 7 white, 3 black, 1 Hispanic, and 1 mixed race) with a mean age of 49±11 years (range: 27 to 66 years), 9 with moderate hypertension (2 women; racial makeup: 4 white, 4 black, and 1 Hispanic) with a mean age of 47±12 years (range: 36 to 62 years), and 9 healthy subjects (2 women; racial makeup: 6 white and 3 black) with a mean age of 46±11 years (range: 32 to 66 years) participated in this study. All of the patients had newly diagnosed essential hypertension and had not been treated with any antihypertensive medicine before the study. Classification of mild (stage 1) and moderate hypertension (stage 2) was based on the average of awake 24-hour ambulatory BP.<sup>1</sup> All of the subjects underwent a thorough medical history and a physical examination, including a regular blood chemistry and echocardiography to exclude the presence of other severe cardiovascular or cerebrovascular disease. For safety concerns, patients with severe hypertension (systolic pressure >180 mm Hg or diastolic pressure >110 mm Hg) were not included. The study was approved by the institutional review boards of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas. One patient with moderate hypertension was lost to follow-up, and 1 patient with mild hypertension developed intolerable adverse effects (sore throat) with low-dose losartan/hydrochlorothiazide and resigned from the study. Therefore, these subjects were not included in the final data analysis of this study.

### Instrumentation

Finger photoplethysmography (Finapres, Ohmeda) was used to measure beat-to-beat changes in BP. The BP transducer was positioned carefully at the heart level in the supine position and during 70° HUT. Intermittent cuff BP was measured at the upper arm using electrophygmomanometry (SunTech). Cardiac output was measured with a modified acetylene rebreathing method. CBF velocity was recorded in the middle cerebral artery (MCA) using transcranial Doppler (Multiflow, DWL). The Doppler probe was placed over the subject's temporal window and fixed at a constant angle with a probe holder that was custom made to fit each subject's facial bone structure. This technique allowed CBF velocity to be measured precisely at the same acoustic window and at the same angle for repeated studies.<sup>11</sup> Heart rate was monitored using ECG. End-tidal CO<sub>2</sub> was monitored via a nasal cannula using a capnograph (Criticare Systems Inc). Blood samples were drawn from the antecubital vein in the supine position and at the end of HUT. Plasma norepinephrine was measured by high-performance liquid chromatography (ARUP Laboratories). Plasma renin activity and aldosterone were measured using radioimmunoassay (ARUP Laboratories). Hematocrit was measured using a microcentrifuge. Plasma volume was measured in 8 patients with mild and 1 with moderate hypertension using Evans blue dye.<sup>12</sup> This measurement was not available for the control subjects, because the manufacturer terminated the Evans blue dye production before the completion of this study.

### Protocol

All of the experiments were performed in the morning ≥2 hours after a light breakfast. The subjects refrained from heavy exercise and caffeinated or alcoholic beverages at least 24 hours before the tests. After ≥30 minutes of supine rest, blood samples were drawn, and cardiac output was measured. Then, 6 minutes of beat-to-beat BP and CBF velocity were measured during spontaneous breathing. During

this time period, arm BP also was measured. Then, subjects were tilted up to a 70° position for 10 minutes. After 2 minutes for stabilization, 6 minutes of continuous data and arm BP were measured. Cardiac output and blood samples were obtained at the end of HUT followed by returning the subjects back to the supine position for recovery.

### Antihypertensive Treatment

After the baseline test, patients were treated with low-dose losartan/hydrochlorothiazide (50/12.5 mg once daily) for 1 week. The dose was increased to 100/25 mg if the reduction in BP was not below a previously determined level of systolic pressure <140 mm Hg and diastolic pressure <90 mm Hg.<sup>1</sup> In 1 patient with mild hypertension who did not respond well to losartan/hydrochlorothiazide, a combination of calcium channel blocker (amlodipine, 10 mg) and hydrochlorothiazide (25 mg) was used to reduce BP. Data obtained from this individual were similar to other patients and, thus, were pooled together for statistical analysis. On reaching the goal of BP control (within 1 to 2 weeks), testing (short-term) was repeated. Treatment was continued for 3 to 4 months, and then testing (long-term) was repeated again. In patients, 24-hour ambulatory BP (Accutracker II, SunTech) was measured before treatment and repeated on the days before the short- and long-term tests. In healthy subjects, 24-hour BP was measured once at baseline and once before the long-term test. The patients took their losartan/hydrochlorothiazide in the morning 2 to 3 hours before the study to ensure its optimal BP reduction effects.<sup>10</sup>

### Data Analysis

Steady-state BP was obtained from the average of ≥3 measurements of arm BP during the 6-minute data collection periods. Steady-state heart rate and CBF velocity were obtained from the average of beat-to-beat data and end-tidal CO<sub>2</sub> from the breath-to-breath data. Total peripheral vascular resistance was estimated as mean BP divided by cardiac output. Cerebrovascular resistance index (CVRI) was calculated as mean BP divided by mean CBF velocity. During HUT, hydrostatic effects of gravity on cerebral perfusion pressure under steady-state conditions were not considered, because gravitational potential energy of blood is likely to be conserved in a closed circulatory system.<sup>13</sup>

The magnitude of beat-to-beat changes in mean BP and CBF velocity was quantified by power spectral analysis. Transfer function and coherence function between these variables was calculated to assess dynamic cerebral autoregulation as described previously (Figure 1).<sup>6</sup> In addition, normalized transfer function gain was derived as the estimated transfer function gain times CVRI to quantify relative changes in CBF velocity in response to relative changes in BP.<sup>14</sup> Because dynamic autoregulation most likely is effective at low frequencies, and estimation of coherence function was high (>0.5) at these frequencies,<sup>4–6,15</sup> spectral power of BP and CBF velocity and mean values of transfer function gain, phase, and coherence were calculated in the low frequency range of 0.07 to 0.20 Hz in this study.

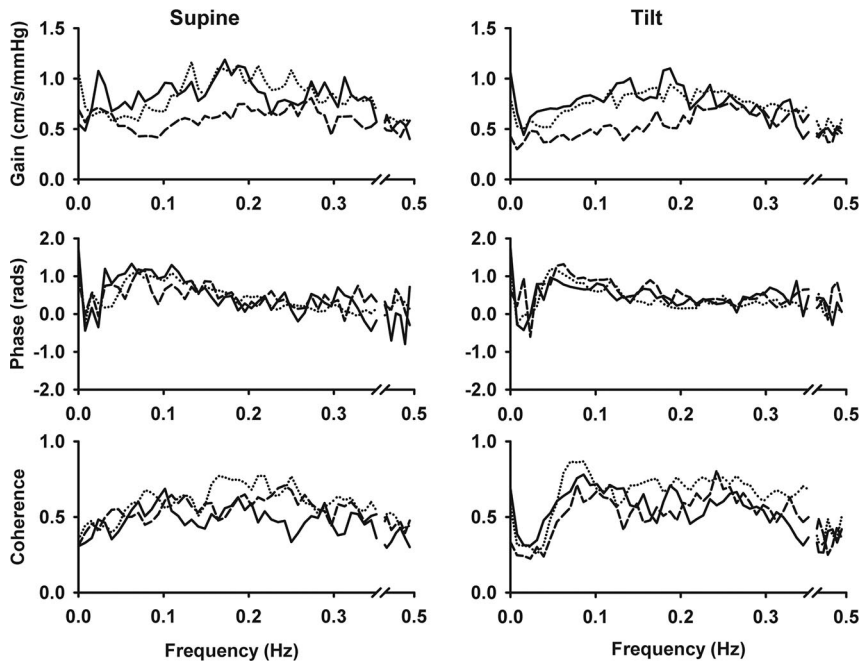
### Statistics

Two-way repeated-measures ANOVA was used to compare the differences and interactions between the subject groups and the effects of antihypertensive treatment, as well as HUT, on the steady-state hemodynamics and spectral and transfer function analysis of BP and CBF velocity. The Holm–Sidak method was used for posthoc multiple comparisons if significant group and/or interaction effects were detected (SigmaStat 3.11, Systat Software). Data are presented as mean±SD. A value of *P*<0.05 was considered statistically significant.

## Results

### Antihypertensive Treatment

Both 24-hour ambulatory BP and mean BP measured under supine resting conditions and during HUT were reduced



**Figure 1.** Group-averaged transfer function gain, phase, and coherence function in the supine position and during HUT before treatment. Solid line, control subject; dotted line, mild hypertension; dashed line, moderate hypertension.

significantly within 1 to 2 weeks of treatment (Tables 1 and 2). The magnitude of reduction in BP while awake was similar to that during sleep (Table 1). However, heart rate did not change after reduction in BP, suggestive of baroreflex resetting (Tables 1 and 2). Reductions in BP were well maintained over the period of 3 to 4 months with the same dose of drugs used in each patient to reduce BP acutely. As expected, plasma renin activity increased significantly after a reduction in BP in moderate hypertension. However, plasma volume did not change (baseline:  $41 \pm 5$  mL/kg, acute:  $41 \pm 6$  mL/kg, chronic:  $44 \pm 5$  mL/kg), consistent with the observation of no change in hematocrit (Table 1).

### Steady-State Hemodynamics

Before treatment, no differences in CBF velocity and cardiac output were observed between control subjects and patients with hypertension (Table 2). However, CVRI and total peripheral vascular resistance were increased significantly in moderate hypertension, suggesting both cerebral and systemic vasoconstriction. After short- and long-term reductions in BP, CBF velocity and cardiac output did not change, whereas CVRI and total peripheral vascular resistance decreased in patients with hypertension (Table 2).

During HUT, when compared with the supine position, CBF velocity, cardiac output, and end-tidal  $\text{CO}_2$  all were

**TABLE 1. Measurement of 24-Hour BP and Heart Rate, Supine Plasma Renin Activity, Aldosterone, and Hematocrit Before and After Short- and Long-Term Treatment**

Variables	Baseline			1 to 2 Weeks			3 to 4 Months		
	Control	Mild	Moderate	Control	Mild	Moderate	Control	Mild	Moderate
Age, y	46 $\pm$ 11	49 $\pm$ 11	47 $\pm$ 12						
Height, cm	175 $\pm$ 12	177 $\pm$ 11	174 $\pm$ 8						
Weight, kg	82 $\pm$ 19	92 $\pm$ 18	86 $\pm$ 21						
SBP awake, mm Hg	120 $\pm$ 7	143 $\pm$ 7*	163 $\pm$ 11*	...	126 $\pm$ 12†	134 $\pm$ 17†	124 $\pm$ 7	123 $\pm$ 8†	129 $\pm$ 12†
DBP awake, mm Hg	74 $\pm$ 6	88 $\pm$ 4*	101 $\pm$ 9*	...	77 $\pm$ 6†	84 $\pm$ 9†	76 $\pm$ 7	77 $\pm$ 7†	79 $\pm$ 9†
SBP sleep, mm Hg	109 $\pm$ 9	121 $\pm$ 9*	148 $\pm$ 13*	...	112 $\pm$ 9†	120 $\pm$ 12†	111 $\pm$ 14	109 $\pm$ 11†	115 $\pm$ 12†
DBP sleep, mm Hg	66 $\pm$ 9	74 $\pm$ 6*	87 $\pm$ 9*	...	68 $\pm$ 6	76 $\pm$ 8†	65 $\pm$ 10	69 $\pm$ 4	68 $\pm$ 12†
HR awake, bpm	72 $\pm$ 8	77 $\pm$ 9	78 $\pm$ 9	...	80 $\pm$ 10	79 $\pm$ 10	72 $\pm$ 8	80 $\pm$ 10	78 $\pm$ 10
HR sleep, bpm	66 $\pm$ 7	67 $\pm$ 11	69 $\pm$ 11		70 $\pm$ 9	78 $\pm$ 12	68 $\pm$ 8	71 $\pm$ 11	73 $\pm$ 15
PRA, ng/mL/h	0.8 $\pm$ 0.5	0.9 $\pm$ 1.0	0.5 $\pm$ 0.4	0.6 $\pm$ 0.4	2.5 $\pm$ 3.1	9.1 $\pm$ 11.2*†	0.8 $\pm$ 0.6	2.2 $\pm$ 2.4	5.4 $\pm$ 6.0†
Aldosterone, ng/dL	4.3 $\pm$ 2.0	6.2 $\pm$ 3.6	5.9 $\pm$ 3.8	3.6 $\pm$ 2.2	5.5 $\pm$ 3.1	6.5 $\pm$ 3.5	5.4 $\pm$ 3.9	4.6 $\pm$ 2.0	8.5 $\pm$ 7.8
Hct, %	42 $\pm$ 2	43 $\pm$ 5	43 $\pm$ 2	42 $\pm$ 2	42 $\pm$ 5	44 $\pm$ 3	41 $\pm$ 3	41 $\pm$ 5	41 $\pm$ 3

Data are mean $\pm$ SD, n=9 for control, n=12 for mild, and n=9 for moderate hypertension. SBP indicates systolic blood pressure; DBP, diastolic blood pressure, HR, heart rate; PRA, plasma renin activity; Hct, hematocrit.

\* $P < 0.05$  comparisons between control subjects and patients with hypertension under same treatment conditions.

† $P < 0.05$  comparisons between baseline and treatment for the same group subjects.

**TABLE 2. Systemic and Cerebral Hemodynamics Under Supine Resting Conditions and During HUT Before and After Short- and Long-Term Treatment**

Variables	Baseline			1 to 2 Weeks			3 to 4 Months		
	Control	Mild	Moderate	Control	Mild	Moderate	Control	Mild	Moderate
<b>Resting</b>									
HR, bpm	59±6	67±12	69±7	59±6	67±9	70±9*	60±8	64±8	65±10
MBP, mm Hg	87±10	100±10*	112±14*	88±10	88±4†	98±9*†	89±12	87±7†	93±9†
CO, L/min	7.4±2.0	6.6±1.4	6.6±1.6	6.9±2.2	6.4±1.3	6.4±1.2	7.3±2.4	6.8±1.3	7.0±1.8
TPR, dyne s cm <sup>-5</sup>	1011±283	1256±249	1456±491*	1115±346	1154±297	1277±264	1087±426	1056±210	1136±356†
CBFV, cm/s	55±12	58±15	50±8	58±16	61±14	55±11	56±13	60±14	54±9
CVRI mm Hg/cm/s	1.6±0.4	1.8±0.4	2.3±0.5*	1.6±0.4	1.5±0.3†	1.9±0.5†	1.7±0.4	1.5±0.3†	1.8±0.4†
ETCO <sub>2</sub> , mm Hg	37±3	37±4	36±5	36±5	36±5	37±4	38±6	35±5	35±5
NE, pg/mL	213±74	277±151	259±92	221±110	328±129	370±137	169±46	278±102	329±168
N Gain <sub>LF</sub>	1.5±0.3	1.5±0.2	1.3±0.4	1.5±0.4	1.5±0.3	1.5±0.3	1.5±0.4	1.4±0.2	1.4±0.5
Coh <sub>LF</sub>	0.5±0.2	0.7±0.1	0.6±0.2	0.5±0.1	0.7±0.1*	0.6±0.2	0.5±0.2	0.7±0.1*	0.6±0.2
<b>HUT</b>									
HR, bpm	75±9‡	86±13‡	81±9‡	75±8‡	88±12*‡	87±15‡	73±10‡	82±10‡	79±16‡
MBP, mm Hg	97±10‡	104±13	126±13*‡	99±11‡	97±12†‡	104±15†	95±10‡	95±15†‡	102±7†‡
CO, L/min	6.2±1.8‡	4.8±1.4‡	5.4±1.7‡	6.0±2.3‡	5.2±1.5‡	5.3±1.0‡	6.3±1.9‡	6.0±1.4†‡	6.1±1.4‡
TPR, dyne s cm <sup>-5</sup>	1348±401	1870±538‡	2158±1208*‡	1457±447‡	1643±547‡	1599±420†‡	1289±281	1346±429†‡	1423±460†‡
CBFV, cm/s	50±11‡	49±15‡	45±6‡	51±10‡	53±16‡	48±10‡	52±16	52±14‡	46±6‡
CVRI mm Hg/cm/s	2.1±0.7‡	2.2±0.6‡	2.9±0.5*‡	2.0±0.5‡	1.9±0.5‡	2.3±0.7†‡	2.0±0.7‡	1.9±0.4†‡	2.3±0.4†‡
ETCO <sub>2</sub> , mm Hg	34±4‡	33±4‡	35±5	34±5	33±5‡	34±4	34±6‡	33±6	32±5
NE, pg/mL	558±304‡	590±242‡	483±111‡	530±284‡	684±209‡	720±303†‡	388±109‡	555±177‡	557±152‡
N Gain <sub>LF</sub>	1.8±0.6‡	1.8±0.3‡	1.4±0.3	1.7±0.4	1.8±0.4	1.5±0.3	1.7±0.4	1.6±0.3‡	1.6±0.3
Coh <sub>LF</sub>	0.7±0.2	0.7±0.2	0.6±0.2	0.5±0.2	0.8±0.2	0.7±0.2	0.6±0.2	0.6±0.2	0.6±0.1

Data are mean±SD, n=9 for control, n=12 for mild, n=9 for moderate hypertension. HR indicates heart rate; MBP, mean blood pressure; CO, cardiac output; TPR, total peripheral vascular resistance; CBFV, cerebral blood flow velocity in the middle cerebral artery; CVRI, cerebrovascular resistance index (MBP/CBFV); NE, plasma norepinephrine; N Gain<sub>LF</sub>, normalized transfer function gain at the low frequencies; Coh<sub>LF</sub>, coherence function at the low frequencies.

\**P*<0.05 comparisons between control subjects and patients with hypertension under the same treatment and postural conditions.

†*P*<0.05 comparisons between baseline and treatment for the same group of subjects and under the same postural conditions.

‡*P*<0.05 comparisons between supine and HUT for the same group subjects and under the same treatment conditions.

reduced, whereas heart rate, mean BP, total peripheral vascular resistance, CVRI, and plasma norepinephrine were increased (Table 2). However, these typical systemic and cerebrovascular responses to orthostatic stress were similar between control subjects and patients with hypertension and persisted after both short- and long-term reduction in BP. Of note, similar to the supine position, when compared with baseline, CVRI during HUT was reduced significantly after reduction in BP (Table 2).

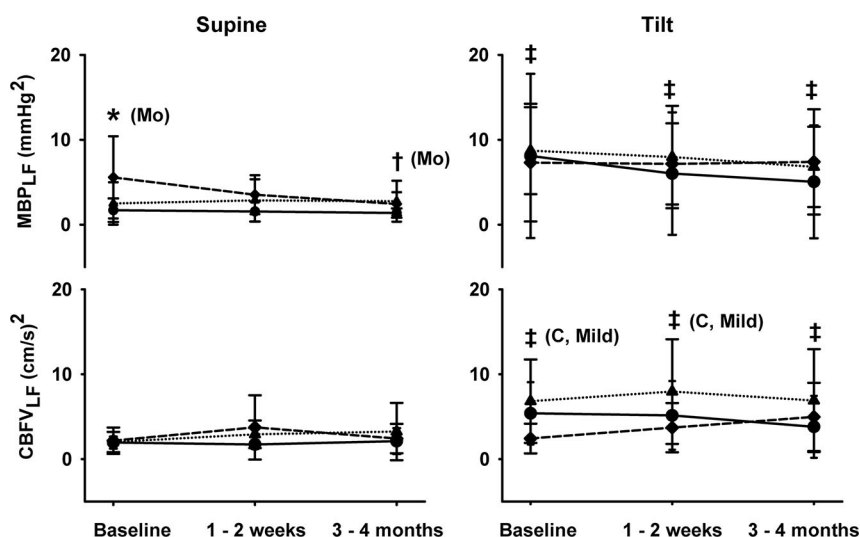
### Transfer Function Gain and Phase

BP and CBF velocity variability in the supine position and during HUT at baseline and after reduction in BP are shown in Figure 2. Before treatment, when compared with control subjects, transfer function gain at the low frequencies was reduced significantly in patients with moderate hypertension (Figures 1 and 3). However, this reduced transfer function gain was restored to the level of control subjects after short- and long-term reduction in BP (Figure 3). Estimation of phase and normalized transfer function gain did not change in patients with hypertension and were not altered after reduction in BP (Figure 3 and Table 2).

During HUT, when compared with the supine position, transfer function gain did not change, whereas phase was reduced and normalized transfer function gain increased in control subjects and in mild hypertension before treatment. However, these changes were not altered after reduction in BP (Figure 3 and Table 2). Estimation of coherence function at the low frequencies was ≥0.5 under all of the experimental conditions (Table 2).

### Discussion

The main findings of this study are threefold. First, CBF velocity did not change after short- and long-term reduction in BP in patients with mild and moderate hypertension. Second, during HUT, CBF velocity and cardiac output were reduced similarly in control subjects and in patients with hypertension. However, both systemic and cerebral hemodynamic responses to HUT were not altered after reduction in BP. Third, transfer function gain between beat-to-beat changes in BP and CBF velocity was reduced significantly in patients with moderate hypertension, a pattern typically associated with improved rather than impaired dynamic autoregulation. However, this reduced transfer function gain



**Figure 2.** Changes in spectral power of mean blood pressure (MBP) and CBF velocity (CBFV) variability in the supine position and during HUT at baseline and after short- and long-term reduction in BP at the low frequencies of 0.07 to 0.20 Hz. Data are mean±SD, n=9 for control (C, solid line), n=12 for mild (dotted line), and n=9 for moderate hypertension (Mo, dashed line). \*  $P < 0.05$ , comparisons between control subjects and patients with moderate hypertension. †  $P < 0.05$ , comparisons between baseline and long-term treatment in moderate hypertension. ‡  $P < 0.05$  comparisons between the supine position and HUT.

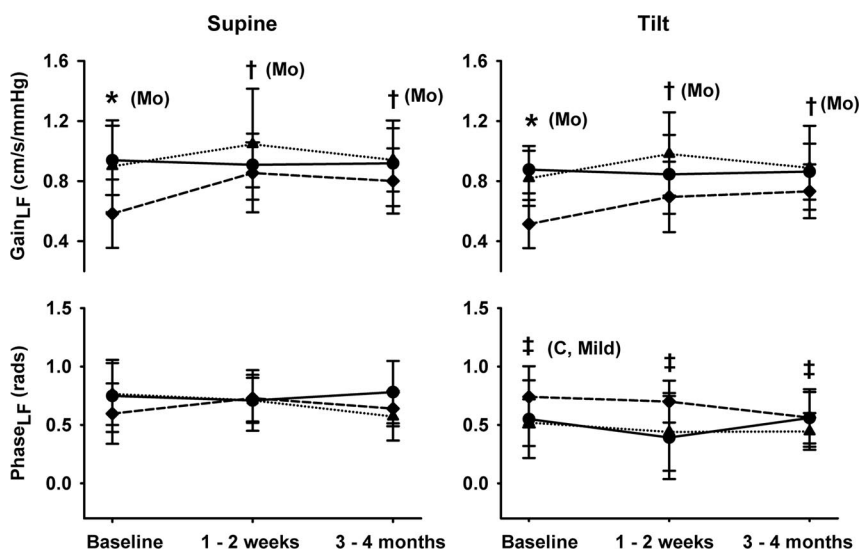
was restored to the level of control subjects after reduction in BP, associated with a reduction in cerebrovascular resistance. Collectively, these findings, contrary to our hypothesis, indicate that, when compared with control subjects, brain perfusion and dynamic autoregulation are not compromised in patients with mild and moderate hypertension and are not compromised after either short- or long-term reduction in BP.

**CBF Under Steady-State Conditions**

When compared with age- and sex-matched normotensive subjects, similar or reduced CBF was observed in patients with hypertension.<sup>3</sup> This study extends these previous observations by showing that steady-state CBF velocity and, presumably, CBF did not change in patients with mild and moderate hypertension and remained unchanged after short- and long-term reduction in BP. Several mechanisms may lead to these observations. First, it is likely that, although there might be a rightward shift of the steady-state cerebral autoregulatory curve to higher BPs in hypertension and these changes may impair CBF responses to hypotensive stimuli,<sup>3</sup> the magnitude of reduction in BP in this study may still be

within the autoregulatory pressure range. Thus, CBF would remain unchanged. However, because the magnitude of reductions in BP while awake was similar to that during sleep (Table 1), it is unknown whether CBF still would remain unchanged for these additional reductions in BP at night, which may fall below the lower limit of autoregulation and, thus, may lead to silent brain ischemia.<sup>16</sup>

Second, the rightward shift of the cerebral autoregulatory curve in hypertension may be normalized acutely (within 1 to 2 week) with administration of AT<sub>1</sub> receptor antagonist (ie, a leftward shift of the curve).<sup>17</sup> In addition, AT<sub>1</sub> receptor blockade, per se, may cause cerebral vasodilation.<sup>18</sup> However, it is not clear whether losartan would pass the blood-brain barrier in humans. If this was the case, CBF also would remain unchanged after reduction in BP. Regardless of the specific mechanisms, the fact that CBF velocity was stable after short-term reduction in BP suggests that there is a rapid adaptation of the cerebral vasculature to protect the brain from hypoperfusion. In contrast, a preserved CBF after long-term antihypertensive therapy most likely is associated with cerebrovascular remodeling.<sup>3,19</sup>



**Figure 3.** Changes in transfer function gain and phase in the supine position and during HUT at baseline and after short- and long-term reduction in BP at the low frequencies of 0.07 to 0.20 Hz. Data are mean±SD, n=9 for control (C, solid line), n=12 for mild (dotted line), and n=9 for moderate hypertension (Mo, dashed line). \*  $P < 0.05$ , comparisons between control subjects and patients with moderate hypertension. †  $P < 0.05$ , comparisons between baseline and short- and long-term reduction in BP in moderate hypertension. ‡  $P < 0.05$  comparisons between the supine position and HUT.

### Dynamic Autoregulation

Several studies have shown that dynamic cerebral autoregulation was not altered in mild and moderate hypertension<sup>5,7,8</sup> but became less effective in severe hypertension.<sup>9</sup> In addition, treatment of hypertension in the elderly for 6 months increased CBF velocity and carotid artery distensibility but did not alter dynamic autoregulation assessed during transient changes in BP.<sup>19</sup>

In the present study, transfer function gain at the low frequencies was reduced in patients with moderate hypertension. These findings are consistent with previous studies suggesting that dynamic autoregulation may be enhanced in patients with moderate hypertension.<sup>5,7</sup> That is, changes in CBF velocity in response to spontaneous oscillations in BP were attenuated in these patients. The new findings of this study are that this reduced transfer function gain increased and was restored to the level of control subjects after reduction in BP.

The specific vascular mechanisms responsible for these observations cannot be determined in this study. However, we speculate that changes in transfer function gain observed in patients with moderate hypertension could be related to changes in cerebrovascular resistance estimated under steady-state conditions. Theoretically, an enhanced cerebrovascular resistance would attenuate CBF responses to changes in arterial pressure not only under steady state but also under dynamic conditions (in analogy to the effect of changes in Ohm's resistance in a circuit on oscillations in current in response to oscillations in electrical potentials).<sup>20</sup> Consistent with this hypothesis, reduction in transfer function gain in moderate hypertension before treatment is likely to be induced by cerebral vasoconstriction and an enhanced cerebrovascular resistance, whereas increases in transfer function gain after treatment are likely to be induced by cerebral vasodilation and decreases in cerebrovascular resistance.

During HUT, estimation of phase was reduced, whereas normalized transfer function gain was increased in control subjects and in mild hypertension. These data suggest that dynamic autoregulation, when quantified by the phase relationship or relative changes in CBF velocity in response to relative changes in BP, becomes less effective under orthostatic stress.<sup>9,21</sup> Interestingly, these changes were not observed in patients with moderate hypertension before treatment in accordance with the argument that dynamic autoregulation may be enhanced in these patients.<sup>5,7</sup>

### Vascular Reactivity During HUT

In this study, reductions in cardiac output, CBF velocity, and end-tidal CO<sub>2</sub> and increases in systemic and cerebrovascular resistance during HUT were similar between control subjects and patients with hypertension. In addition, these systemic and cerebrovascular responses during HUT were not altered after either short or long-term reduction in BP. Because sympathetic activation during HUT is likely to be similar between normotensive subjects and patients with hypertension,<sup>22</sup> these findings suggest that systemic and cerebral vascular reactivity to sympathetic neural or CO<sub>2</sub> stimuli were not altered in patients with hypertension and remained unchanged after antihypertensive treatment. However, whether

age and sex differences would affect these observations needs to be determined in future studies.<sup>23</sup>

### Study Limitations

Several methodologic limitations should be discussed. First, the number of subjects in this study is relatively small. Therefore, small changes in CBF velocity after reduction in BP may not be detectable. However, the observation of stable or slightly increased CBF velocity after treatment suggest that BP lowering, if anything, may have increased rather than decreased blood flow (Table 2). This possibility needs to be tested in large-scale clinical trials.

Second, changes in CBF were assessed indirectly by the measurement of CBF velocity in the MCA using transcranial Doppler. Changes in CBF velocity reflect changes in blood flow only if the insonated MCA diameter remains constant. Several studies have demonstrated that there are no significant changes in the MCA diameters under moderate changes in BP or end-tidal CO<sub>2</sub>.<sup>24</sup> However, we cannot exclude the possibility that vasodilation of the MCA may have occurred after BP reduction. If this was the case, CBF would have been increased in patients with hypertension as discussed above. However, this possibility will strengthen rather than weaken the conclusion of the present study. Relevant to this discussion, special caution also should be taken when comparing cerebrovascular resistance based on the estimates of CVRI between control subjects and patients with hypertension. Such comparisons may not be valid if MCA diameters were different between the subject groups. For these reasons, it is the longitudinal relative changes in CVRI within each patient group after reduction in BP, rather than the absolute values of CVRI, that should be emphasized to reflect changes in cerebrovascular resistance.

Third, changes in mean BP measured at heart level were used to estimate changes in cerebral perfusion pressure both in the supine position and during HUT. This estimation is based on the assumption that intracranial and cerebral venous pressures are relatively low and constant and that, during HUT, hydrostatic components of intracranial and cerebral venous pressure at head level are reduced commensurate with arterial pressure for a closed circulatory system.<sup>13</sup> However, controversies regarding these assumptions must be recognized.<sup>25</sup> Currently, there are no experimental data that either unequivocally support or disprove this theory.<sup>26</sup> Thus, for this study, changes in cerebral hemodynamics in the same body position after reduction in BP or the comparisons made between the subject groups in response to HUT should be emphasized, because changes in cerebral arterial or venous hydrostatic pressure during HUT, whether or not commensurate, should be similar among subjects with a similar height (Table 1).

### Perspectives

Hypertension has been widely recognized as one of the important risk factors in stroke, development of dementia, and other cerebral and cardiovascular diseases. In this study, we found that steady-state CBF velocity and dynamic cerebral autoregulation were not compromised in patients with mild and moderate hypertension after short- or long-term

reduction in BP with administration of losartan/hydrochlorothiazide. These findings support a clinical strategy of lowering of BP rapidly in middle-aged patients with mild and moderate hypertension without fear of compromising brain perfusion and dynamic autoregulation. Future studies are warranted to determine the effects of antihypertensive therapy on cerebral hemodynamics in patients with severe hypertension, especially in the elderly. It is likely that aging, in combination with hypertension, may cause cerebrovascular damage and, thus, lead to a deterioration of cerebrovascular function under these conditions.

### Acknowledgments

We thank all of the subjects for their willingness to participate in this study. We also thank Drs Wanpen Vongpatanasin, Shawna Nesbitt, and Ronald Victor at the Hypertension Division University of Texas Southwestern Medical Center at Dallas for their support of this study.

### Source of Funding

This study was supported in part by a grant from the American Heart Association Texas Affiliate 0060024Y.

### Disclosures

None.

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