

# Transdermal Glyceryl Trinitrate Lowers Blood Pressure and Maintains Cerebral Blood Flow in Recent Stroke

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**Abstract**—High blood pressure (BP) is common in acute stroke and is independently associated with a poor outcome. Lowering BP might improve outcome if it did not adversely affect cerebral blood flow (CBF) or cerebral perfusion pressure. We investigated the effect of glyceryl trinitrate (GTN) an NO donor on quantitative CBF, BP, and cerebral perfusion pressure in patients with recent stroke. Eighteen patients with recent (<5 days) ischemic (n=16) or hemorrhagic (n=2) stroke were randomly assigned (2:1) to transdermal GTN (5 mg) or control. CBF (global, hemispheric, arterial territory, and lesion, using xenon computed tomography) and BP (peripheral and central) were measured before and 1 hour after treatment with GTN. The effects of GTN on CBF and BP were adjusted for baseline measurements (ANCOVA). GTN lowered peripheral systolic BP by (mean) 23 mm Hg (95% CI, 2 to 45;  $P=0.03$ ) and central systolic BP by 22 mm Hg (95% CI, 0 to 44;  $P=0.048$ ). In contrast, GTN did not alter CBF (mL/min per 100 g): global  $-1.2$  (95% CI,  $-6.5$  to  $4.2$ ;  $P=0.66$ ) and ipsilateral hemisphere  $-1.4$  (95% CI,  $-7.6$  to  $4.9$ ;  $P=0.65$ ) or area of stroke oligemia, penumbra, or core (as defined by critical CBF limits). Contralateral CBF did not change: hemisphere 0 (95% CI,  $-7$  to  $6$ ;  $P=0.96$ ). GTN did not alter cerebral perfusion pressure or zero-filling pressure. Significant reductions in BP after transdermal GTN are not associated with changes in CBF or cerebral perfusion pressure or cerebral steal in patients with recent stroke. Trials need to assess the effect of lowering BP on functional outcome. (*Hypertension*. 2006;47:1209-1215.)

**Key Words:** stroke ■ hypertension, arterial ■ cerebral arteries ■ nitric oxide ■ nitroglycerin

High blood pressure (BP) is present in more than three quarters of patients at presentation with acute ischemic stroke and is independently associated with a poor outcome and early recurrence.<sup>1,2</sup> Similar findings have been reported for patients with primary intracerebral hemorrhage.<sup>3</sup> These observational data raise the possibility that lowering BP might improve functional outcome provided that both cerebral blood flow (CBF) and cerebral perfusion pressure (CPP) do not fall.

Drugs that lower BP in patients with recent ischemic stroke vary in their effect on CBF. Calcium channel blockers reduced cerebral perfusion in parallel with their effect on BP.<sup>4,5</sup> In contrast, angiotensin modifying drugs, such as captopril and perindopril (angiotensin-converting enzyme inhibitors) and losartan (angiotensin receptor antagonist) did not seem to alter CBF or middle cerebral artery blood velocity.<sup>6–8</sup> Hence, the effect of altering BP on CBF may be drug or class specific.

CPP is the difference between upstream (mean arterial pressure) and downstream pressure, the latter being determined by intracranial pressure (ICP) and central venous pressure. Cerebral vasodilators may increase or decrease CPP depending on their relative effects on these 3 measures; for example,

venodilators may both increase cerebral blood volume and reduce central venous pressure, thereby maintaining ICP. Previous work has shown that vasodilators, including nitrous oxide,<sup>9</sup> can increase CPP by reducing zero-flow pressure (ZFP), a measure of cerebral downstream (venous) pressure.

We reported previously that transdermal glyceryl trinitrate (GTN), an NO donor, lowered both peripheral and central BP in a dose-dependent manner, improved aortic compliance, and did not alter platelet function or activation.<sup>10,11</sup> Indirect evidence also suggested that nitrates lowered BP without attenuating CBF, confirming preclinical data.<sup>12–14</sup> Sodium nitroprusside did not alter CBF, assessed qualitatively using single-photon emission computed tomography.<sup>15</sup> Similarly, GTN did not change the middle cerebral artery blood velocity and pulsatility index, these being indirect measures of CBF.<sup>11</sup> The aim of the present study was to assess simultaneously the effects of GTN on BP, CBF, and CPP.

## Methods

We performed a prospective, single-center, patient- and measurement-blinded, randomized, controlled trial. Approval was obtained from the local research ethics committee (EC01/69) and Medicines Control Agency (DDX MF8000/13187). Patients gave written informed

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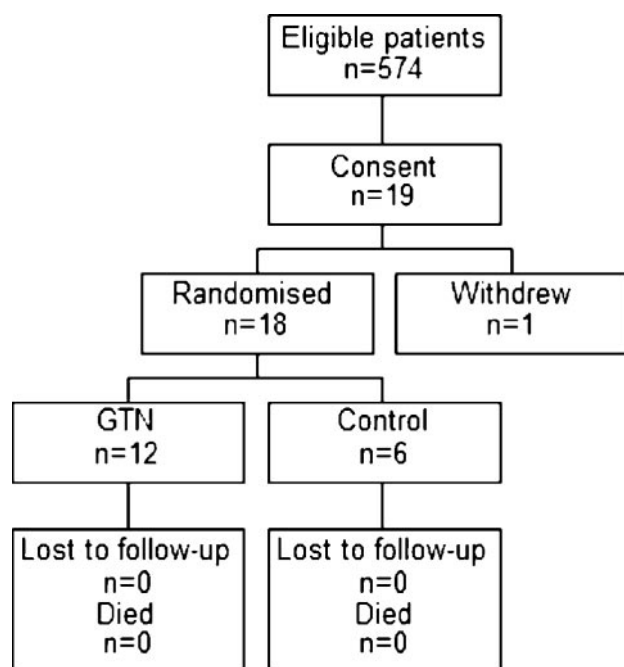
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**Figure 1.** Trial flow profile. Withdrawal because of intolerance of xenon CT procedure.

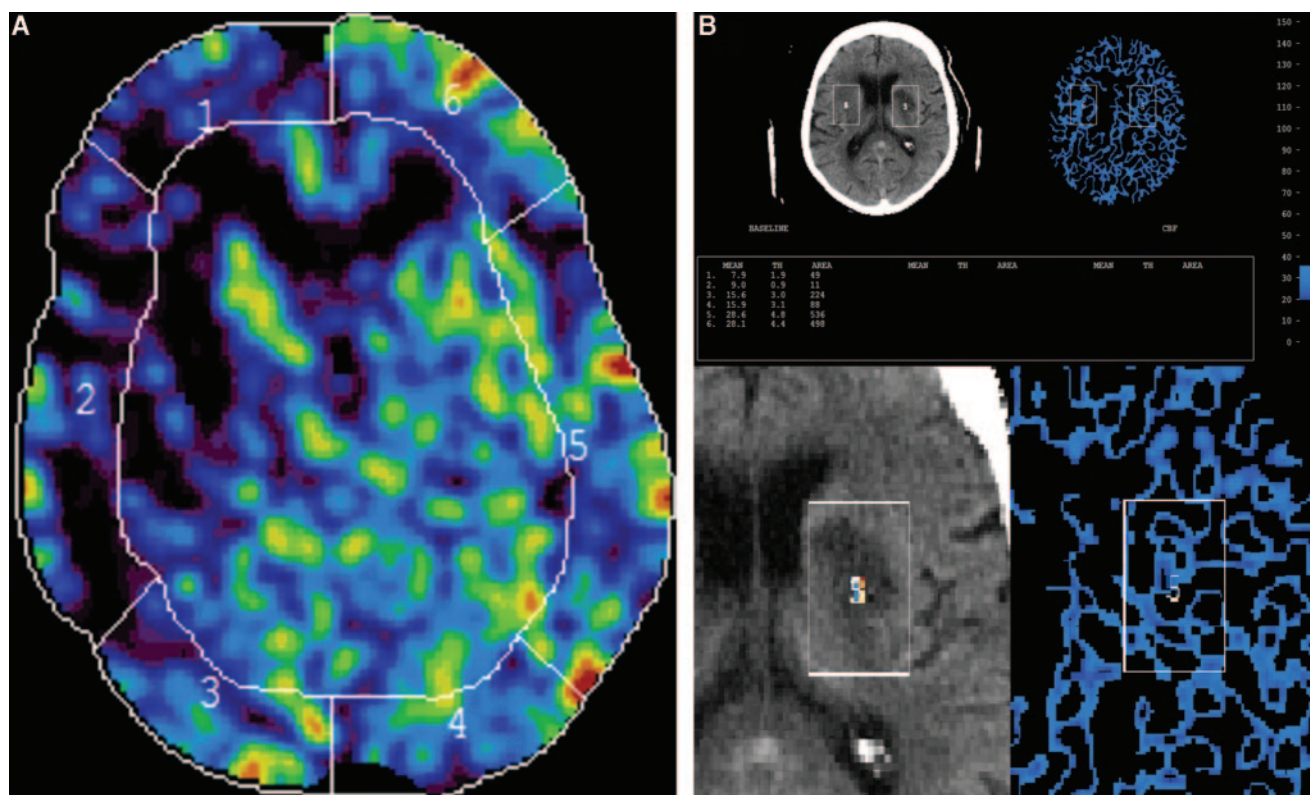
consent to participate; assent was obtained from the next of kin if the patient was unable to give consent. Enrollment into the study was made before neuroimaging or estimation of CBF. The study conformed to the Declaration of Helsinki and International Conference

on Harmonisation guidelines. Enrollment took place between September 2002 and September 2004.

Eighteen previously independent (modified Rankin Scale, 0 to 2) adult patients with a clinical stroke syndrome and limb weakness (Scandinavian Stroke Scale, arm and/or leg <6) were recruited within 5 days of ictus (Figure 1). All of the subjects had an elevated systolic BP (140 to 220 mm Hg) at enrollment. Subjects were excluded if they had a requirement for, or a contraindication to, nitrate therapy; had a definite need for previous antihypertensive therapy or vasoactive drugs; or could not cooperate with scanning.

Subjects were randomly assigned using computerized minimization (on age, sex, baseline systolic BP, baseline Scandinavian Stroke Scale, hours from onset, and the presence of a visible stroke lesion on computed tomography [CT]) to receive either a 5-mg GTN patch (Transiderm-Nitro 5, Novartis Pharmaceuticals) or control in a ratio of 2:1. Treatment was given once daily for 7 days. Patients and the assessor who performed hemodynamic and xenon CT measurements (M.W.) were blinded to treatment by placement of a large gauze dressing over the patch or empty skin to conceal treatment status. GTN patches were changed at 8:00 AM each day and kept on for a full 24 hours. Any previous antihypertensive medication was discontinued at the time of admission, as is routine at our institution.

Quantitative regional CBF was measured using the stable xenon CT method (Diversified Diagnostic Products XeCT system 2).<sup>16</sup> A baseline CT head scan was performed to confirm the diagnosis of stroke (ischemia, hemorrhage) and to obtain a "scout" image; subsequent scans were composed of 4 adjacent 10-mm-thick slices chosen to encompass the maximum axial dimensions of the stroke lesion. If no lesion was visible, slices included the basal ganglia and internal capsule. The patient was connected to the XeCT system via a face mask and breathed room air for 30 seconds while 2 baseline sets of images were recorded. Subsequently, the patient breathed a mix of xenon (28%) and oxygen (25%) with monitoring of end tidal



**Figure 2.** (A) Example of template for anterior cerebral artery (areas 1 and 6), middle cerebral artery (2 and 5), and posterior cerebral artery (3 and 4) cortical ROIs in a patient with a large right hemisphere infarct. (B) Measurement of cerebral blood flow in an ROI encompassing an area of oligemia (20 to 36 mL/min per 100 g) in a patient with a left hemisphere infarct. Similar CBF filters were used to identify lesion core (CBF < 10 mL/min per 100 g) and penumbra (CBF 10 to 20 mL/min per 100 g).

**TABLE 1. Demographic Characteristics of Patients**

Characteristics	Control	GTN
Subjects	6	12
Age, y*	70.3 (10.8)	69.0 (5.6)
Sex, male, %*	3 (50)	2 (17)
Previous hypertension, %	4 (67)	3 (25)
Previous antihypertensive therapy, %	3 (50)	3 (25)
Previous stroke, %	1 (17)	2 (17)
Smoker, current, %	3 (50)	8 (67)
Stroke to randomization, h†*	77 (54)	79 (38)
Scandinavian stroke scale, /58†*	47 (18)	42 (11)
Stroke type, ischemic, %	5 (83)	11 (92)
Cortical syndrome, %	1 (17)	5 (42)

Mean (SD), median (interquartile range), or frequency (%).

\*Minimization variable.

†Median.

xenon concentration. Additional sets of images were then collected over 5 minutes. A second xenon CT scan series was performed 1 hour after administration of GTN or control; careful positioning of the patient ensured that near-identical brain slices as determined by

**TABLE 2. Hemodynamic Measurements at Baseline**

Measurement	Control N=6	GTN N=12
BP, mm Hg		
Peripheral		
Systolic*	166 (18)	162 (16)
Diastolic	87 (10)	92 (17)
Central		
Systolic	151 (17)	152 (13)
Diastolic	91 (15)	95 (16)
Heart rate, bpm	66 (15)	69 (14)
Cerebral blood flow, mL/min per 100 g		
Global	31.1 (6.0)	38.4 (10.6)
Ipsilateral		
Hemisphere	30.4 (4.9)	37.8 (12.8)
ACA territory	32.3 (14.7)	38.4 (12.4)
MCA territory	32.1 (5.7)	42.1 (15.0)
PCA territory	30.0 (9.2)	40.6 (17.5)
Contralateral		
Hemisphere	31.9 (7.8)	39.4 (8.9)
ACA territory	34.0 (9.9)	40.4 (11.5)
MCA territory	38.2 (10.0)	45.8 (10.3)
PCA territory	29.8 (12.4)	38.9 (12.1)
Lesion area, pixels		
Oligemia	364 (221)	351 (140)
Penumbra	258 (196)	262 (197)
Core	207 (273)	235 (288)
CPP, mm Hg	59.7 (12.0)	43.4 (18.0)
ZFP, mm Hg	59.5 (14.8)	72.5 (26.6)

Mean (SD). ACA indicates anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.

\*Minimization variable.

neuroradiological landmarks were imaged in pre-GTN and post-GTN scans.

CBF was calculated on a PC using XeCT software in an identical manner for pre-GTN and post-GTN scans. Images with excessive movement artifact or where an old stroke lesion was present were discarded. Analyses (by M.W.) were blinded to treatment and concentrated on the slice with the largest visible area of stroke lesion. If no lesion was visible, an appropriate level was selected according to the clinical presentation. Global and hemispheric regions of interest (ROIs) were sited using a rectangular-shaped template, the former touching the inside of the skull anteroposteriorly and laterally and the latter dividing the skull at the midline. Anterior, middle, and posterior cerebral artery territory ROIs were placed over the cortex using a template generated by the XeCT software (Figure 2a).

An additional pixel-based analysis was used to assess the effect of GTN on CBF in the stroke lesion, if visible. A rectangular ROI was placed to cover the whole of the stroke lesion and surrounding brain tissue (Figure 2b). A CBF filter was then used to determine the number of pixels within the ROI matching prespecified CBF values for “core” (<10 mL/min per 100 g), “penumbra” (10 to 19 mL/min per 100 g), and “oligemia” (20 to 36 mL/min per 100 g).<sup>17–20</sup> Matching ROIs were sited on pretreatment and posttreatment scans to ensure consistency, and the areas (in pixels) of reduced CBF were compared.

Middle cerebral artery blood velocity was determined bilaterally by transcranial Doppler (Nicolet EME Companion, Kleinfeltheim) with the transtemporal window accessed at depths from 30 to 60 mm.<sup>21</sup> Duplicate mean, systolic, and diastolic velocities and pulsatility index were measured separately for affected and unaffected hemispheres.<sup>10,11</sup>

BP was measured immediately before the baseline xenon CT scan and immediately after the posttreatment scan. Duplicate measurements of peripheral systolic and diastolic BP were measured in the nonhemiparetic arm with a validated digital readout oscillometric device (Omron HEM-705CP, Omron Corp).<sup>22</sup> Central BP was assessed by applanation tonometry of the left radial artery and using the Pulse Wave Analysis system (Sphygmocor).<sup>11</sup> Duplicate recordings were taken, composed of a screen of data satisfying the quality control criteria of the Pulse Wave Analysis system (pulse height and diastolic variability ≤10%). The recorded radial artery pressure wave was transformed to the corresponding central wave using a validated transfer function and central BP derived automatically.

CPP and ZFP were estimated noninvasively from measures of middle cerebral artery blood flow velocity (FV), assessed using transcranial Doppler, and peripheral BP using the following method<sup>9,23</sup>:

$$\text{CPP} = [\text{mean FV} / (\text{mean FV} - \text{diastolic FV})] \times (\text{mean BP} - \text{diastolic BP}) \quad (1)$$

$$\text{ZFP} = \text{mean BP} - \text{CPP} \quad (2)$$

The study assumed that a between-group difference in CBF of 10 mL/min per 100 g (SD, 6) would be of clinical relevance. We calculated a sample size of 18, assuming significance 0.05, power 0.80, and 2:1 randomization, and accepted that this would lead to results with large CIs. Data were entered and analyzed by intention-to-treat using SPSS (Apple Mac version 11.0.2, SPSS Inc). Mean (SD), median (interquartile range) or frequencies (%) are given. All of the comparisons of hemodynamic and BP data between the treatment groups were analyzed with adjustment for baseline values using ANCOVA. Linear regression was used to assess the relationship between on-treatment CBF and BP with adjustment for baseline values. Significance was set at  $P < 0.05$ .

## Results

Subject characteristics were balanced between the 2 groups, except that more patients randomly assigned to GTN were female or had a cortical-based stroke on CT scan (Table 1).



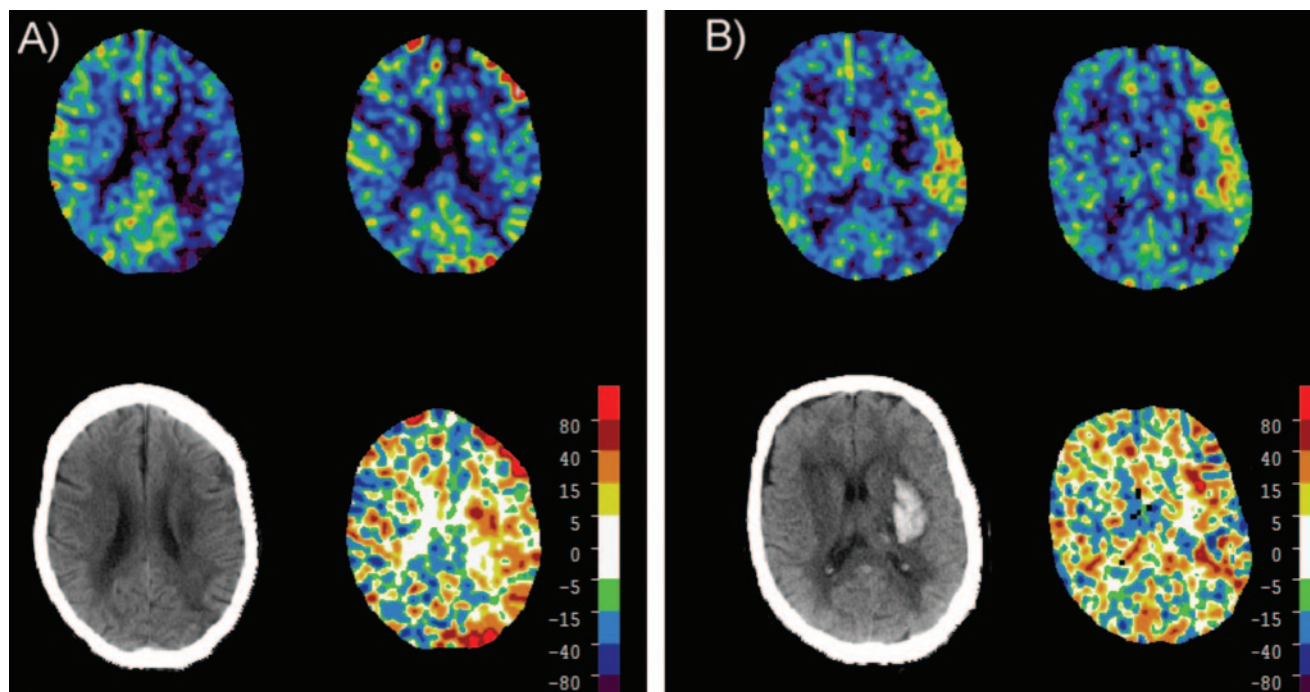
**TABLE 3. Effect of Transdermal GTN on CBF and Estimates of CPP**

Measurement	Control, Subjects	GTN, Subjects	Control	GTN	Difference, 95% CI	2P
CBF, mL/min per 100 g	6	12	32.8 (7.3)	37.8 (9.7)	−1.2 (−6.5 to 4.2)	0.66
Global	6	12	32.8 (7.3)	37.8 (9.7)	−1.2 (−6.5 to 4.2)	0.66
Ipsilateral						
Hemisphere	6	12	33.4 (8.3)	37.2 (9.8)	−1.4 (−7.6 to 4.9)	0.65
ACA territory	6	12	30.3 (8.0)	39.5 (14.6)	6.3 (−6.5 to 19.0)	0.31
MCA territory	6	12	37.0 (10.8)	43.5 (10.8)	0.6 (−8.4 to 9.6)	0.89
PCA territory	6	12	35.3 (10.2)	39.1 (11.8)	−0.7 (−11.4 to 10.1)	0.90
Contralateral						
Hemisphere	6	12	32.2 (6.3)	38.4 (10.0)	0 (−7 to 6)	0.96
ACA territory	6	12	33.3 (8.1)	41.1 (16.8)	5.7 (−10.6 to 21.9)	0.47
MCA territory	6	12	35.3 (9.6)	44.2 (10.8)	4.6 (−5.5 to 14.7)	0.35
PCA territory	6	12	32.7 (7.3)	42.0 (15.1)	2.6 (−8.6 to 13.9)	0.63
Lesion area, pixels						
Oligemia	4	9	329 (146)	355 (167)	35 (−120 to 191)	0.63
Penumbra	4	9	222 (166)	247 (141)	23 (−76 to 123)	0.62
Core	4	9	243 (318)	266 (290)	−2 (−210 to 206)	0.98
CPP, mm Hg	3	10	59.1 (32.4)	50.9 (15.8)	−4.4 (−37.4 to 28.6)	0.77
ZFP, mm Hg	3	10	73.4 (47.2)	60.8 (10.5)	−13.6 (−48.8 to 21.5)	0.41

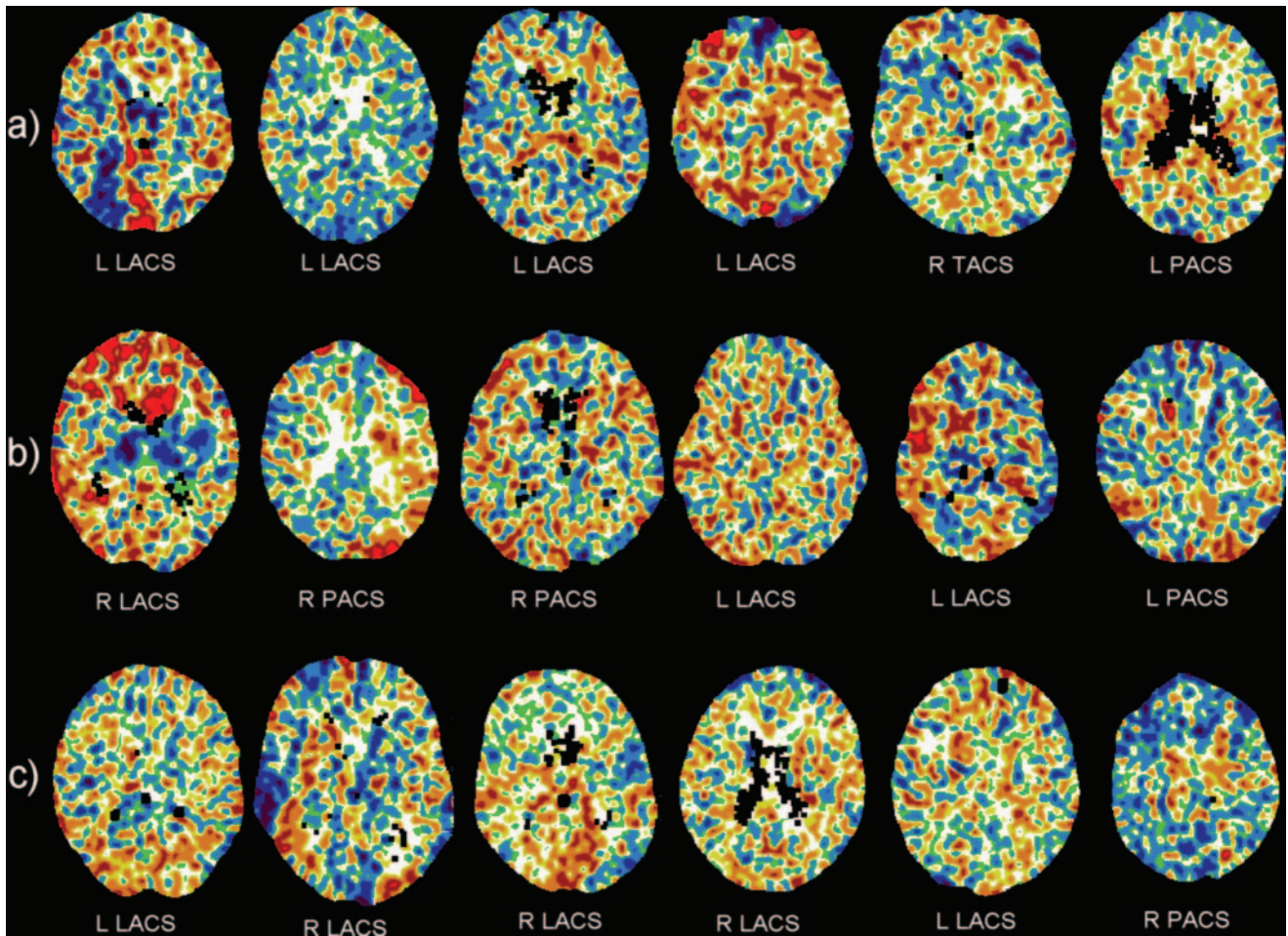
Mean (SD), 95% CI, comparison by ANCOVA with adjustment for baseline values.

Most patients had a mild–moderate stroke severity reflecting the fact that only one third had a middle cerebral artery cortical lesion visible on CT scan; the remaining patients had a lacunar stroke. The time between stroke onset and treatment was similar between the 2 groups [median (range), control 77 (22–92) hours; GTN, 79 (28–116) hours]. Peripheral BP was

elevated at baseline and higher than central BP. No patients had significant carotid stenosis. Although the mean areas of oligemia, penumbra, and core were similar in size between the 2 groups, baseline measures of global, hemispheric, and regional CBF, both ipsilateral and contralateral to the lesion, and ZFP were nonsignificantly higher in patients randomly



**Figure 3.** (A) Patient with a left hemisphere borderzone infarct (bottom left); cerebral blood flow before (top left) and 1 hour after GTN (top right); cerebral blood flow has increased with GTN in and around the hypodense lesion, and no cerebral steal is present, as shown by the difference between prescans and postscans (bottom right). (B) Patient with a left intracranial hemorrhage (bottom left); cerebral blood flow before (top left) and 1 hour after GTN (top right); cerebral blood flow has increased with GTN around the bleed, and no cerebral steal is present, as shown by the difference between prescans and postscans (bottom right).



**Figure 4.** Cerebral blood flow difference scans (post-GTN, baseline) for all patients. Patients receiving active treatment: rows a and b; control: row c. Axial slices are shown at level of the largest lesion diameter or an appropriate level for the clinical presentation if no lesion was visible on the CT scan. The side of lesion (R indicates right; L, left) and Oxfordshire Community Stroke Project classification (LACS indicates lacunar syndrome; PACS, partial anterior circulation syndrome; TACS, total anterior circulation syndrome) are given for each scan.

assigned to GTN (Table 2). Patients randomly assigned to control tended to have higher CPP.

GTN lowered peripheral and central systolic BP by 23 mm Hg (14%) and 22 mm Hg (13%), respectively ( $P=0.034$ ;  $P=0.048$ ). Nonsignificant reductions in peripheral and central diastolic BP were present, at 4 mm Hg (3%) for each ( $P=0.47$ ;  $P=0.55$ ). GTN did not alter heart rate. In contrast to BP, GTN did not alter any measure of global, hemispheric, or regional CBF whether on the side ipsilateral or contralateral to the lesion (Table 3 and Figures 2a, 3, and 4). Nevertheless, the CIs were wide, and GTN might have reduced ipsilateral hemispheric CBF by 7.6 mL/min per 100 g or increased it by 4.9 mL/min per 100 g. When defined by blood flow levels, GTN had no effect on the size of presumptive core, penumbra, or oligemic areas (Figure 2b). Similarly, GTN did not significantly alter estimates of CPP and ZFP (Table 3). There was no association between on-treatment measures of ipsilateral CBF and systolic BP ( $P=0.83$ , with adjustment for baseline CBF and systolic BP) in patients randomized to GTN.

All of the patients completed 7 days of treatment. One serious adverse event occurred during the treatment phase; a

patient receiving GTN had a nonhypotension-related fall leading to trauma of the affected arm. Headache occurred in 1 GTN patient. There were no deaths, and the modified Rankin Scale (telephone assessment by B.W. blinded to treatment) did not differ between the groups at 90 days [median (interquartile range): GTN, 2 (1); control, 2 (1); Mann-Whitney U test<sup>24</sup>  $2P=0.89$ ].

## Discussion

We have shown that transdermal GTN lowers BP modestly (by 14.3%) without having any detrimental effect on CBF or CPP in patients with recent stroke. The neutral effect on CBF was present whether global CBF, ipsilateral and contralateral hemispheric CBF, or ipsilateral and contralateral arterial ROIs were studied. Similarly, GTN did not alter the size of lesion core or penumbral or oligemic areas, as defined by prespecified CBF levels, and did not seem to cause a “cerebral steal” effect.

Examination of the results for individual patients (Figure 3a) suggest that GTN may, in some cases, increase CBF both within and around the hypoattenuated tissue and both superficially and deep within the brain. Similarly, an increase in



perilesional CBF was seen in a patient with a primary intracerebral hemorrhage (Figure 3b).

Acute stroke, whether of ischemic or hemorrhagic type, is associated with dysfunctional cerebral autoregulation so that, in the extreme, cerebral perfusion becomes dependent on systemic BP. The mechanism by which GTN can lower BP while maintaining CBF was not addressed in this study. However, GTN forms NO, which is a potent modulator of cerebrovascular reactivity, especially in collateral vessels, such as pial arteries.<sup>25,26</sup> Vascular NO levels are low in stroke,<sup>27</sup> so collateral vessels may not be maximally dilated. Hence, CBF might be held constant with GTN if moderate reductions in systemic BP were counterbalanced by increases in collateral blood supply, which would be potentially beneficial in acute stroke. Clearly a larger study including patients at a broader range of stroke subtypes and of acute times after stroke is required to confirm these observations.

It is commonly held that cerebral vasodilators will reduce CPP through increasing cerebral blood volume and ICP. However, this hypothesis neglects the effect that such drugs will have on ZFP, a measure of downstream pressure. We estimated CPP and ZFP and found that GTN did not alter either significantly. The observation that GTN did not alter CPP is new and contrary to the expectation that cerebral vasodilators inevitably increase ICP and, therefore, reduce CPP; presumably, venodilation increases blood flow out of the cranium, thereby maintaining CPP (and ICP).

Several caveats should be placed on our study. First, it was small, and the CIs for the hemodynamic effects of GTN were wide, such that GTN could have moderately reduced or increased CBF and CPP. Nevertheless, the point estimates for differences in a variety of CBF measurements (and lesion areas) for GTN and control-treated patients all lay on or close to zero. Second, we assessed the effect of GTN on CBF and CPP in patients with recent stroke (ie, acute and subacute phases of stroke, median time to randomization, 78 hours) and cannot comment on the effect that GTN has on CBF during the hyperacute period. Third, we included patients irrespective of stroke type, because the CT diagnosis of stroke type was only made at the time of study to reduce radiation doses; because only 2 patients with primary intracerebral hemorrhage were included (1 in each group), we cannot specifically address the effect of GTN on CBF in primary intracerebral hemorrhage, although blood flow was seen to increase adjacent to the hemorrhage in 1 patient. Fourth, few patients with cortical syndromes were included, reflecting the problems of intensive studying of such patients who are often agitated and confused. Fifth, we did not titrate the dose of GTN to BP response, instead choosing to use a fixed-dose GTN patch, so cerebral and systemic hemodynamic measures will have varied somewhat between patients. Finally, we did not directly measure ICP, but rather used an indirect estimate of CPP<sup>9,23</sup> to avoid the need for measuring invasive pressure transducers.

## Perspectives

It is possible to lower BP with transdermal GTN without reducing CBF or CPP, or inducing cerebral steal, in patients with acute stroke. These data support testing the effect of

lowering BP in patients with acute stroke and high BP with the aim of improving functional outcome and reducing stroke recurrence, as we are doing in the Efficacy of Nitric Oxide in Stroke (ENOS) Trial.<sup>28</sup>

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