Blood Pressure and Vessel Recanalization in the First Hours After Ischemic Stroke

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Background and Purpose—Transient elevation of arterial blood pressure (BP) is frequent in acute ischemic stroke and may help to increase perfusion of tissue jeopardized by ischemia. If this is true, recanalization may eliminate the need for this BP elevation.

Methods—We analyzed BP in 149 patients with acute ischemic stroke on admission to the hospital and 1 and 12 hours after intraarterial thrombolysis. BP values of patients with adequate recanalization were compared with BP values of patients with inadequate recanalization. Recanalization was determined on cerebral arteriography after thrombolysis using thrombolysis in myocardial infarction grades.

Results—Systolic, mean, and diastolic arterial BP decreased significantly from admission to 12 hours after thrombolysis in all patients (P<0.001). Before thrombolysis, patients with adequate and inadequate recanalization showed equal systolic (147.4 and 148.0 mm Hg), mean (102.1 and 104.1 mm Hg), and diastolic (79.5 and 82.1 mm Hg) BP values. Twelve hours after thrombolysis, patients with adequate recanalization had lower values than those with inadequate recanalization (systolic BP, 130 versus 139.9 mm Hg; mean BP, 86.8 versus 92.2 mm Hg; and diastolic, BP 65.2 versus 68.3 mm Hg). Two-way repeated ANOVA analysis showed a significant group × time interaction for systolic BP, indicating a larger systolic BP decrease when recanalization succeeded (P=0.019).

Conclusion—The course of elevated systolic but not diastolic BP after acute ischemic stroke was found to be inversely associated with the degree of vessel recanalization. When recanalization failed, systolic BP remained elevated longer than when it succeeded. (Stroke. 2005;36:264-269.)

Key Words: blood pressure ■ stroke, acute

Hypertension is the most prevalent modifiable risk factor for ischemic and hemorrhagic stroke. Approximately two-thirds of the cerebrovascular disease burden are attributable to nonoptimum blood pressure (BP). Blood pressure levels are positively and continuously associated with the risk of stroke in a log-linear fashion for first-ever and recurrent stroke.1,2 Lowering BP reduces the risk, both in primary and secondary prevention, and larger reductions in BP produce larger reductions in stroke risk.3

Up to 80% of patients show elevated BP values within the first 24 to 48 hours after stroke onset, which subside over the next few days or weeks.4 However, unlike the well-established knowledge of BP management to prevent stroke, few data are available about handling BP in the acute setting. The pathophysiology of high BP in acute stroke is complex and poorly understood, and there is a lack of adequate evidence to guide therapeutic decisions. Thrombotic or embolic occlusion of a cerebral artery is the cause of acute ischemic stroke and therefore also the first link in the pathogenetic chain of BP elevation. Therefore, the reverse should also be true. If the occluded vessel is recanalized, BP should decline more rapidly than with persistent occlusion. To verify or reject this hypothesis, we correlated BP values and the grade of recanalization in a series of patients who were treated with intraarterial thrombolysis.

Materials and Methods

From January 2000 to December 2003, 160 patients with acute ischemic stroke were treated with intra-arterial thrombolysis (IAT) at our institution. Many aspects of some of these patients and the technique used for IAT have been published previously.5–7 All patients were evaluated by a neurologist after arrival at the emergency department and a computed tomography or magnetic resonance imaging scan was obtained to rule out hemorrhage or other nonischemic causes of the ictus, patients underwent arteriography, and, if feasible (and visible artery occlusion on arteriography), thrombolysis. When BP exceeded 185/110 mm Hg antihypertensive agents were given. The first-line agent was labetalol. Second-line drugs were angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists and rarely nitroglycerine or nitroprusside.
After thrombolysis, all patients were transferred to the intensive care unit and usually 1 day later (median 2 days) to the department of neurology, internal medicine, or a regional hospital.

For this study we collected BP recordings of the 160 patients at admission and at 1 and 12 hours after thrombolysis. BP was measured with the traditional Riva Rocci method using an arm cuff and a sphygmomanometer. Systolic BP (SBP) and diastolic BP (DBP) values were noted and mean BP (MBP) values were calculated according to the formula MBP = DBP + 1/3 (SBP - DBP). The BP values were related with the degree of vessel recanalization as seen on the angiographic films at the end of thrombolysis. Eleven of the 160 patients had to be excluded from this analysis, because the BP recordings at admission (n = 4) or after thrombolysis could not be retrieved (n = 6), or because of death before 12 hours after thrombolysis (n = 1). After exclusion of the patients with missing data, 149 patients remained in the study (72 women and 77 men). In 17 patients the internal carotid artery, in 64 the M1 segment of the middle cerebral artery, in 25 the M2 segment, and in 17 the M3/M4 segments, in 1 the anterior cerebral artery, in 1 the posterior cerebral artery, and in 24 patients the basilar artery were occluded. The BP values at admission were extracted from the patient records of the emergency department before thrombolysis. The intensive care unit documents furnished the 1- and 12-hour BP readings after thrombolysis. In addition, all the patient records including the documents from the emergency department and the intensive care unit were screened for use of antihypertensive agents given before, during, or within 12 hours after thrombolysis. A logistic regression analysis was performed to search for predictors of outcome.

Results

The demography of the patients is given in Table 1. The mean and median intervals from symptom onset to intra-arterial treatment were 271 and 262 minutes, respectively. Fourteen patients were treated within <180 minutes and 12 (9 with basilar artery and 3 anterior circulation strokes) were treated >360 minutes after symptom onset. Mean SBP at admission was 148 mm Hg (SD, 24.8), mean MBP was 103 mm Hg (SD, 16.4), and mean DBP was 80 mm Hg (SD, 15.1). SBP was elevated (>140 mm Hg) in 92 and DBP was elevated (>90 mm Hg) in 46 patients. SBP or DBP or both were increased in 95 patients (63.8%). The strokes were on average fairly severe (mean NIHSS score, 15.8). Thrombolysis achieved adequate recanalization in 98 patients (65.8%). Patients with adequate and inadequate recanalization did not differ regarding age, sex, stroke severity, time from symptom onset to treatment, frequency of hypertension, or use of antihypertensive agents. The localization of vessel occlusions did not show any association with the BP.

The SBP, MBP, and DBP of the 149 patients decreased significantly from admission to 12 hours after thrombolysis (P < 0.001) (Table 2 and Figure). The SBP decline was 14.2, 14.2, and 14.1 mm Hg for the 3 variables. At admission there was no significant difference of SBP, MBP, or DBP between patients with adequate and those with inadequate recanalization (P > 0.05 for all 3 variables). One hour after thrombolysis, patients with adequate recanalization tended to have lower BP values than patients with inadequate recanalization. The absolute SBP decline from admission to 12 hours after thrombolysis was 14.2, 14.2, and 14.1 mm Hg for the 3 variables. The Mann–Whitney test was used to compare the admission BP values of patients with adequate and those with inadequate recanalization. To investigate the time course of BP values, we performed a repeated measure variance analysis (2-way repeated ANOVA: between: group [adequate recanalization/inadequate recanalization]; within: time [admission/1 hour/12 hours]) with tests of within-subject contrasts as post-hoc test. To test a possible influence of previous hypertension in the groups with adequate and inadequate recanalization, a covariance analysis with correction for preexisting hypertension was performed. To rule out the effect of antihypertensive agents, some analyses were performed separately for patients who did not receive such agents before, during, or after thrombolysis. Last, a logistic regression analysis was performed to search for predictors of outcome.

### Table 1. Patient Characteristics

<table>
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<tr>
<th>No. of patients</th>
<th>Adequate Recanalization, TIMI 2/3 (%)</th>
<th>Inadequate Recanalization, TIMI 0/1 (%)</th>
<th>Difference Between TIMI 2/3 and TIMI 0/1 Groups, P</th>
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<td>All Patients (%)</td>
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<td>No. of patients</td>
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<td>Mean NIHSS at admission</td>
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<td>Mean interval from symptom onset to intra-arterial thrombolysis</td>
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<td>Use of antihypertensive agents before thrombolysis or during the 12 hours thereafter</td>
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NIHSS indicates National Institutes of Health Stroke Scale; SD, standard deviation; TIMI, thrombolysis in myocardial infarction.
hours after thrombolysis was larger in patients with adequate recanalization compared with patients with inadequate recanalization. The 2-way repeated measures ANOVA showed a significant group × time interaction for SBP, indicating a larger SBP decline in the group with adequate recanalization within 12 hours after therapy (P=0.019). With 2-way repeated measures ANOVA with tests of within-subject contrasts as post-hoc test, the resulting probability values were 0.001 for DBP. After correction for previous hypertonia, the group × time interaction term for SBP remained significant in covariance analysis (P=0.019). For MBP and DBP, the result was not significant.

Of the 149 patients, 123 (84 [85.7%] with adequate and 39 [76.5%] with inadequate recanalization) did not receive any antihypertensive drugs from admission to 12 hours after thrombolysis (Table 3). The BP decline showed the same characteristics as in the whole group of 149 patients. There was no association between BP at admission or 12 hours after thrombolysis and severity of stroke measured with the NIHSS. Clinical outcome assessed with the modified Rankin scale 3 months after the stroke was better in patients with adequate recanalization (P=0.005, Mann–Whitney test). However, there was no association between the absolute BP decline and outcome (P>0.05). A logistic regression analysis found that independent predictors of poor outcome (Rankin, 3 to 6) were age (P=0.014), NIHSS at admission (P<0.001), and the degree of vessel recanalization (P=0.041). BP, BP on admission, BP 12 hours after therapy, and BP decline between admission and 12 hours after thrombolysis did not predict outcome (P>0.05 for all parameters).

Discussion

A systematic review of high BP in acute stroke and subsequent outcome showed that death, dependency, and the risk of stroke recurrence were more likely in ischemic stroke patients with higher BP values. In addition, low BP is an independent prognostic risk factor for poor outcome after stroke. Prognosis is worse in patients with extreme BP values at both ends of the spectrum, indicating a J- or U-shaped relationship between BP and outcome in acute stroke. The relationship appears to be mediated above all by increased rates of early recurrence and early death resulting from presumed cerebral edema in patients with high BP and noncerebral mechanisms such as increased coronary heart disease events in those with low BP.

A transient elevation of arterial BP is observed in up to 80% of patients with acute ischemic stroke. In our series, BP at admission was elevated in 95 patients (63.8%). In addition, in acute stroke the circadian BP rhythm is disrupted, and there is a reduced physiological night-time pressure decline. The underlying mechanisms of this BP elevation and dysregulation are poorly understood. One of many possible reasons might be a locally disturbed autoregulation of cerebral blood flow within the ischemic penumbra. If cerebrovascular autoregulation is lost, perfusion becomes a linear function of BP. In this case, poststroke hypertension may aim to enhance the perfusion in the penumbra to save the tissue jeopardized by ischemia. From this we derived the hypothesis that recanalization, which will likely help to reperfuse the ischemic tissue, lowers BP elevation more rapidly than BP declines in patients with persistent occlusion of the cerebral vessel.

Our results indicate a relationship between BP course and vessel recanalization. When thrombolysis succeeded to reopen the occluded vessel responsible for the stroke, SBP 12 hours after thrombolysis declined significantly faster than when recanalization failed. Recanalization also improved the clinical outcome of our patients, a relationship that has been shown previously by other investigators as well. Therefore, our results may explain clinical observations published earlier. First, poor recanalization, slower BP de-
cline, and subsequent unfavorable outcome are related to each other. Second, a greater decline of mean arterial BP from admission to the second day increased the chances of full recovery.8 Because a full recovery is more likely with recanalization, our findings of a greater BP decline associated with adequate recanalization are in line with this observation. Third, elevated 24-hour SBP values in the acute stroke period were shown to be associated with brain edema and brain edema with poor recanalization.8,23 However, brain edema was less frequent in patients with a greater BP decline, which is consistent with our finding that the downhill course of elevated BP after stroke is accelerated with recanalization.23

The natural response of the organism to persistent vessel occlusion in the acute stroke phase seems to keep the BP elevated, whereas the physiological course after recanalization is a pressure decline and more rapid return toward prestroke levels than in stroke victims with persistent vessel occlusions. A cautious conclusion is that BP elevation may be needed to help perfuse salvageable tissue and to minimize the ischemic damage, as has been supposed decades ago.19 This supports current guidelines of acute stroke management that caution BP lowering in the acute phase of stroke. An adverse effect of BP-lowering has been observed in a recent case series in which 59% of the patients received antihypertensive medication within 24 hours of stroke onset.24 Acute stroke trials using vaso-active drugs such as beta-receptor antagonists and calcium channel blockers have resulted in neurological worsening with lowering BP.25,26 Furthermore, our findings support advocates who stop antihypertensive agents in acute stroke or even raise BP. Both animal studies and small randomized trials in humans that induced BP elevation have failed to show any benefit.27,28 In conclusion, our study demonstrates a relationship between SBP elevation in the first hours after stroke and patenty of the initially occluded vessel. In acute stroke patients, elevated SBP at admission shows a downward course in the following hours, which is accelerated by recanalization, and recanalization increases the chances of a favorable outcome.

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References
Elevated blood pressure (BP) in the typical presentation of stroke belongs to those few physiological variables that a physician truly has the power of controlling. Association of early elevated BP with poor outcome in observational studies1-3 has motivated some to recommend moderate BP reduction to improve outcome. Interventional randomized controlled studies focused on BP reduction have not been conducted, which would be necessary to prove a causal relationship between early BP elevation and unfavorable outcome. The nature of this relationship has been debated over decades,4-6 but surprisingly few randomized controlled studies have since been conducted with agents that reduce BP.

Cerebral blood flow in the human ischemic brain is passively dependent on the mean arterial pressure, because autoregulation is defective.6 Therefore, low BP or abrupt decreases in it are hazardous and risk enlargement of the initial infarction. Elevated BP, on the other hand, effects to maintain cerebral blood perfusion. This leads us to the 2 fundamental pathophysiological dogmas in considering therapeutics of acutely elevated BP. First, poststroke hypertension may be deleterious by facilitating edema and hemorrhage formation in the ischemic tissue where blood–brain barrier is damaged. Secondly, antihypertensive drugs may influence BP apart from another nominal effect. Although these dogmas in considering therapeutics of acutely elevated BP have been clouded by diverse studies focusing on very different time periods considered to be acute and the fact that intracerebral hemorrhages are included in some studies and others lack neurological scoring on admission.1,2,12 Studies have indicated that in the very acute phase (<12 hours), mild spontaneous decrease in hypertensive BP is associated with mild stroke,7,9 but thereafter (within 1 or 5 days) spontaneous decreases in BP correlate with poor prognosis.3,12,13 However, contrasting evidence does exist.14

Data are available from interventive trials based on agents that influence BP apart from another nominal effect. Although these results are also conflicting, one study used a neuroprotective occluded vessel is associated with BP reduction. The mechanism of the acute vasopressor response has been debated. The Cush- ing reflex has been suggested to mediate it to maintain adequate cerebral perfusion. However, it pertains to situations where the intracranial pressure is increased, and this is not the case in the early minutes of focal cerebral ischemia. More likely, it reflects increased activity of the sympathetic nervous system10 to increase cardiac contractility, heart rate, and vessel tone.

Acute BP elevation in stroke seems to be a moderately good marker of prior hypertension, which means that acutely hypertensive patients also experience more end-organ morbidity.11 This may partly explain why patients with highest BP in the acute phase might be destined to poorer prognosis. More importantly, studies show that the initial stroke severity influences the course of BP, not vice versa.7 BP fall within the first 4 hours was associated with mild stroke and a good outcome, whereas a sustained high BP associated with severe stroke and poor outcome. These observational data cohere nicely with the PROACT II study: a randomized controlled trial: Prolyse in Acute Cerebral Thromboembolism. JAMA. 1999;282:2003–20011.

The central question is, why does BP initially rise in the acute stroke? Hospitalization with paralysis is obviously a tremendous stress and has been viewed to explain BP elevation.7 However, because BP has been found to be elevated already during the first minutes after the onset of stroke symptoms,8 it seems more likely that it is intimately associated with the vascular occlusion. The study reported in this issue of Stroke by Mattle et al9 confirms this by demonstrating that recanalization of the initially occluded vessel is associated with BP reduction. The mechanism of the acute vasopressor response has been debated. The Cush- ing reflex has been suggested to mediate it to maintain adequate cerebral perfusion. However, it pertains to situations where the intracranial pressure is increased, and this is not the case in the early minutes of focal cerebral ischemia. More likely, it reflects increased activity of the sympathetic nervous system10 to increase cardiac contractility, heart rate, and vessel tone.

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The field is clouded by diverse studies focusing on very different time periods considered to be acute and the fact that intracerebral hemorrhages are included in some studies and others lack neurological scoring on admission.1,2,12 Studies have indicated that in the very acute phase (<12 hours), mild spontaneous decrease in hypertensive BP is associated with mild stroke,7,9 but thereafter (within 1 or 5 days) spontaneous decreases in BP correlate with poor prognosis.3,12,13 However, contrasting evidence does exist.14

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compound nimodipine and indicated a clear dose-dependent worsening of outcome when BP was reduced 10 to 20 or >20% from baseline.\textsuperscript{15} A meta-analysis of BP-reducing agents was reported recently, showing a similar observation.\textsuperscript{16} Another major reason for withholding antihypertensive treatment is that ultra-acutely elevated BP drops spontaneously in >80% of the patients during the first minutes or hours after the onset.\textsuperscript{8,17} So where is the evidence that very high BP harms the prognosis? The International Stroke Trial (IST) study demonstrated that systolic hypertension is not linked with cerebral hemorrhages.\textsuperscript{2} It has been associated with extensive cerebral edema or mortality associated with presumed cerebral edema in some studies.\textsuperscript{1,2} However, it cannot be ruled out that an initially large infarct, with the vessel nonrecanalized, induced the hypertensive reaction, but there was already a large area of brain to be subjected to blood-brain barrier failure and cumulative edema. Unremitting high BP increases the likelihood of a severe neurological damage already on admission, or persistence of the occlusion, and acute pharmacologic BP reduction will not reverse either one. Surely, especially after the presumed penumbra no longer exists (>24 hours), there is no reason to maintain overtly elevated BP that drives plasma to the intracranial space. Other reasons to decrease very high BP, include myocardial ischemia, imminent cardiac failure, acute renal failure, hypertensive encephalopathy, and aortic arch dissection.\textsuperscript{20}

What is the relationship between BP reduction and stroke prognosis in thrombolytic therapy? Two studies suggest that if the thrombolysed patient is hypertensive and antihypertensives are given, the prognosis is poorer than if BP is not medicated.\textsuperscript{18,19} In view of the novel pathophysiological data in this study,\textsuperscript{9} the patient with persistently elevated BP is likely to have still ongoing vessel occlusion. We cannot deviate from the guidelines used to control BP during thrombolysis (<180/110 mm Hg),\textsuperscript{20,21} which are well based on clinical data from existing thrombolysis databases showing baseline hypertension on admission as a risk factor for parenchymal hemorrhage.\textsuperscript{22–24} What should be studied next in these databases and other stroke thrombolysis registries is how the follow-up BP level up to 24 hours, treated or not treated, relates with the risk of hemorrhage or edema formation after thrombolysis. This would help in determining whether high postthrombolytic BP continues to be a risk or only a risk marker and how it should be best managed.

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