

Blood Pressure Management in Patients With Acute Ischemic Stroke

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Case

A 68-year-old right-hand-dominant man was brought to the hospital because of a speech disturbance and right arm and leg weakness. He awoke with these deficits and was last known to be symptom-free when retiring to bed the previous evening 8 hours earlier. His past medical history was notable for coronary heart disease, the patient having undergone coronary artery bypass surgery 7 years previously for unstable angina, but he had no known history of myocardial infarction. He also had hypertension and hyperlipidemia, and smoked 1 pack of cigarettes daily for more than 40 years. He had no history of calf claudication. His hypertension was being treated with a diuretic and β -adrenergic receptor blocker. He was also prescribed 325 mg of aspirin daily and an HMG CoA-reductase inhibitor (statin); however, his wife remarked that he often forgot to take his medications. His last total cholesterol was 240 mg/dL, with LDL cholesterol of 130 mg/dL. He had a strong family history of coronary heart disease after the age of 50. He had no known drug allergies.

Physical Examination

The patient's blood pressure was 195/100 mm Hg in both arms, with a regular pulse of 90 bpm. His weight was 225 lb (body mass index: 31.4 kg/m²). His lungs were clear to auscultation. Cardiac examination showed a laterally displaced point of maximum impulse with an S₄ gallop and a soft nonradiating systolic murmur at the base. His abdomen was obese without organomegaly and no abdominal bruits were detected. He had no rashes and no joint deformities. The left superficial temporal artery pulse was stronger than the right. There were soft bilateral anterior cervical bruits, left louder than right, but no supraclavicular bruits. There were bilateral femoral bruits. Radial pulses were 2⁺ and symmetric. Dorsalis pedis and posterior tibial pulses were 1⁺. There was no pretibial or ankle edema.

Neurological Examination

The patient was alert. He spoke haltingly and made frequent paraphasic errors, using inappropriate words and occasional neologisms. He was able to follow simple verbal commands but had difficulty with repetitions. Further cognitive evaluation could not be performed because of the language distur-

bance. Cranial nerve examination revealed a right homonymous visual field deficit to threat. Funduscopic examination disclosed arteriolar narrowing with arteriolar-venous nicking, but no hemorrhages. There were no Hollenhorst plaques. There was a left gaze preference with otherwise full extraocular movements and no nystagmus. Pupillary light reflexes were normal. The right corneal response was diminished and there was a mild right lower facial paresis. His gag response was absent and his tongue deviated to the right. Motor examination revealed normal bulk with diminished tone in his right arm. He had 3/5 proximal and 2/5 distal strength in the right arm, 4/5 strength in the right leg, and full strength in his left arm and leg. He had a coordination deficit consistent with the weakness in his right arm and leg and normal coordination on the left. Sensory examination was limited by his language disturbance, but there appeared to be right-side deficits to pinprick and light touch sensibilities. Deep tendon reflexes were diminished on the right, with a right plantar-extensor response. Gait was not tested.

Initial Laboratory Studies

Complete blood count, electrolytes, blood glucose, and renal function were unremarkable. Prothrombin and activated partial thromboplastin times were normal. Erythrocyte sedimentation rate was 35 mm/h. ECG showed left ventricular hypertrophy by voltage criteria. Brain computed tomographic (CT) scan showed poor gray-white distinction in the left temporal-parietal region and decreased attenuation in the periventricular white matter but was otherwise unremarkable.

Discussion

This man with several cardiovascular risk factors presents with symptoms and signs consistent with a left temporal-parietal lesion with cortical involvement. The acute onset of his symptoms suggests a vascular cause. Pathophysiologically, parenchymal hemorrhage and ischemia need to be considered. The majority of nontraumatic, parenchymal hemorrhages in nonanticoagulated adults occur in hypertensive adults in the thalamus/basal ganglia, pons, or cerebellum. Although this patient was hypertensive, his clinical examination is not consistent with an abnormality in one of these locations, making a primary hemorrhage less likely. How-

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ever, CT scan is required to exclude hemorrhage and to help identify nonvascular causes of the patient's symptoms.¹ In this case, the CT scan excluded hemorrhage and showed changes consistent with early ischemia.² His neurological examination further showed deficits consistent with a lesion in the distribution of temporal–parietal branches of the left middle cerebral artery. This could be related to cardiogenic embolization, but the patient had no history or current evidence of atrial fibrillation and no significant cardiac murmur. A second possibility is that the stroke was related to atheroembolism from the carotid artery (the cervical portion of the carotid artery is most commonly affected), carotid artery occlusion with partial preservation of left hemisphere function through collateral blood supply, or from other less common causes. Findings on examination suggesting he has cervical carotid artery disease include the presence of anterior cervical bruits and a relatively stronger left superficial temporal artery pulse.^{3,4} The latter finding may indicate the presence of a high-grade left internal artery stenosis or occlusion with augmented flow through the left external carotid artery. Further testing is required to establish the most likely pathophysiological diagnosis.

Although this case raises many issues regarding acute treatment and long-term secondary prophylaxis, the main subject for the present discussion is his blood pressure management. Several studies show that stroke recurrence is reduced with antihypertensive treatment. For example, the UK TIA study found that each 10 mm Hg decrease in systolic BP was associated with 28% decrease in stroke risk.⁵ Other studies also show the long-term benefit of antihypertensives in stroke survivors.^{6,7} The issue is not whether the patient should be treated with antihypertensives, but rather when that treatment should begin.

The first consideration in blood pressure management in the setting of acute ischemic stroke is to determine whether the patient might otherwise be a candidate for treatment with intravenous tissue plasminogen activator (t-PA). Given in accord with a strict protocol, t-PA administration is associated with a 12% absolute (32% relative) increase in the proportion of patients with acute ischemic stroke who are free of disability after 3 months, with the benefit sustained after 1 year.^{8,9} This patient did not qualify for treatment with intravenous t-PA because the time of onset of his symptoms, taken as the last time he was known to be symptom-free, was the previous evening (ie, more than 3 hours previously).

Despite being extraordinarily common, there remain no specific clinical trial data to guide blood pressure management in patients with acute ischemic stroke. Several lines of reasoning based on available experimental and clinical data support caution outside of the setting of malignant hypertension. Cerebral blood flow (CBF) (averaging 50 mL/100 g per minute in normal subjects)¹⁰ is determined by the cerebral perfusion pressure (CPP) divided by cerebrovascular resistance (CVR).¹¹ This equation reflects the cerebral autoregulatory relationship. To keep CBF constant, decreases in CPP are matched by decreases in CVR (ie, cerebral vasodilatation), and increases in CPP are matched by increases in CVR (ie, cerebral vasoconstriction). CPP is determined by the difference between mean arterial pressure (MAP) and venous

backpressure. Venous backpressure is insignificant outside of the setting of venous occlusion and certain other pathological conditions. Therefore, $CPP = MAP/CVR$. To maintain CPP, changes in MAP must be matched by compensatory changes in CVR. In normal nonhypertensive subjects, CBF is relatively constant with CPPs (or MAPs) ranging from approximately 60 to 150 mm Hg.¹¹

The cerebral autoregulatory relationship is disrupted in the setting of acute ischemia.¹² This occurs because of a failure in the responsiveness of CVR to changes in CPP. Although the mechanisms are not completely understood, a variety of physiological factors are known to affect cerebral arteriolar vasomotor responses. PaCO₂ level has a potent effect on CVR that is believed to be mediated through changes in local pH.¹³ Reduction in PaCO₂ results in the vasoconstriction underlying the use of hyperventilation in patients with acutely raised intracranial pressure. The local acidosis that accompanies brain ischemia leads to maximal vasodilatation. Therefore, changes in MAP (ie, CPP) are directly reflected in changes in local CBF. A significant negative relationship was found between blood pressure decrease and improvement in cerebral blood flow as measured by single photon emission tomography after ischemic stroke in humans.¹⁴

The impact of reduced CBF is related to the magnitude of the decrease and its duration. Profound, but brief, reductions in CBF may not lead to permanent brain injury. Neuronal death occurs when CBF is reduced below 10 to 15 mL/100 g per minute for more than a short period of time, because of an irreversible loss of energy-dependent cellular ion gradients causing cytotoxic edema.¹⁵ Local CBF levels between approximately 15 and 20 mL/100 g per minute lead to neuronal electrical quiescence (ie, functional impairment), but a preserved capacity to maintain membrane ion gradients.¹⁶ Neurons in this “penumbral” region are potentially salvageable but can also go on to die.^{17–20} In humans, the penumbra can be demonstrated with positron emission tomography and is defined as a region with reduced CBF, an elevated oxygen extraction fraction, and preserved cerebral metabolic rate for oxygen.²¹ Other imaging modalities are also available.²² Although some controversy remains, MRI can also be used to show potentially reversible areas of brain ischemia by comparing diffusion-weighted and perfusion-weighted images.^{23–25} In contrast to MRI-based techniques that are limited to relative measures of cerebral perfusion, dynamic CT scan methods can give absolute perfusion levels that reflect ischemic, but potentially salvageable, tissue.^{26,27} The combination of the possible presence of brain tissue that is ischemic, but not infarcted, and an impaired autoregulatory response provides a major argument against lowering systemic blood pressure in patients with acute ischemic stroke. In the zone of ischemia, CBF will be reduced with reductions in MAP, potentially below the threshold of viability.

There are at least 3 additional concerns with lowering the blood pressure of the present patient. First, the patient has a history of long-standing hypertension, including evidence of hypertensive retinopathy. The lower and upper limits of autoregulation are shifted to higher values in patients with chronic hypertension as compared with those without hypertension.^{11,28} As a result, CBF decreases at a relatively higher

MAP than in normotensive subjects. Hypertensive retinopathy is also highly correlated with similar changes in cerebral vessels,²⁹ and collateral blood flow can be compromised.²⁸ Therefore, patients with chronic hypertension may be particularly vulnerable to the effects of lowering blood pressure in the acute setting. An additional concern based on the patient's examination is the possibility that he may have an ipsilateral high-grade extracranial carotid artery stenosis. Although the patient had an anterior cervical bruit, the presence of a carotid bruit alone is not a reliable indicator of carotid stenosis.^{30,31} In patients with anterior cervical bruits who are subsequently studied with cerebral angiography, the false-positive rate for significant ipsilateral carotid artery stenosis is 13% to 70%, and the false-negative rate is 12% to 71%.^{32,33} However, in addition to the presence of a bruit, the patient had a relatively augmented left (symptomatic side) superficial temporal artery pulse. The ipsilateral superficial temporal artery pulse may be increased because of collateral flow in patients with high-grade stenosis or occlusion of the internal carotid artery.^{3,4} An acute reduction in blood pressure could further compromise flow through a stenotic carotid artery and tenuous collateral vessels.³⁴ Finally, blood pressure in patients with ischemic stroke often spontaneously declines without specific treatment.^{14,35–39}

Arguments favoring treatment of acute hypertension have not changed since Powers' excellent review two decades ago and include reduction in edema, decreasing the risk of hemorrhagic transformation, limiting further vascular injury, and minimizing the likelihood of early recurrence.^{1,11} However, experimental evidence supporting these potential benefits is lacking or contradictory.¹¹

Clinical data are sparse and show no clear relationship between acute elevations in blood pressure and neurological worsening or outcome after ischemic stroke.^{36,40–43} However, some clinical data suggest that lowering blood pressure in patients with acute ischemic stroke may be harmful. For example, a double-blind, placebo-controlled trial evaluated the impact of the calcium channel antagonist nimodipine administered orally and started within 48 hours of ischemic stroke.⁴⁴ Nimodipine significantly reduced systolic and diastolic blood pressures over the first week with higher 1-month ($P=0.004$) and 3-month ($P=0.30$) mortality rates. The Intravenous Nimodipine West European Stroke Trial (INWEST) also provides clinical data consistent with the theoretical concerns related to acute blood pressure lowering.⁴⁵ INWEST was a double-blind, placebo-controlled trial of intravenous nimodipine started within 24 hours of acute ischemic stroke and initially administered at doses of 1 or 2 mg/h. Treated patients fared significantly worse than controls in a dose-dependent fashion. Exploratory analysis showed a significant relationship between the level of diastolic blood pressure reduction and outcome. Irrespective of treatment group, the odds of death or dependency at 21 days was 2.60 (95% CI: 0.82, 8.27) for those with a <10% early decrease in diastolic blood pressure, 2.97 (95% CI: 1.16, 7.63) for those with a 10% to 20% decrease, and 4.36 (95% CI: 1.63, 11.7) for those with a $\geq 20\%$ decrease.⁴⁶ The effect was only present in those without a total anterior circulation distribution infarction.⁴⁷ These patients likely had large volumes of infarction with

relatively small penumbral zones. Another study prospectively evaluated factors affecting the 3-month outcome of a consecutive series of 115 patients with ischemic stroke.⁴⁸ Poor outcome was independently associated with the degree of systolic blood pressure reduction during the first 24 hours (OR=1.89 for poor outcome per 10% decrease; 95% CI: 1.02, 1.87). However, not all studies show these types of relationships. A retrospective analysis of blood pressure data from the Glycine Antagonist in Neuroprotection International (GAIN) Trial found that 11% of the 1455 patients had a 30% decrease in mean arterial pressure over the first 2.5 days, with no independent effect on 3-month outcome.⁴³ It is not clear whether blood pressure decreased precipitously in these patients. Those patients (6%) that had a 30% increase in mean arterial blood pressure over this same period had significantly poorer outcome. However, it is also not clear whether this increased blood pressure led to poorer outcome or reflected other predictors of poor outcome.

Although the question remains unsettled, because of the theoretical issues that have been reviewed, the weight of retrospective analyses of clinical data, and case series experience, a scientific statement from the Stroke Council of the American Stroke Association recommended that blood pressure generally not be lowered in patients with acute ischemic stroke who are not otherwise thrombolytic candidates (grade C; supported by data from nonrandomized concurrent cohort studies, nonrandomized cohort studies with historical controls, or anecdotal case series).¹ Based on this and all of the considerations previously discussed, the current patient's blood pressure should not be treated in the acute period.

Exceptions to the recommendation to avoid treatment of acute hypertension noted in the American Stroke Association scientific statement include patients with hypertensive encephalopathy, aortic dissection, acute renal failure, acute pulmonary edema, acute myocardial infarction, or severe hypertension (Table 1). There are no specific data defining the levels of hypertension that should trigger treatment in these settings. By consensus, it was also recommended that acute treatment be withheld in patients without one of these conditions unless the systolic blood pressure is >220 mm Hg or the diastolic blood pressure is >120 mm Hg (Table 1; level V data).¹ Drugs that can lead to precipitous declines in blood pressure such as sublingual calcium channel antagonists should be avoided (Table 1).

Although not applicable to this patient because the time of onset of his symptoms was beyond the 3-hour treatment window, one additional exception to the recommendation to avoid lowering blood pressure in most patients with acute ischemic stroke applies to those who are otherwise candidates for treatment with intravenous t-PA (Table 1). Based on concern for increased bleeding risk, patients with systolic blood pressures >185 mm Hg or diastolic blood pressures >110 mm Hg were excluded from the National Institute of Neurological Disorders and Stroke t-PA trial.⁸ However, these patients were treated with t-PA if their blood pressures decreased to below these levels without the need for aggressive treatment (either spontaneously or with the application of 1 to 2 inches of nitropaste or the administration of 1 to 2 doses of labetalol, 10 to 20 mg intravenous;¹ those requiring

TABLE 1. Approach to Elevated Blood Pressure in Acute Ischemic Stroke¹

Clinical Situation	Recommendation
Systolic BP <220 mm Hg; diastolic BP <120 mm Hg	Observe BP unless there is other end organ involvement, such as aortic dissection, renal failure, or acute myocardial infarction that would mandate emergent treatment.
Systolic BP >220 mm Hg or diastolic BP 121–140 mm Hg	Labetalol 10–20 mg IV over 1–2 min. May repeat or double every 10 min to a maximum dose of 300 mg OR nicardipine 5 mg/h IV infusion as initial dose; titrate to desired effect by increasing by 2.5 mg/h every 5 min to maximum of 15 mg/h (target 10%–15% reduction)
Diastolic BP >140 mm Hg	Sodium nitroprusside 0.5 μ m/kg per min IV with continuous BP monitoring (target 10%–15% reduction)
Patient otherwise candidate for intravenous rt-PA	If systolic BP >185 mm Hg or diastolic BP >110 mm Hg, intravenous labetalol, 10–20 mg over 1–2 min, or 1–2 inches of nitropaste; if BP is not reduced and maintained at desired levels (<185 mm Hg systolic BP and <110 mm Hg diastolic BP), do not administer rt-PA

BP indicates blood pressure.

intravenous nitroprusside or repeated administration of other intravenous antihypertensives were excluded).⁴⁹ This patient's initial blood pressure was 190/100 mm Hg. If his elevated systolic blood pressure was his only contraindication for intravenous t-PA and did not decline spontaneously, his blood pressure could have been carefully lowered as outlined. Blood pressure after t-PA administration should be carefully monitored and managed (Table 2).¹

If blood pressure lowering in patients with acute ischemic stroke is potentially hazardous based on theoretical concerns and available clinical data, then one might expect that artificially raising blood pressure could be beneficial. Phenyphrine has been used for this purpose, but the data remain preliminary and the approach is not currently recommended.^{1,50} Further, the retrospective data previously reviewed suggest that patients having a significant increase in blood pressure over the first days after ischemic stroke may have poorer outcomes.⁴³ Although rapid acute blood pressure reductions need to be avoided, there may be potential benefit from acute antihypertensive therapy. A double-blind, placebo-controlled, multicenter phase II study (Acute Cand-

estartan Cilexetil Therapy in Stroke Survivors [ACCESS] Study) randomized 342 hypertensive patients with ischemic stroke to candesartan cilexetil over the first 7 days, targeting a 10% to 15% reduction in blood pressure in the first 24 hours or placebo.⁵¹ There were no significant differences in blood pressures between the active treatment and placebo patients over the first week. Both groups received candesartan cilexetil after 7 days (started in 164 of 166 of the original placebo patients because of hypertension). There were no differences in outcome at 3 months but a significant reduction in 12-month mortality rate and the number of vascular events with treatment over the first week (OR=0.475; 95% CI: 0.252, 0.895). The mechanism by which acute treatment led to this difference at 12 months but not at 3 months is uncertain.

A systematic review of studies assessing the effect of lowering or elevating blood pressure in persons with acute stroke performed by the Cochrane Stroke Group includes data from 32 trials involving 5368 patients and concluded that there was not enough evidence to reliably evaluate the effect of altering blood pressure on outcome.⁵² Further studies will be required to determine the optimal management of blood pressure and the use of antihypertensives in this patient population.

TABLE 2. Blood Pressure Management After Intravenous rt-PA¹

Recommendations
Measure blood pressure every 15 min for the first 2 h, every 30 min for the next 6 h, and then every 1 h until 24 h from treatment
Increase the frequency of BP measurements if a systolic BP >180 mm Hg or diastolic BP of >105 mm Hg is recorded; administer antihypertensive medications to maintain BP at or below these levels
If diastolic BP 105–120 mm Hg or systolic BP 180–230 mm Hg, intravenously administer 10 mg labetalol over 1–2 min; may repeat or double the dosage of labetalol every 10–20 min to a maximum dose of 300 mg; as an alternative, can start with the initial bolus dose of labetalol and then follow-up with a continuous labetalol infusion administered at a rate of 2–8 mg/min
If diastolic BP 121–140 mm Hg or systolic BP >230 mm Hg, intravenously administer 10 mg labetalol over 1–2 min; may repeat or double labetalol every 10 min to a maximum dose of 300 mg or can start with the initial bolus dose of labetalol and then follow-up with a continuous labetalol infusion administered at a rate of 2–8 mg/min; as an alternative, nicardipine 5 mg/h IV infusion as initial dose, titrate by increasing 2.5 mg/h every 5 min to maximum of 15 mg/h. If the blood pressure is not controlled, consider starting an infusion of sodium nitroprusside
If diastolic BP >140 mm Hg, start infusion of sodium nitroprusside at a rate of 0.5 μ m/kg per min and titrate to desired BP

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Blood Pressure Management in Patients With Acute Ischemic Stroke

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Correction

In the Hypertension Grand Rounds article by Larry B. Goldstein in the February 2004 issue (*Hypertension*, 2004;43:137–141), a measurement unit was incorrectly edited in Tables 1 and 2. The unit of measurement should be μg , not μm . The corrected tables appear below. The *Journal* regrets the error.

TABLE 1. Approach to Elevated Blood Pressure in Acute Ischemic Stroke¹

Clinical Situation	Recommendation
Systolic BP <220 mm Hg; diastolic BP <120 mm Hg	Observe BP unless there is other end organ involvement, such as aortic dissection, renal failure, or acute myocardial infarction that would mandate emergent treatment.
Systolic BP >220 mm Hg or diastolic BP 121–140 mm Hg	Labetalol 10–20 mg IV over 1–2 min. May repeat or double every 10 min to a maximum dose of 300 mg <u>OR</u> nicardipine 5 mg/h IV infusion as initial dose; titrate to desired effect by increasing by 2.5 mg/h every 5 min to maximum of 15 mg/h (target 10%–15% reduction)
Diastolic BP >140 mm Hg	Sodium nitroprusside 0.5 $\mu\text{g}/\text{kg}$ per min IV with continuous BP monitoring (target 10%–15% reduction)
Patient otherwise candidate for intravenous rt-PA	If systolic BP >185 mm Hg or diastolic BP >110 mm Hg, intravenous labetalol, 10–20 mg over 1–2 min, or 1–2 inches of nitropaste; if BP is not reduced and maintained at desired levels (<185 mm Hg systolic BP and <110 mm Hg diastolic BP), <u>do not</u> administer rt-PA

BP indicates blood pressure.

TABLE 2. Blood Pressure Management After Intravenous rt-PA¹

Recommendations
Measure blood pressure every 15 min for the first 2 h, every 30 min for the next 6 h, and then every 1 h until 24 h from treatment
Increase the frequency of BP measurements if a systolic BP >180 mm Hg or diastolic BP of >105 mm Hg is recorded; administer antihypertensive medications to maintain BP at or below these levels
If diastolic BP 105–120 mm Hg or systolic BP 180–230 mm Hg, intravenously administer 10 mg labetalol over 1–2 min; may repeat or double the dosage of labetalol every 10–20 min to a maximum dose of 300 mg; as an alternative, can start with the initial bolus dose of labetalol and then follow-up with a continuous labetalol infusion administered at a rate of 2–8 mg/min
If diastolic BP 121–140 mm Hg or systolic BP >230 mm Hg, intravenously administer 10 mg labetalol over 1–2 min; may repeat or double labetalol every 10 min to a maximum dose of 300 mg or can start with the initial bolus dose of labetalol and then follow-up with a continuous labetalol infusion administered at a rate of 2–8 mg/min; as an alternative, nicardipine 5 mg/h IV infusion as initial dose, titrate by increasing 2.5 mg/h every 5 min to maximum of 15 mg/h. If the blood pressure is not controlled, consider starting an infusion of sodium nitroprusside
If diastolic BP >140 mm Hg, start infusion of sodium nitroprusside at a rate of 0.5 $\mu\text{g}/\text{kg}$ per min and titrate to desired BP

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