Nimodipine and Perfusion Changes After Stroke

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Background and Purpose—Meta-analysis of previous trials of oral nimodipine in acute stroke has suggested a benefit when commenced within 12 hours of onset. We sought to study the effect of oral nimodipine on reperfusion after acute stroke and the relation between reperfusion and outcome.

Methods—Fifty patients with acute middle cerebral artery territory cortical infarction were blindly randomized within 12 hours of onset to either oral nimodipine (30 mg every 6 hours) or placebo. Treatment was continued for 2 weeks. Cerebral blood flow was assessed with the use of $^{99m}$Tc–hexamethylpropyleneamine oxime single-photon emission CT before therapy, 24 hours later, and at 3 months. Hypoperfusion was measured by a validated volumetric technique. Neurological impairment and functional outcome were assessed with the Canadian Neurological Scale and Barthel Index, respectively. Tissue loss was measured with CT at 3 months. Four patients were excluded from analysis for technical reasons.

Results—Twenty-three patients received nimodipine, and 23 received placebo. In the nimodipine group, there was early reperfusion that was not maintained at outcome ($P=0.01$). In the placebo group, mean infarct hypoperfusion volumes showed no overall change. Nonnutritional reperfusion in nimodipine-treated patients was associated with adverse neurological ($P=0.05$) and functional outcome ($P=0.06$). There was, however, no difference in clinical outcome between the 2 groups.

Conclusions—Oral nimodipine administered within 12 hours enhanced acute reperfusion, but this was largely nonnutritional. Larger studies using a shorter treatment delay are required to evaluate the clinical efficacy of nimodipine in acute ischemic stroke. (Stroke. 1999;30:1417-1423.)

Key Words: calcium channel blockers ■ cerebral blood flow ■ cerebrovascular disorders ■ nimodipine ■ reperfusion ■ tomography, emission computed

Nimodipine, a 1,4-dihydropyridine, has been the most widely studied calcium channel blocker in the treatment of acute cerebral ischemia. The rationale for its use in acute focal cerebral ischemia relates to its ability to produce selective cerebral vasodilatation and block calcium entry into neurons by a direct action on L-type voltage-sensitive calcium channels (VSCCs).1–3 Its efficacy in reducing infarct volume and improving neurological outcome has been demonstrated in animal models of focal cerebral ischemia,4–10 and this may be due primarily to improved cerebral blood flow (CBF)1,11 or to a direct cytoprotective effect.5,8,9 In aneurysmal subarachnoid hemorrhage, it has been shown to reduce the incidence of poor outcome due to delayed cerebral ischemia associated with vasospasm by $\approx 24\%$12 and as a result has been approved for this cerebrovascular indication. Despite initial clinical success in early trials of oral nimodipine for acute ischemic stroke,13 subsequent studies have failed to demonstrate a benefit over placebo,14–16 but many of these studies began treatment as late as 48 hours after stroke onset. Meta-analysis of 9 of the oral nimodipine trials has, however, supported the hypothesis that early treatment with nimodipine, commencing within 12 hours, would be beneficial.17 Imaging with $^{99m}$Tc–hexamethylpropyleneamine oxime (HMPAO) single-photon emission CT (SPECT) is useful for evaluating reperfusion after acute stroke therapies. We have recently studied the effect of streptokinase on reperfusion after acute stroke18,19 and found that acute reperfusion consisted of nutritional and nonnutritional components. This emphasized that acute SPECT studies need to be supplemented by studies obtained at the chronic phase. Clinical outcome and adverse events after streptokinase were related to the relative proportions of nutritional and nonnutritional...

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reperfusion as well as timing of therapy. There have been no published studies evaluating nimodipine after stroke using HMPAO SPECT. A small number of studies have used either $^{133}$Xe SPECT, positron emission tomography (PET), but none of these included outcome studies.

In this study we sought to evaluate the effect of oral nimodipine on reperfusion, compared with that of placebo, when administered within 12 hours after acute ischemic cortical stroke. We then intended to examine the relation between perfusion changes and both clinical outcome and tissue loss. The choice of treatment window was based on previous meta-analysis. Although nimodipine has been extensively investigated in previous therapeutic trials, it is widely held that it has not been adequately evaluated with a narrow time window. It should be emphasized, however, that this study was not designed to evaluate the efficacy of nimodipine for acute ischemic stroke.

**Subjects and Methods**

We prospectively studied 50 patients (26 men and 24 women; mean [SD] age, 70 [12] years; range, 32 to 90 years) with acute middle cerebral artery (MCA) territory cortical infarction who presented to either of our participating hospitals between November 1993 and May 1996. Patients were eligible for inclusion in this study if they presented with MCA cortical infarction and if it was possible to obtain acute CT and SPECT scans, complete the randomization procedure, and commence nimodipine (or placebo) therapy within 12 hours of stroke onset. This project was approved by the ethics committees of both hospitals; informed consent was obtained for all patients.

Diagnosis of MCA cortical infarction was made on the basis of either (1) presence of cortical neurological deficits such as dysphasia, anosognosia, visual or sensory inattention, dyspraxia, or parietal sensory deficit or (2) evidence of cortical infarction on the acute CT scan. Exclusion criteria were (1) presence of cerebral hemorrhage or noncerebrovascular pathology such as tumor on the acute CT scan; (2) previous cerebral pathology (infarction, hemorrhage, or tumor) interfering with assessment of CBF; (3) presence of other neurological, systemic, or psychiatric illness interfering with neurological or functional assessments or with the patient’s ability to return for 3-month follow-up; (4) concurrent use of other dihydropyridine calcium antagonists; and (5) presence of 1 or more contraindications to the use of calcium antagonists (such as pregnancy or postpartum period; significant hepatic, renal, or cardiac disease; or drugs affecting hepatic metabolism).

Patients were randomized in a double-blind manner to receive either nimodipine 120 mg/d orally in 4 divided doses (30 mg every 6 hours) or an equivalent regimen of placebo tablets, similar in appearance to nimodipine, for 14 days. Therapy was commenced within 12 hours of stroke onset. In patients unable to swallow because of either bulbar paresis or depressed conscious state, the drug was administered by nasogastric tube.

CBF was assessed with the use of HMPAO SPECT performed, when possible, at 3 defined stages in all patients. The first scan (stage 1: pretherapy) was performed before commencement of nimodipine therapy. The second scan (stage 2: after therapy commencement) was performed 24 hours after the pretherapy scan, and the third scan (stage 3: outcome) was performed at least 3 months after the ictus when neurological and functional recovery had reached a plateau. SPECT studies were acquired with triple-headed systems (Siemens Multispect 3 in 32 and Trionix Triad in 18). For each patient, all SPECT scans were performed with the same camera.

Infarct hyperperfusion on SPECT was measured with a validated volumetric technique as previously described. Briefly, this method of volumetric analysis integrates both the size and severity of the infarct hyperperfusion deficit and yields an equivalent volume measure (in cubic centimeters) of cortical tissue having zero blood flow. This technique is highly accurate and reproducible between different observers and different camera systems. Infant hyperperfusion analysis was performed with knowledge of infarct lateralization but blinded to the clinical and radiological data.

With the use of the hyperperfusion volumes obtained from the 3 SPECT studies, the amount of perfusion change, or reperfusion, occurring between studies could be calculated. Perfusion changes were defined, on the basis of serial perfusion changes seen in several of our previous publications, as follows: (1) Early perfusion change (stage 1 to 2) was defined as pretherapy hyperperfusion volume minus posttherapy (24-hour) hyperperfusion volume. A decrease in hyperperfusion volume between these 2 stages would yield a positive value and indicate early reperfusion. Any early reperfusion might consist of both nutritional and nonnutritional components. (2) Late perfusion change (stage 2 to 3) was defined as outcome (3-month) hyperperfusion volume minus posttherapy hyperperfusion volume. An increase in hyperperfusion volume between posttherapy and outcome stages would reflect that part of early reperfusion not sustained at outcome, ie, nonnutritional reperfusion. (3) Total perfusion change (stage 1 to 3) was defined as pretherapy hyperperfusion volume minus outcome hyperperfusion volume. A decrease in hyperperfusion volume between pretherapy and outcome stages would indicate that part of early reperfusion that was maintained at outcome, ie, nutritional reperfusion. When these definitions were used, early perfusion change (stage 1 to 2) could be calculated only in those patients having both pretherapy and posttherapy SPECT scans. Late perfusion change (stage 2 to 3) could be calculated only in those having both posttherapy and outcome scans, while total reperfusion could be calculated only in those having both pretherapy and outcome scans.

In 4 patients, there were technical problems with both early SPECT scans, making it impossible to analyze perfusion changes. These 4 patients were therefore excluded from subsequent data analysis. Pretherapy SPECT scans were performed in the remaining 46 patients at a mean of 7.5 (2.7) hours after stroke onset. Posttherapy scans could be performed in 41 of the 46 patients at a mean of 24.2 (4.1) hours after the first scan (31.6 [5.2] hours after stroke onset). Outcome SPECT scans could be performed in 33 of the 46 patients 3.3 (0.7) months after the ictus. All 3 SPECT scans were successfully performed in 30 patients. Posttherapy SPECT scans could not be performed in 5 of the 46 patients for the following reasons: 3 patients were medically unstable owing to the development of severe cerebral edema in 2 (1 of whom died a day later) and hemorrhagic transformation in 1. One patient died suddenly as a result of myocardial rupture after an acute myocardial infarction 12 days earlier. One patient declined to undergo the 24-hour SPECT scan but subsequently agreed to undergo the outcome scan. Outcome SPECT studies could not be performed in 13 of the 46 patients for the following reasons: 6 had died in the first week after their stroke; 1 had returned to an overseas residence; 5 refused; and 1 who, at the time of the 3-month review, was hospitalized at another institution suffering from an unrelated condition was too medically unstable and subsequently died. Two of the 46 patients suffered another stroke after the 24-hour SPECT study but before the 3-month outcome study 2 and 7 days after the initial stroke, respectively.

Neurological impairment was assessed before therapy, after therapy, and at outcome concurrently with SPECT studies with a modified Canadian Neurological Scale (CNS) (scored from 0 to 11.5). Functional disability was measured at outcome with the Barthel Index (BI) (scored from 0 to 20). Clinical follow-up was accomplished in all 46 patients except 1. Outcome CNS was obtained in 39 of the 46 patients, while outcome BI was obtained in 45. In the 6 patients who died after their stroke, outcome CNS and BI were scored as zero on the basis that this represented the worst possible neurological and functional outcome. Many of these patients were severely neurologically impaired and functionally disabled before death. In the 7 patients who were unable or declined to return for further examination, outcome CNS could not be obtained. Outcome BI was obtained in 6 of these 7 by telephone interview with the patients or their caregivers, which has been shown to be reliable. The remaining patient who was medically unwell, as
previously mentioned, could not be neurologically or functionally assessed with regard to the stroke. Outcome CT scans were performed on the same day as the outcome SPECT to assess tissue loss. These were completed in all 33 patients returning for SPECT scans, but tissue loss could not be determined in 2 because the electronic data were lost. Tissue loss was therefore determined in 31 patients. This was measured volumetrically (in cubic centimeters), as previously described, by a neuroradiologist blinded to the clinical and CBF results.

Differences in mean hypoperfusion volumes and in means of reperfusion variables between patient groups were assessed by unpaired Student’s t test. Differences in mean hypoperfusion volumes with time were analyzed by repeated-measures ANOVA. Differences in mean hypoperfusion volumes with time were analyzed by repeated-measures ANOVA. Differences in proportions of patients were assessed with Fisher’s exact and χ² tests. Associations between reperfusion variables, tissue loss, and clinical variables were evaluated by linear regression. The regression coefficient b, its standard error, and nominal P value are presented. Findings were considered significant if the nominal P value was <0.05.

Results

Of the 46 patients in whom reperfusion could be analyzed, 23 received nimodipine and 23 received placebo. No serious side effects of nimodipine therapy, such as hypotension or arrhythmia, were observed in any of the patients. All surviving patients were able to complete their course of nimodipine (or placebo) treatment.

To determine whether the 4 excluded patients differed clinically from the remaining 46 patients, we compared mean pretherapy CNS, posttherapy CNS, and outcome BI between the 2 groups and found no significant differences. We then tried to identify any differences between the 30 patients who had all 3 SPECT scans (pretherapy, posttherapy, and 3-month outcome) and the remaining 16 patients who did not successfully complete all 3 SPECT scans, excluding the 6 who died. We compared mean pretherapy hypoperfusion volume, pretherapy CNS, posttherapy CNS, outcome CNS, and outcome BI between these 2 groups and found no significant differences.

Baseline clinical and SPECT data in patients who received nimodipine and those who received placebo were well matched (Table 1). There were no differences in clinical or radiological outcome between nimodipine and placebo groups (Table 1). Of the 6 patients who died, equal numbers received either nimodipine or placebo.

Effect of Nimodipine on Reperfusion

Early perfusion change (stage 1 to 2) could be measured in 41 patients who had both pretherapy and posttherapy SPECT scans; it was positive (early reperfusion) in 16 of 21 nimodipine-treated patients (76%) compared with 12 of 20 placebo-treated patients (60%). This difference was not statistically significant. The magnitude of mean early perfusion change (stage 1 to 2) was, however, significant in

| TABLE 1. Baseline and Outcome Variables According to Treatment Group |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                 | Nimodipine (n=23) | Placebo (n=23) |
| Mean | SE | Mean | SE | P |
| Age, y | 69.8 | 2.5 | 70.7 | 2.3 | 0.8 |
| Delay to pretherapy SPECT, h | 7.1 | 0.6 | 7.8 | 0.5 | 0.4 |
| Treatment delay, h | 8.2 | 0.6 | 8.7 | 0.5 | 0.5 |
| Pretherapy CNS | 5.8 | 0.6 | 6.4 | 0.7 | 0.5 |
| Pretherapy HP volume, cm³ | 59.9 | 12.1 | 49.0 | 9.2 | 0.5 |
| Outcome CNS | 6.7 | 0.9 | 7.5 | 0.9 | 0.5 |
| Outcome BI | 12.5 | 1.7 | 13.8 | 1.6 | 0.6 |
| Tissue loss, cm³ | 68.9 | 19.4 | 41.3 | 14.2 | 0.3 |

HP = hypoperfusion.

| TABLE 2. Perfusion Changes According to Treatment |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                 | Nimodipine | Placebo |
| Mean | SE | n | P* | Mean | SE | n | P* |
| Patients with pretherapy and posttherapy SPECT scans (n=41) |
| Pretherapy HP volume, cm³ | 60.8 | 13.2 | 21 | 49.5 | 10.3 | 20 | 0.5 |
| Post-therapy HP volume, cm³ | 48.0 | 11.4 | 21 | 50.5 | 13.0 | 20 | 0.9 |
| Early perfusion change, cm³ | 12.8 | 5.3 | 21 | 0.02 | -1.0 | 6.4 | 20 | 0.9 |
| Patients with posttherapy and outcome scans (n=30) |
| Posttherapy HP volume, cm³ | 38.1 | 9.5 | 14 | 42.0 | 13.0 | 16 | 0.8 |
| Outcome HP volume, cm³ | 60.6 | 12.0 | 14 | 46.5 | 12.4 | 16 | 0.4 |
| Late perfusion change, cm³ | 22.5 | 8.0 | 14 | 0.005 | 4.5 | 5.7 | 16 | 0.4 |
| Patients with pretherapy and outcome scans (n=33) |
| Pretherapy HP volume, cm³ | 54.9 | 11.7 | 15 | 38.4 | 7.2 | 18 | 0.2 |
| Outcome HP volume, cm³ | 64.8 | 11.9 | 15 | 43.2 | 11.3 | 18 | 0.2 |
| Total perfusion change, cm³ | -9.8 | 6.6 | 15 | 0.13 | -4.8 | 7.0 | 18 | 0.5 |

HP indicates hypoperfusion.

*Significance of reperfusion variables (change in HP volumes) within each treatment group.
†Significance of differences in HP volumes and reperfusion variables between groups.
nimodipine-treated patients but not in placebo-treated patients (Table 2). Late perfusion change (stage 2 to 3) could be measured in 30 patients who had both posttherapy and outcome scans; it was positive (nonnutritional reperfusion) in 11 of 14 nimodipine-treated patients (79%) and in 10 of 16 placebo-treated patients (63%), but this difference did not reach statistical significance. The magnitude of mean late perfusion change (stage 2 to 3) was significant only in nimodipine-treated patients (Table 2). Total perfusion change (stage 1 to 3) could be measured in 33 patients who had both pretherapy and outcome scans. It was positive (nutritional reperfusion) in more placebo-treated patients (11/18 or 61%) than nimodipine-treated patients (4/15 or 27%); this difference did not reach statistical significance. The magnitude of mean total perfusion change (stage 1 to 3) was, however, not significant in either patient group.

Serial changes in mean hypoperfusion volume across all 3 stages could be assessed in the 30 patients who had 3 SPECT scans. Fourteen of the 30 patients received nimodipine and 16 received placebo. In nimodipine-treated patients, mean hypoperfusion volume decreased over the first 24 hours after the start of therapy but increased again at 3 months (Figure 1). This variation with time in the nimodipine group was not consistent with chance ($P=0.01$). In patients receiving placebo, there was no significant variation in mean hypoperfusion volume with time. Hence, in nimodipine-treated patients, mean early perfusion change (stage 1 to 2) indicated early reperfusion over the first 24 hours. Mean late perfusion change (stage 2 to 3) in nimodipine-treated patients indicated increasing hypoperfusion between the 24-hour and 3-month studies and therefore represented the nonnutritional component of early reperfusion. In contrast, mean total perfusion change (stage 1 to 3) was not significant, implying that mean nutritional reperfusion was negligible.

Relation Between Reperfusion and Outcome

The relations between reperfusion variables and outcome variables were analyzed separately for each treatment group. This is because the respective serial perfusion changes (above) were so dissimilar.

We initially examined the relation between early perfusion change (stage 1 to 2) and the variables outcome CNS, outcome BI, and tissue loss. In nimodipine-treated patients, early perfusion change (stage 1 to 2) was marginally associated with worse outcome. It was marginally associated negatively with outcome BI ($b=-0.13\pm0.07$, $P=0.08$) and positively with tissue loss ($b=1.20\pm0.60$, $P=0.07$) but not with outcome CNS ($b=-0.050\pm0.035$, $P=0.2$). In contrast, in placebo-treated patients, early perfusion change (stage 1 to 2) was associated with improved outcome. It was associated positively with outcome BI ($b=0.14\pm0.05$, $P=0.02$), negatively with tissue loss ($b=-1.62\pm0.32$, $P<0.001$) and positively, but only marginally, with outcome CNS ($b=0.054\pm0.029$, $P=0.09$).

We then analyzed the relation between late perfusion change (stage 2 to 3) and each of the outcome variables. In nimodipine-treated patients, late perfusion change (stage 2 to 3) was marginally associated with adverse outcome (BI: $b=-0.13\pm0.06$, $P=0.06$; CNS: $b=-0.048\pm0.022$, $P=0.05$; tissue loss: $b=1.08\pm0.56$, $P=0.08$). In placebo-treated patients, late perfusion change (stage 2 to 3) was not significantly related to any of the outcome variables.

We next analyzed the relation between total perfusion change (stage 1 to 3) and each of the outcome variables. In nimodipine-treated patients, total perfusion change (stage 1 to 3) was not significantly associated with outcome. In placebo-treated patients, total perfusion change (stage 1 to 3) was associated with better outcome. It was negatively associated with tissue loss ($b=-1.44\pm0.35$, $P=0.009$) and positively associated, but only weakly, with both outcome BI ($b=0.080\pm0.050$, $P=0.1$) and outcome CNS ($b=0.041\pm0.023$, $P=0.1$).

Effect of Treatment Delay on Reperfusion

To determine whether the amount of either early (stage 1 to 2), late (stage 2 to 3), or total perfusion change (stage 1 to 3) was dependent on treatment delay, we examined the relation between these variables. The distribution of treatment delay among the 46 patients is shown in Table 3. There was a negative but marginal association between treatment delay and early perfusion change (stage 1 to 2) for both treatment groups combined ($b=-3.1\pm1.7$, $P=0.07$) such that earlier treatment correlated with greater early reperfusion. Associations of similar magnitude were found in each treatment group, but these did not reach statistical significance. There was no significant relation between treatment delay and either late (stage 2 to 3) or total perfusion change (stage 1 to 3) in either treatment group.

**Discussion**

This is the largest reported study to date of the effects of nimodipine on CBF after acute ischemic stroke and the only

### Table 3. Distribution of Treatment Delay in the 46 Patients According to Treatment Group

<table>
<thead>
<tr>
<th>Treatment Delay, h</th>
<th>Nimodipine</th>
<th>Placebo</th>
</tr>
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<tbody>
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<td>0&lt;t=2</td>
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</tr>
<tr>
<td>10&lt;t=12</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

1 indicates treatment delay.
study to also investigate CBF at outcome. It highlights several important differences between reperfusion that occurs spontaneously and that which occurs after nimodipine administration within 12 hours of acute MCA stroke. Spontaneous but incomplete reperfusion occurred in ~60% of placebo-treated patients, as recently reported by Barber et al. Nimodipine did not significantly increase the proportion of patients experiencing reperfusion but did increase the magnitude of reperfusion in those patients in whom it occurred. This increased reperfusion associated with nimodipine was not maintained at outcome and was therefore of no nutritional benefit. Furthermore, both early and nonnutritional reperfusion after nimodipine had an adverse effect on outcome. In contrast, spontaneous reperfusion in placebo-treated patients had a favorable effect on outcome. The enhanced reperfusion induced by nimodipine, therefore, differed not only quantitatively from that occurring naturally but also qualitatively as well. This might explain the lack of difference in clinical and radiological outcome between the 2 treatment groups despite the enhanced reperfusion in the nimodipine group, although it may also have been due to type II error.

This study demonstrates the usefulness of HMPAO SPECT in measuring reperfusion after experimental stroke therapies. It additionally emphasizes the importance of outcome SPECT studies in retrospectively distinguishing the nutritional and nonnutritional components of early reperfusion. Previously published studies by our group and others have shown that acute reperfusion after therapeutic intervention does not necessarily correlate with clinical gains. By supplementing early studies with studies in the chronic phase, we have shown that the enhanced early reperfusion after nimodipine did not correlate with clinical improvement because it was transient and occurred in nonviable tissue. It was therefore nonnutritional in nature. These characteristics of nonnutritional reperfusion are consistent with the excessive perfusion relative to metabolism observed subacutely with PET and attributed to luxury perfusion. Conversely, nutritional reperfusion is that proportion of early reperfusion that is maintained at outcome and is accompanied by clinical gains. Examples of nutritional and nonnutritional reperfusion are shown in Figures 2 and 3, respectively. There are other possible interpretations for the observed serial perfusion changes in the nimodipine-treated patients. One is the occurrence of arterial reocclusion after initial recanalization or vasodilatation. Indeed, 2 patients clinically deteriorated because of presumed further ischemia, but these patients both received placebo. Furthermore, none of the nimodipine-treated patients had a clinical deterioration attributable to further cerebral ischemia. A second explanation is the presence of a late cerebral steal phenomenon in which there is an increase in CBF in unaffected brain regions, shunting perfusion away from ischemic vasoparalyzed regions. It would, however, be unusual for this to be preceded by significant reperfusion or an inverse steal phenomenon. Nonnutritional reperfusion, or luxury perfusion, is therefore a more tenable explanation.

The lack of clinical efficacy of nimodipine in many previous stroke trials might be related to 2 factors demonstrated in this study. First, the effect of nimodipine on early reperfusion, at the dose tested in this study, was only modest. The magnitude of mean early reperfusion after nimodipine was only 12.8±5.3 cm³ (Table 2) or 21% of the mean pretherapy hypoperfusion volume. Interestingly, this was significantly smaller than mean early reperfusion observed after streptokinase in a previous study by our group (52.8±18.8 cm³ or 66% of mean pretherapy hypoperfusion volume; P=0.008, unpaired Student’s t-test). Although these 2 studies used different treatment windows, their protocols were otherwise alike. Therefore, nimodipine might not be as potent as streptokinase at improving reperfusion after acute ischemic stroke, which is compatible with their respective mechanisms of action: recanalization versus vasodilatation. It is possible that the potency of nimodipine on reperfusion might have been improved by earlier administration, since earlier treatment tended to be associated with greater early reperfusion.

Second, the modest reperfusion attributed to nimodipine was nonnutritional in nature and correlated with adverse
outcome. This correlation may reflect reperfusion injury. Reperfusion injury is thought to be mediated by intracellular calcium overload accompanying reperfusion, which, through production of toxic free radicals and numerous enzymatic processes, exacerbates tissue damage. This may lead to the speculation that any cytotoxic action of nimodipine may have been either ineffective or overwhelmed. One might then presume that calcium influx at other VSCCs (T- or N-types) not blocked by dihydropyridines or at agonist-operated calcium channels such as the N-methyl-D-aspartate glutamate receptor is more substantial than at L-type VSCCs. This is somewhat controversial, since the importance of L-type VSCCs in calcium influx after energy failure has been reaffirmed by recent in vitro data. Timing of therapy might be a more likely explanation for the apparent reperfusion injury exhibited in this study.

Nutritional reperfusion in this study, in contrast, was associated with favorable outcome in patients receiving placebo but was not present in an adequate number of nimodipine-treated patients to a sufficient degree to have had a clinically beneficial effect. Therefore, the potential clinical benefit of therapeutic reperfusion after stroke relates to the balance between its nutritional and nonnutritional components. We have previously found that nutritional reperfusion associated with favorable outcome in patients receiving placebo but was not present in an adequate number of nimodipine-treated patients to a sufficient degree to have had a clinically beneficial effect. Therefore, the potential clinical benefit of therapeutic reperfusion after stroke relates to the balance between its nutritional and nonnutritional components. We have previously found that nutritional reperfusion is favored by earlier timing of therapy, but we were unable to demonstrate this in the present study, probably because of the relatively small number of patients treated under 6 hours.

Timing of therapy is important for stroke therapies that seek to improve reperfusion or prevent calcium entry into neurons. In animal models, nimodipine has either been started before MCA occlusion or within 15 to 60 minutes. Studies of the time course of nimodipine binding and of calcium-calmodulin binding in ischemic brain suggest that the window of opportunity for intervention with calcium antagonists might be as short as 4 hours. Similarly, studies of temporal flow thresholds in animal models suggest that the window of opportunity for reperfusion might also be as short as 3 to 4 hours. This is further supported by recent thrombolytic trials. 

Figure 3. Nonnutritional reperfusion. Serial SPECT scans of a patients with left MCA cortical infarction before therapy (left), 24 hours later (middle), and at 3 months (right). These scans show early reperfusion that is not maintained at outcome. This reperfusion is therefore nonnutritional in nature.

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