Published in final edited form as:

J Hypertens. 2009 November ; 27(11): 2218–2222. doi:10.1097/HJH.0b013e328330a9a7.

Autoregulation after ischaemic stroke

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Abstract

Objectives—Absent outcome data from randomized clinical trials, management of hypertension in acute ischaemic stroke remains controversial. Data from human participants have failed to resolve the question whether cerebral blood flow (CBF) in the peri-infarct region will decrease due to impaired autoregulation when systemic mean arterial pressure (MAP) is rapidly reduced.

Methods—Nine participants, 1–11 days after hemispheric ischaemic stroke, with systolic blood pressure more than 145 mmHg, underwent baseline PET measurements of regional CBF. Intravenous nicardipine infusion was then used to rapidly reduce mean arterial pressure 16 ± 7 mmHg and CBF measurement was repeated.

Results—Compared with the contralateral hemisphere, there were no significant differences in the percent change in CBF in the infarct ($P = 0.43$), peri-infarct region ($P = 1.00$) or remainder of the ipsilateral hemisphere ($P = 0.50$). Two participants showed CBF reductions of greater than 19% in both hemispheres.

Conclusion—In this study, selective regional impairment of CBF autoregulation in the infarcted hemisphere to reduced systemic blood pressure was not a characteristic of acute cerebral infarction. Reductions in CBF did occur in some individuals, but it was bihemispheric phenomenon that likely was due to an upward shift of the autoregulatory curve as a consequence of chronic hypertension. These results indicate individual monitoring of changes in global CBF, such as with bedside transcranial Doppler, may be useful to determine individual safe limits when MAP is lowered in the setting of acute ischaemic stroke. The benefit of such an approach can only be demonstrated by clinical trials demonstrating improved patient outcome.

Keywords

autoregulation; blood pressure; cerebral infarction; cerebrovascular circulation

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Case 3 has previously been reported (Zazulia AR, Videen TO, Powers WJ. Symptomatic autoregulatory failure in acute ischaemic stroke. *Neurology* 2007; **68**: 389–390.)

There are no conflicts of interest.

Introduction

In the absence of outcome data from randomized clinical trials, the management of hypertension in acute ischaemic stroke remains controversial [1–3]. Under normal conditions, changes in mean arterial pressure (MAP) over a wide range have little effect on cerebral blood flow (CBF) [4]. In most studies, the limits of autoregulation in normal participants are from approximately 70–150 mmHg [4,5]. [A contrasting viewpoint has been offered by Schmidt *et al.* [6] who used a new computer method to determine the lower limit of autoregulation at 85 mmHg.] Below the lower limit of autoregulation, further decreases in MAP lead to a decrease in CBF. Chronic arterial hypertension shifts the lower limit of autoregulation upwards, such that reductions in whole brain (global) CBF occur at higher MAP [7].

A series of pioneering human CBF studies using intra-carotid radiotracer injection following acute ischaemic stroke showed focal impairment of autoregulation to changes in systemic arterial blood pressure. Most of these studies employed increases in blood pressure only and none could distinguish the infarct from the peri-infarct region [8–11]. Recently, several studies of blood pressure reduction in hours or days following acute ischaemic stroke using different methods for CBF measurement have found no evidence of autoregulatory impairment in patients with recent ischaemic stroke [12]. However, due to a variety of methodological shortcomings, these studies have failed to resolve the question whether CBF in the peri-infarct (penumbra) region will decrease when systemic arterial pressure is quickly reduced due to regional impairment of autoregulation [12]. These studies were either performed with SPECT or xenon-CT (which have limited spatial resolution and thus may have failed to detect localized peri-infarct changes), used longer acting oral agents to reduce MAP, did not measure the effects of MAP reduction on CBF acutely or failed to report both hemispheric and peri-infarct values [12]. To provide more data relevant to the clinical situation in acute ischaemic stroke when rapid blood pressure reduction is contemplated, we performed a high resolution, quantitative PET study in nine patients with hemispheric stroke to evaluate hemispheric and focal peri-infarct autoregulation of CBF to rapid reductions in MAP.

Materials and methods

Participants

Patients hospitalized at Barnes–Jewish Hospital with acute ischaemic stroke were eligible for inclusion if they met the following criteria: age 18 years or older, diagnosis of hemispheric cerebral infarction by history, clinical examination, systolic blood pressure more than 145 mmHg by intra-arterial blood pressure recording at the completion of the baseline CBF measurements, and computed tomography (CT) scan within the previous 14 days. CT of the head did not need to show an appropriate focal area of decreased attenuation, but was required to rule out other conditions such as intracranial haemorrhage, tumour, etc. The following were reasons for exclusion: inability to cooperate with the performance of a detailed neurological examination and PET, decreased level of consciousness (NIHSS 1a > 2) and high baseline NIHSS (left hemisphere > 20 or right hemisphere > 15), pregnancy, compelling clinical reason to lower blood pressure (such as ongoing cardiac ischaemia, congestive heart failure, aortic dissection, hypertensive encephalopathy, malignant hypertension or acute renal failure), bilateral carotid artery stenosis at least 70%, concurrent treatment with alpha-1 receptor blockers (doxazosin, terazosin, prazosin) or hydralazine, known allergy to calcium channel blockers, or haemodynamically significant aortic valve stenosis.

Stroke onset was defined by the onset of symptoms. If the participant awoke with symptoms or if the exact onset of symptoms could not be determined, the time of onset was considered to be the time at which the patient was last known to be at his usual state of health. The type of ischaemic stroke was classified according to the Oxfordshire Community Stroke Project. This is a classification of subtypes of cerebral infarction (total or partial anterior circulation infarction, lacunar infarction, or posterior circulation infarction) based on clinical data only [13].

PET studies

All participants were studied on the Siemens model 961 ECAT EXACT HR 47 PET scanner (Siemens/CTI, Knoxville, Tennessee, USA) located in the Neurology-Neurosurgery Intensive Care Unit at Barnes-Jewish Hospital. This scanner collects 47 contiguous transverse slices encompassing an axial field of view of 15 cm. Spatial resolution is approximately 4.3 mm full width at half maximum (FWHM) at the centre of the field of view. All patients had one radial arterial catheter placed for blood sampling and two venous catheters placed in a peripheral arm vein for administration of radiotracers and for nicardipine infusion. Attenuation data were obtained using ^{68}Ge - ^{68}Ga rotating rod sources to enable quantitative reconstruction of subsequent emission scans. The PET scanner was calibrated for conversion of PET counts to quantitative radiotracer concentrations using standards counted in a well counter. Emission data were obtained in the 2D mode (interslice septa extended).

CBF was measured with an adaptation of the Kety autoradiographic method using intravenous bolus injection of 50 mCi of ^{15}O labelled water [14,15]. Simultaneously with acquisition of the PET emission data, arterial blood was sampled and the arterial activity curve was determined using a scintillation counter calibrated to the same well counter as the PET scanner. The arterial time-radioactivity curve recorded by the sampler was corrected for delay and dispersion using previously determined parameters. Baseline measurements of CBF were performed in triplicate. Participants whose systolic blood pressure was more than 145 mmHg at the end of the third baseline CBF scan received an intravenous infusion of nicardipine starting at 2.5 mg/h upto a maximum of 15 mg/h to achieve a reduction in MAP by 15 ± 5 mmHg from baseline in two steps of 7.5 mmHg. A clinical assessment was performed at each blood pressure step. Mild sedation with fentanyl 25–100 μg IV upto a total dose of 300 μg was used as needed.

Immediately after the PET scan patients who had not had MRI performed for clinical purposes underwent MRI including T2 and diffusion weighted studies to delineate the infarct. Participants with contraindications for MRI such as history or documentation of implanted ferromagnetic material or other devices (e.g. cardiac pacemaker) or claustrophobia underwent CT.

Written informed consent was obtained from all participants or, if the participant was incapable of giving informed consent, from the participant's legally authorized representative in accordance with Missouri state law. This protocol was approved by the Washington University Human Studies Committee (IRB).

Data analysis

PET 2D-acquisitions following bolus water injection were reconstructed with measured attenuation and scatter corrections using filtered backprojection to a 3D resolution of 4.3 mm FWHM. Seven participants had magnetic resonance (MR) imaging and two had CT imaging. These were standard clinical scans from a variety of scanners (Siemens Magnetom Vision, Expert, Symphony, or Trio for MRI and Siemens Sensation 16 or Somatom Plus 4

for CT). Anatomical images had less than 1 mm in-plane resolution but had slice sampling ranging from 3.0–7.8 mm. All PET images were coregistered to each other using Automated Image Registration software (AIR, Roger Woods, University of California, Los Angeles, California, USA) [16]. Anatomical images were also coregistered and resliced to the PET images using AIR [17].

The ipsilateral hemisphere was divided into areas of infarction, the peri-infarct area and the remainder. Brain tissue was segmented from either MR FLAIR or CT. Infarcted areas (ranging from 0.5–340 ml) were identified either from MR diffusion weighted images or CT. One cm annular peri-infarct regions were created by 2D dilation around each infarct, conditionally restricted to noninfarcted ipsilateral brain tissue. The remaining ipsilateral hemispheric CBF measurements excluded the infarct and peri-infarct regions. All CBF values were computed using mean PET counts within the volume of interest on the original PET images (4.3 mm resolution). Mean counts were then converted to CBF (ml/100 g per min) [15].

In a previous study of nine normal individuals in which 18 sets of four sequential CBF measurements at stable clamped plasma glucose were performed, the maximum decrease in hemispheric CBF between the mean of the first three studies and the fourth study was 18.9% [18]. Therefore, we considered a reduction in contralateral hemispheric CBF in an individual subject more than 19% between the mean of the three baseline studies and the study during blood pressure reduction to be abnormal.

With selective regional impairment of autoregulation, there will be a consistently greater decrease in CBF during blood pressure reduction in the region with selective impairment than in the contralateral control hemisphere. To determine if this was the case, we compared the percentage change in CBF in the contralateral control hemisphere to the infarct, the peri-infarct region and the remainder of the ipsilateral hemisphere by paired *t*-test. All statistical analyses were performed with SPSS 16.0 for Windows (SPSS, Inc, Chicago, Illinois, USA).

Results

Twelve participants were enrolled in this study. One participant was unable to undergo PET because he could not lie still. PET studies could not be performed in another because of inability to insert a radial artery catheter. One was found subsequently to have a pontine infarct. Clinical characteristics and physiological data during PET for the remaining nine participants are shown in the Tables 1 and 2. Two received fentanyl during the the baseline series of scans: Case 8 62.5 µg and Case 9 25 µg. Carotid ultrasound in seven participants and arteriography in one showed less than 50% cervical stenosis bilaterally in all. Case 7 did not undergo carotid imaging because her thalamic infarct was not in the carotid arterial territory.

IV nicardipine was administered starting at 2.5 mg/h and then adjusted every 10 min. MAP was reduced by 8–30, mean 16 ± 7 (SD) mmHg over 33–83 (mean 63) min. MAP was held constant at this level for at least several minutes prior to the CBF measurement, sufficiently long to permit the cerebrovascular responses to MAP reduction to reach a new steady state [19]. Six of the nine participants reached the target of 10–20 mmHg reduction (Table 3) The percent change in CBF in the peri-infarct region ($-10.9 \pm 16.0\%$) was the the same as the contralateral hemisphere ($-10.9 \pm 12.3\%$, $P = 1.00$, paired *t*-test). Similar data were obtained for the remainder of the ipsilateral hemisphere. In the infarct itself, CBF changes were more variable but still did not show a significant difference from the control contralateral hemisphere (Table 3). Thus, there was no evidence of selective focal impairment of autoregulation in any of the regions in the ipsilateral hemisphere. In two

participants, both contralateral and ipsilateral hemispheric CBF decreased during pharmacological blood pressure reduction more than the maximum test–retest normal range of 19%. One (Case 3) clinically worsened; the other (Case 6) showed no clinical change. The PET study on Case 3 was stopped when he became neurologically worse. Details of this case have previously been reported [20]. No other participant had a change in signs or symptoms.

There was no correlation between any of the percentage CBF changes in any of the four regions (infarct, peri-infarct, remaining ipsilateral hemisphere or contralateral hemisphere) and infarct size, MAP percentage change, baseline CBF or time after onset (all $r < 0.18$, all $P > 0.66$).

Discussion

In this study of nine human participants who had suffered acute ischaemic stroke within the previous 11 days, we did not find autoregulatory impairment in the infarct, peri-infarct region or remaining ipsilateral hemisphere during rapid reductions in systemic arterial blood pressure. Unlike previous studies, we rapidly reduced MAP with an intravenous infusion, used a high resolution quantitative method to measure regional CBF and report regional CBF data from both hemispheric, the peri-infarct region and the infarct [12].

In two of our individuals we found global reductions of hemispheric CBF with MAP reductions. The lower levels of MAP achieved in these two individuals were 123 and 127 mmHg, well above the normal lower limit for autoregulation. Both had longstanding hypertension manifested by left ventricular hypertrophy on echocardiography. The findings in these two participants are consistent with a shift upwards in the whole brain autoregulatory curve due to chronic hypertension [5,7]. One of these two patients developed transient worsening of his focal neurological deficit during blood pressure reduction. Such focal worsening with blood pressure reduction has been ascribed to further reducing CBF in presumed areas of focally impaired autoregulation in the peri-infarct region [1,21]. The findings in this case that focal worsening occurred with global reduction in CBF suggest another explanation: When MAP is reduced below the lower limit of autoregulation (which may be shifted upward due to chronic hypertension), CBF will decrease uniformly in the whole brain. In the setting of acute ischaemic stroke, neurons in the peri-infarct area with CBF values just above the threshold for normal neuronal function will be the first to become dysfunctional as CBF decreases globally. Thus, although the CBF reduction is uniformly global, the symptoms may be a focal worsening of the existing neurological deficit.

The CBF responses to changes in MAP that we have measured have recently been termed static cerebral autoregulation to differentiate them from measurements of cerebral blood flow velocity with Doppler in response to more rapid fluctuations in MAP or ICP, termed dynamic cerebral autoregulation [22]. Studies of dynamic autoregulation following acute ischaemic stroke have described both unilateral and bilateral abnormalities [23]. This methodology is not spatially sensitive enough to detect selective regional impairment in the peri-infarct area. The physiological relation between static and dynamic autoregulation is not clear. Abnormalities of dynamic cerebral autoregulation may be associated with normal or abnormal static autoregulation [24,25].

Our study is based on a small number of participants, mostly with small to moderate sized infarcts. The earliest study was performed the day after onset. All had evidence of preexisting arterial hypertension. Therefore, these findings cannot be assumed to apply to patients with larger infarcts, those in the very acute period or those without preexisting hypertension.

In conclusion, focally impaired autoregulation to reduced blood pressure in the infarct, peri-infarct area and remaining ipsilateral hemisphere was not a characteristic of acute cerebral infarction in this study. When blood pressure was lowered, reductions in global cerebral blood flow did occur in some individuals. Thus, the CBF response to MAP reduction in hypertensive patients with acute ischaemic stroke was primarily a global phenomenon and varied from individual to individual. This is similar to patients with chronic arterial hypertension without stroke and is likely related to a variable upward shift of the autoregulatory curve as a consequence of chronic hypertension [4,5,7]. Therefore, individual monitoring of changes in global CBF, such as with bedside transcranial Doppler, may be useful to determine individual safe lower limits when MAP is lowered in the setting of acute ischaemic stroke. However, the benefit of such an approach can only be demonstrated by clinical trials demonstrating improved patient outcome.

Acknowledgments

Sources of Support: This research was supported by the following grants from the National Institutes of Health: NS35966 and NS44885.

Abbreviations

CBF	cerebral blood flow
CT	computed tomography
FWHM	full width at half maximum
MAP	mean arterial pressure

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Patient characteristics

Table 1

Case	Age	Sex	Days after stroke	OCSP stroke type	Infarct size (ml)	Hx HTN	Previous HTN Rx	Echo LVH	Anti-HTN meds in 24 h
1	66	F	1	PACI	5	Y	Y	Y	clon, met
2	64	F	2	PACI	0.5	Y	Y	N	None
3	50	M	3	PACI(BZ)	22.1	Y	Y*	Y	None
4	59	M	4	LACI	19.2	Y	Y	N	None
5	70	M	5	PACI	24.4	Y	Y	N	lis, met
6	54	M	6	PACI	1.4	N	N	Y	amlo, met
7	62	F	6	LACI	1.1	Y	Y	Y	nif, lis
8	63	M	8	PACI	66.4	ND	ND	Y	cap, amlo
9	59	M	11	TACI	339.7	Y	Y	N	met, ver

ND, no data; amlo, amlodipine; anti-HTN meds in 24 h, antihypertensive medications taken within the 24 h prior to PET; BZ, borderzone; cap, captopril; clon, clonidine; days p stroke, days poststroke PET scan performed; echo LVH, echocardiographic evidence of left ventricular hypertrophy; F, female; Hx HTN, history of hypertension; LACI, lacunar infarct; lis, lisinopril; M, male; met, metoprolol; N, No; nif, nifedipine; OCSP, Oxfordshire Community Stroke Project; PACI, partial anterior circulation infarct; Previous HTN Rx, treatment for hypertension prior to stroke onset; TACI, total anterior circulation infarct; ver, verapamil; Y*, yes, had not been taking medications; Y, yes.

Table 2

Physiological measurements during PET

Case	Hct	pCO ₂ (mmHg)		MAP (mmHg)	
		BL	NI	BL	NI
1	22	30	34	137	119
2	39	38	37	106	97
3	43	36	34	130	123
4	38	38	41	117	102
5	31	46	41	151	143
6	45	34	36	147	127
7	35	37	37	133	117
8	41	31	32	166	148
9	38	NA	NA	135	105
Mean $\pm$ SD		36 $\pm$ 5	37 $\pm$ 3	136 $\pm$ 18	120 $\pm$ 18

BL, baseline; Hct, hematocrit; MAP, mean arterial pressure; NA, not available; NI, nicardipine infusion.

Table 3

Cerebral blood flow during nicardipine infusion

Case	MAP			Contralateral hemisphere CBF			Ipsilateral hemisphere CBF			1 cm perinfarct CBF			Infarct CBF		
	Change	BL	NI	Change	BL	NI	Change	BL	NI	Change	BL	NI	Change	BL	NI
1	-18	21.8	20.1	-8.0%	19.3	17.9	-7.4%	19.6	20.7	5.6%	14.4	15.9	10.1%		
2	-9	23.7	20.8	-12.2%	22.1	19.1	-13.8%	15.5	13.6	-12.5%	16.3	7.7	-53.1%		
3	-7	37.7	24.1	-36.1%	37.8	23.5	-37.8%	39.6	24.0	-39.3%	38.6	25.7	-33.4%		
4	-15	34.5	31.7	-8.0%	35.4	33.0	-6.9%	33.2	29.8	-10.3%	25.3	24.2	-4.4%		
5	-8	41.5	40.9	-1.3%	41.0	40.8	-0.3%	36.0	35.9	-0.4%	53.8	55.3	2.9%		
6	-20	31.5	25.3	-19.5%	29.7	23.9	-19.4%	28.2	19.7	-30.1%	24.2	16.4	-32.3%		
7	-16	42.3	45.5	7.4%	39.4	46.4	17.6%	40.3	44.7	11.0%	22.3	52.1	133.4%		
8	-18	24.0	22.9	-4.7%	24.4	22.9	-6.4%	27.7	25.1	-9.2%	29.8	25.6	-14.0%		
9	-30	25.4	21.5	-15.4%	27.1	23.2	-14.2%	25.4	22.2	-12.7%	22.8	20.9	-8.4%		
Mean ± SD	-16 ± 7	31.4 ± 8.0	28.1 ± 9.3	-10.9 ± 12.3%	30.7 ± 8.0	27.9 ± 10.0	-9.8 ± 14.9%	29.5 ± 8.6	26.2 ± 9.4	-10.9 ± 16.0%	27.5 ± 12.1	27.1 ± 16.2	-0.1 ± 53.8%		
Paired <i>t</i> -test vs. contralateral hemisphere				<i>P</i> = 0.43			<i>P</i> = 1.00			<i>P</i> = 0.50					

BL, Baseline; CBF, cerebral blood flow ml 100 g⁻¹ min⁻¹; MAP, mean arterial pressure mmHg; NI, nicardipine infusion; SD, standard deviation. Ipsilateral Hemispheric CBF excludes infarct and peri-infarct regions. Two participants with reductions in bihemispheric CBF outside the normal range are shown in bold.