Management of Acute Hypertensive Response in Patients With Ischemic Stroke

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Abstract

High blood pressure (BP) >140/90 mm Hg is seen in 75% of patients with acute ischemic stroke and in 80% of patients with acute intracerebral hemorrhages and is independently associated with poor functional outcome. While BP reduction in patients with chronic hypertension remains one of the most important factors in primary and secondary stroke prevention, the proper management strategy for acute hypertensive response within the first 72 hours of acute ischemic stroke has been a matter of debate. Recent guidelines recommend clinical trials to ascertain whether antihypertensive therapy in the acute phase of stroke is beneficial. This review summarizes the current data on acute hypertensive response or elevated BP management during the first 72 hours after an acute ischemic stroke. Based on the potential deleterious effect of lowering BP observed in some clinical trials in patients with acute ischemic stroke and because of the lack of convincing evidence to support acute BP lowering in those situations, aggressive BP reduction in patients presenting with acute ischemic stroke is currently not recommended. While the early use of angiotensin receptor antagonists may help reduce cardiovascular events, this benefit is not necessarily related to BP reduction.

Keywords

stroke, cerebrovascular disorders, hypoxia-ischemia, brain, cerebrovascular disorders, ischemic attack, transient, cerebrovascular disorders

Introduction

More than 6 of every 10 patients with an acute stroke experience an acute hypertensive response within the first 24 hours of the onset of symptoms, manifesting as an elevation of blood pressure (BP) above normal and premorbid values.¹ Each year, 980 000 patients are admitted with a stroke in the United States, meaning 500 000 patients per year experience an acute hypertensive response.² Worldwide, a total of 15 million patients experience a stroke each year, with an expected prevalence of 10 million patients per year having an acute hypertensive response.³

Based on the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)⁴ and the 2003 World Health Organization/International Society of Hypertension statement,⁵ hypertension is defined as a consistent BP of >140/90 mm Hg, recorded on multiple separate days. This number is used as a threshold to initiate long-term use of antihypertensive medications. It is an evidence-based treatment, based on randomized trials and clinical population-based data, which has revealed a reduction in cardiovascular events by lowering BP below threshold values.⁶

High BP >140/90 mm Hg is seen in 75% of patients with acute ischemic stroke and in 80% of patients with acute

intracerebral hemorrhages and is independently associated with poor functional outcome.^{6,7} To remain consistent with the International Society of Hypertension statement, acute hypertensive response is defined as an elevated systolic BP of >140, or diastolic BP > 90, recorded on 2 occasions 5 minutes apart within the first 24 hours of symptoms onset.⁶ Unlike chronic hypertension, this definition is not used as a threshold for treatment but rather as a uniform standard for measuring the prevalence of hypertensive response in patients with acute stroke.⁶

While BP reduction in patients with chronic hypertension remains one of the most important factors in primary and secondary stroke prevention, the proper management strategy of acute hypertensive response within the first 72 hours of acute ischemic stroke has been a matter of debate.⁶ Recent guidelines recommend clinical trials to ascertain whether antihypertensive

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therapy in the acute phase of stroke is beneficial.⁸ This review summarizes the current data on acute hypertensive response or elevated BP management during the first 72 hours after an acute ischemic stroke.

Pathophysiology of Acute Hypertensive Response

The reasons for acute hypertensive response in the setting of acute ischemic stroke are still not very well understood.⁹ Most explanations are based on the premise that acute hypertensive response is secondary to the stroke, an increase in intracranial pressure, a response to increased plasma catecholamines, secondary to the stress of hospital admission, a full bladder, nausea, pain, or a physiological response to hypoxia.⁹ Of course, the acute hypertensive response in a portion of these patients reflects undetected or inadequately treated chronic hypertension.¹⁰

Cushing's phenomenon (increased BP secondary to elevated intracranial pressure) cannot be blamed as a major contributor, except in a case of a massive infarct.¹¹ There seems to be no definite correlation with ischemic lesion size or location.⁸ In addition, the BP tends to spontaneously go down in few days following the stroke in most patients, when the infarct tends to swell and intracranial pressure increases.^{12,13} This decline in BP starts within 90 minutes after the onset of stroke symptoms.^{8,14,15} It is also difficult to attribute the acute hypertensive response solely to ischemic damage to the insular cortex, nucleus or tractus solitarius, or other structures that play a role in the regulation of BP.^{16,17}

Cerebral Autoregulation and the Ischemic Penumbra

Cerebral precapillary arterioles, under normal circumstances, accommodate to changes in BP (in the range of mean arterial pressures between 60 and 150 mm Hg) by changing arteriolar diameter, which maintains constant cerebral perfusion in the capillary bed.¹⁸ Such response to pressure pulsations is usually initiated by a fast dynamic response, followed by a slow static response that restores cerebral perfusion.¹⁹ The mechanism underlying this response is myogenic and metabolic.¹⁹ Arterioles respond to a decrease in BP by vasodilation to restore blood flow, but when vasodilation reaches a maximal limit blood flow decreases (perfusion pressure $\leq$ 60 mm Hg). If perfusion pressure continues to fall, an increase in the oxygen extraction fraction maintains cerebral oxygen metabolism.²⁰ Once this mechanism becomes maximal, usually at perfusion pressures $\leq$ 30 mm Hg, further decline in blood flow leads to substrate depletion, energy failure, disruption of cellular homeostasis, and ultimately, ischemic necrosis.²⁰

On the other hand, when BP increases, arteriolar vasoconstriction occurs. With higher elevations in BP, vasoconstriction progresses to a point where it can no longer occur.¹⁹ When the upper limit of autoregulation has been exceeded,

breakthrough vasodilation follows, which increases cerebral blood flow and leads to cerebral edema and blood-brain barrier dysfunction.¹⁹

As a result of vessel wall thickening and luminal narrowing, the ability of resistance vessels to dilate or constrict to meet the demands of autoregulation becomes limited. Patients with chronic hypertension tend to have the lower end of their autoregulation curve shifted to high BP values.²¹

Patients presenting with an acute stroke may have autoregulation impairment in the ischemic region.²² Recent data have revealed impairment in autoregulation in response to rapid changes in systemic BP (dynamic initial response), even when it is preserved for controlled changes (static responses).²³ This could also be the case in the contralateral hemisphere, where in response to tissue ischemia and acidosis, dilation of cerebral resistance vessels occurs to restore blood flow.²²

Patients with ischemic stroke have a window of opportunity for therapeutic intervention to restore regional cerebral blood flow and salvage ischemic brain tissue.^{24,25} The ischemic penumbra is the region with reduced regional cerebral blood flow and viable tissue, which is at risk for irreversible damage over 6 to 9 hours.²⁶⁻²⁸ Because some degree of blood flow is still maintained by collateral circulation, the ischemic penumbra remains viable for hours. However, because of impaired regional autoregulation,²³ this area becomes at risk of ischemic injury when BP decreases,²⁹ even at more risk when the BP falls rapidly.⁶ For this reason, lowering the systemic BP pharmacologically in acute ischemic stroke may have disastrous consequences and a cautious approach to managing BP in the first 72 hours is very important.

The situation may be different when dealing with cerebral ischemia and reperfusion therapy (eg, when using rtPA). Lowering BP has been shown to reduce infarct size and deficits in experimental models of focal cerebral ischemia and reperfusion.³⁰ Therefore, there may be a time period when brain tissue is vulnerable to progression of ischemic deficits if the BP is lowered, but a benefit from BP reduction might exist after that.⁶

Types of Acute Hypertensive Response

Patients presenting with an ischemic stroke and acute hypertensive response could have different underlying pathophysiology that mandate different approaches in management.⁶

Blood pressure elevation in the acute hypertensive response can fall into one of the following categories:⁶

1. Blood pressure declines spontaneously without antihypertensive medications.
2. Blood pressure doesn't decline despite the use of antihypertensive medications or becomes elevated.
3. Blood pressure responds with modest decline (10%-15% from baseline) in response to the use of antihypertensive medications.

4. Blood pressure responds with an intense decline ($\geq 20\%$ from baseline value) in response to the use of antihypertensive medications.

It is important to consider these differences when interpreting the results of clinical trials that investigate the best approach for dealing with hypertensive response in the acute setting of ischemic stroke since they are confounded by these 4 categories of BP response with a varying level of overlap.⁶

Another point to consider is that many patients presenting with an acute stroke could have intravascular volume depletion on admission.⁶ Early identification of dehydration is important,³¹ since it could result in a physiologic hypertensive or hypotensive response or an exaggerated decline in BP as a response to the use of antihypertensive medications.^{32,33} Starting fluids in a dehydrated patient before administering antihypertensive medications is essential to have a controlled response to treatment.⁶

Clinical Trials and Observational Studies

A few preliminary randomized trials of BP lowering in acute ischemic stroke have been performed. Below is a brief review of the literature that disclaims, supports, or shows neutral results about BP control in the setting of an acute ischemic stroke:

Studies Arguing Against Early Antihypertensive Therapy

1. The Intravenous Nimodipine West European Stroke Trial,³⁰ an acute ischemic stroke treatment trial testing the therapeutic effects of nimodipine (a calcium channel blocker) as cytoprotective therapy within 24 hours after onset of ischemic stroke, found that prominent reduction in BP in patients randomized to intravenous nimodipine was associated with worse clinical outcomes at 21 days. Statistically significantly higher rates of death and disability were seen in association with a decrease in diastolic BP $>20\%$ or a diastolic BP <60 mm Hg.³⁰
2. Oral nimodipine started within 48 hours after ischemic stroke was tested in a placebo-controlled randomized trial on 350 patients.³⁴ The nimodipine group had significantly lower systolic and diastolic BP. Even though functional outcomes at 3 months were similar in both groups, mortality was significantly higher in the nimodipine group.³⁴
3. An observational study that involved 115 patients admitted within 24 hours of ischemic stroke found systolic BP of patients declined by 28% during the first day, whether or not antihypertensive medications were administered. An adverse effect on outcomes was noted with magnitude of decline in the BP within the first 24 hours after an ischemic stroke, with an odds ratio of 1.89 for unfavorable outcome with each 10% drop in

BP. The detrimental effect was similar in strata defined by age or National Institutes of Health Stroke Scale scores.³⁵

4. Another observational study demonstrated that a 20 mm Hg or greater reduction in systolic or diastolic BP was associated with serious adverse effects and outcomes in a consecutive series of patients with ischemic stroke admitted within 24 hours of symptom onset. Early neurological worsening, larger volumes of infarction, and higher rates of poor outcome or death were among the adverse outcomes. Administering antihypertensive agents early to patients with systolic BP ≤ 180 increased the likelihood of early deterioration, poor neurological outcome, or death.⁶⁰
5. In the candesartan for treatment of acute stroke trial (SCAST),³⁶ 2029 patients presenting within 30 hours of an acute stroke were randomly allocated to receive candesartan versus placebo. Blood pressures were significantly lower in the candesartan group compared to placebo within the 7-day treatment period. At 6 month follow-up, the candesartan group had higher risk of poor functional outcome. The study concluded BP lowering with candesartan showed no benefit in patients with acute stroke. If anything, the evidence suggested a harmful effect.

Studies Supporting Early Antihypertensive Therapy

1. Controlling Hypertension and Hypotension Immediately Post-Stroke³⁷: In this multicenter, prospective, randomized, double-blind, placebo-controlled titrated-dose trial, patients with acute stroke were divided into 2 groups. The first group consisted of patients who had symptom onset <36 hours and hypertension (systolic BP >160), and the second group had patients with symptoms onset <12 hours and hypotension (systolic BP <140 mm Hg). Patients were allocated to either the pressor or the depressor arm depending on BP at randomization. The pressor arm was closed early because of problems with recruitment, so no conclusions could be drawn regarding this therapy. In the depressor arm, oral and sublingual Lisinopril and oral and intravenous labetalol did not increase the likelihood of early neurological deterioration. The study was not sufficiently powered to detect a difference in disability or death at 2 weeks. However, that the 3-month difference in mortality favored active treatment is of interest, although care must be taken in interpretation of the results.
2. The Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS)³⁸ study aimed to evaluate the safety of modest lowering of BP with candesartan in the early treatment of stroke. The study showed that, in the absence of BP lowering, candesartan treatment for 7 days started within 24 hours of stroke onset reduced the

cumulative 12-month mortality rate (7.2% and 2.9% for placebo and candesartan, respectively) and vascular events (18.7% and 9.8% for placebo and candesartan, respectively). The study concluded that candesartan is safe to use in the prevention and treatment of acute stroke and may provide therapeutic benefits. However, there was no difference in BP between the candesartan and placebo arms of this trial, neither within the first 7 days nor at 12 months.

Studies With Neutral Results

1. Continue or Stop Post-Stroke Antihypertensive Collaborative Study (COAAACS):³⁹ This UK trial recruited adult patients who were taking antihypertensive drugs and were enrolled within 48 hours of stroke and the last dose of antihypertensive drug. Patients were randomly assigned to either continue or stop pre-existing antihypertensive drugs for 2 weeks. Continuation of antihypertensive drugs did not reduce 2-week death or dependency, cardiovascular event rate, or mortality at 6 months. Lower BP levels in those who continued antihypertensive treatment after acute mild stroke were not associated with an increase in adverse events. These neutral results might be because the study was underpowered owing to early termination of the trial and support the continuation of ongoing research trials.
2. In The China Antihypertensive Trial in Acute Ischemic Stroke,⁴⁰ 4071 patients who presented within 48 hours of onset of stroke and had elevated systolic BP were randomly assigned to receive antihypertensive treatment or to discontinue all antihypertensive medications during hospitalization. The study concluded that BP reduction had no effect on the incidence of death and major disability at 14 days or at hospital discharge when compared with the absence of hypertensive medications in patients who presented with an acute ischemic stroke and didn't receive TPA. There was also no difference in the outcome of death or major disability at 3 months between the 2 groups.

Blood Pressure and Intravenous rt-PA Administration. Patients with acute ischemic stroke, who receive thrombolysis, usually have transient acute hypertensive response⁴¹ that resolves after recanalization.^{6,42} However, prior to receipt of thrombolysis, high BP is associated with an increased incidence of intracranial hemorrhage.⁶ Results of the Australian Streptokinase trial⁴³ show that patients with ischemic stroke treated with streptokinase who had a systolic BP more than 165 mm Hg had a higher incidence of intracranial hemorrhage. This was also confirmed by another observational study.⁴⁴

There is not enough data to determine the level of risk of intracranial hemorrhage in patients undergoing thrombolysis who have a high initial BP, since many randomized controlled studies have excluded such patients.⁴⁵ Current American heart association/American Stroke association guidelines

recommend a systolic BP below 185 prior to receiving intravenous (IV) rt-PA.⁸

Perfusion Computed Tomography and Magnetic Resonance Imaging

In recent years, advanced imaging modalities such as perfusion-weighted computed tomography and perfusion-weighted magnetic resonance imaging have been incorporated into the diagnosis of acute ischemic stroke.⁸ The benefit of using perfusion studies, when combined with parenchymal studies, is to delineate the ischemic penumbra.^{8,46-54} These imaging modalities can also define areas of infarct that are no longer salvageable.⁸ Because treating the acute hypertensive response in ischemic stroke theoretically puts the ischemic penumbra at risk of infarction, perfusion imaging may identify patients at highest risk of negative outcomes with BP lowering therapies.

Recommendations

Due to the lack of reliable evidence, the ideal strategy of managing hypertension in acute ischemic stroke remains a matter of debate.⁶ Unlike the use of antihypertensive medications in chronic hypertension, the benefit of acutely lowering BP in the setting of ischemic stroke is still unclear.⁴¹

Extreme elevations in BP are clearly harmful, since they could result in encephalopathy, renal insufficiency, or cardiac complications. On the other hand, extremely low BP is also clearly harmful, since it could lead to worsening of an existing ischemic brain injury by decreasing blood perfusion to the stroke and penumbra area,⁸ and it can lead to worsening outcome, defined as dependency or death.

Thus, an ideal BP target within this range likely exists, but it needs to be determined on an individual basis based on stroke subtype and other patient comorbidities and it has not yet been scientifically determined.⁸

Based on the potential deleterious effect of lowering BP observed in some clinical trials in patients with acute ischemic stroke and because of the lack of convincing evidence to support acute BP lowering in those situations, aggressive BP reduction in patients presenting with acute ischemic stroke is currently not recommended.⁶ While the early use of angiotensin receptor antagonists may help reduce cardiovascular events, this benefit is not necessarily related to BP reduction.⁵⁵

Based on the 2013 consensus of the American Heart Association/American Stroke Association panel, and in the absence of definitive benefit, the long-standing recommendation of treating BP only when the systolic exceed 220 mm Hg or the diastolic 120 mm Hg remains reasonable. When there are other clinical conditions that mandate lowering BP, such as myocardial ischemia, aortic dissection, or heart failure, the threshold for BP treatment needs to be modified.⁸ No studies have shown that, in patients without such comorbidities, these high BP values are especially dangerous or that immediate

Table 1. Pharmacological Characteristics of Antihypertensive Agents Recommended in the Stroke Council, American Heart Association's Statements for Healthcare Professionals.

Agent	Mechanism of Action	Dose	Onset of Action	Half-life	Side Effects	Special Indications
Labetalol	Adrenergic blocker	5 to 20 mg bolus every 15 minutes, up to 300 mg	5 to 10 minutes	3 to 6 hours	Nausea, vomiting, agitation, muscle twitching, sweating, cutis anserina (if BP is reduced too rapidly), thiocyanate, and cyanide toxicity	Should be avoided in patients with asthma and acute left ventricular failure
Hydralazine	Direct relaxation of arteriolar smooth muscle	5 to 20 mg bolus every 15 minutes	10 to 20 minutes	1 to 4 hours	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia
Nitroprusside	Releases nitric oxide	Infusion of 0.2 to 10 g/kg/min	Within seconds	2 to 5 minutes	Nausea, vomiting, agitation, muscle twitching, sweating, cutis anserina (if BP is reduced too rapidly), thiocyanate, and cyanide toxicity	Should be used cautiously in patients with high intracranial pressure or azotemia
Nitroglycerine	Releases nitric oxide	20 to 40 g/min	3 to 5 minutes	1 to 2 minutes	Headache, tachycardia, nausea, vomiting, apprehension, restlessness, muscular twitching, palpitations, methemoglobinemia, tolerance with prolonged use	Myocardial ischemia, heart failure
Nitropaste	Releases nitric oxide	0.2 to 0.4 mg/h up to 0.8 mg/h	1 to 2 minutes	3 to 5 minutes	Headache, tachycardia, nausea, vomiting, apprehension, restlessness, muscular twitching, palpitations, methemoglobinemia, tolerance with prolonged use	Myocardial ischemia, heart failure
Nicardipine	Calcium channel blocker	5 to 15 mg/h	5 to 10 minutes	0.5 to 4 hours	Tachycardia, headache, flushing, local phlebitis	Should be used cautiously in patients with myocardial ischemia or acute heart failure
Esmolol	Beta adrenergic blocker	250 g/kg bolus followed by 25 to 300 g/kg/min	5 minutes	9 minutes	Hypotension, nausea	Aortic dissection perioperatively
Enalapril	ACE inhibitor	1.25 to 5 mg every 6 hours	15 minutes	1 to 4 hours	Precipitous fall in BP in high-renin states, variable response	Should be avoided in acute MI and acute left ventricular failure.

Abbreviations: BP, blood pressure; MI, myocardial infarction.

^aTable was reproduced from Qureshi et al¹ and Merck Manual (online professional version).

treatment is needed. The panel recommendations are based on the concern that aggressive lowering of BP could be detrimental.⁹

Intravenous labetalol or other short-acting antihypertensive drugs are recommended for a systolic BP of >220 mm Hg and a diastolic pressure of >120 mm Hg. A cautious 15% to 25 % BP reduction should be achieved for the first 24 hours.⁹ An individualized approach for selecting the IV medication is recommended, since no single optimal medication has been determined (Table 1).⁴²

When there is an indication to lower BP due to a specific medical condition in the setting of an acute ischemic stroke, it should be done in a controlled manner to decrease the associated risk.⁸ A reasonable approach would be to lower the systolic BP initially by 15% and monitor the patient for

neurological deterioration. Careful, serial neurological examinations are critical in this setting. Since no ideal approach has been determined yet, BP targets are based on physician judgement.⁸

Due to the dynamic nature of BP, it is also important to frequently monitor BP especially in the first day after an acute ischemic stroke and identify extreme fluctuations of BP that might require an intervention.⁸ Wide fluctuations of BP values in the first few hours may be associated with a higher risk of death at 90 days.^{56,57}

In patients who are receiving rt-PA, a systemic BP goal of <185/110 mm Hg should be achieved prior to thrombolytic administration.⁸ Once patients received IV rt-PA, the BP must be kept <180/105 mm Hg to minimize risk of intracerebral hemorrhage (Table 2).⁸

Table 2. Management of Acute Hypertensive Response in Patients With Acute Ischemic Stroke, Who are Candidates for rt-PA.

Prior to Receiving rt-PA

1. If BP is not maintained at or below 185/110 mm Hg, do not administer rtPA.
2. Management of blood pressure could be achieved using:
 - a. Labetalol 10 to 20 mg IV over 1 to 2 minutes may repeat 1 time.
 - b. Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5 to 15 minutes, maximum 15 mg/h.
 - c. Hydralazine, enalaprilat, and so on may be considered when appropriate

During and After rt-PA

1. Maintain BP at or below 180/105 mm Hg.
2. Monitor BP every 15 minutes for 2 hours from the start of rtPA therapy, then every 30 minutes for 6 hours, and then every hour for 16 hours.
3. If systolic blood pressure is >180 to 230 mm Hg or diastolic blood pressure >105 to 120 mm Hg: labetalol 10 mg IV followed by continuous IV infusion 2 to 8 mg/min; or nicardipine 5 mg/h IV, titrate up to desired effect by 2.5 mg/h every 5 to 15 minutes, maximum 15 mg/h.
4. If BP not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside.

Abbreviations: BP, blood pressure; IV, intravenous.

^aTable was reproduced from Guidelines for the Early Management of Patients With Acute Ischemic Stroke, 2013⁷, copyright permission was granted.

Holding and Restarting Oral Medications

Oral antihypertensive medications that patients were using before the stroke can be temporarily withheld (or sometimes reduced to avoid antihypertensive withdrawal syndrome, particularly with β -blockers)⁵⁸ at the onset of acute ischemic stroke to avoid unintentionally dramatic reductions in BP.⁸

The optimal time to restart oral antihypertensive medications should be individualized based on various patient and stroke characteristics since an ideal time has not been established.⁸ Nonetheless, in most cases, initiating antihypertensive therapy after the first 24 to 48 hours from stroke onset is reasonable^{6,8,37} since the ischemic penumbra resolves after the first 24 hours.⁶ The ACCESS trial, mentioned earlier, supports a gradual titration of oral antihypertensive based on BP values toward more aggressive BP control.^{6,38}

The JNC 7 report⁴ recommends intermediate BP values around 160/100 to be maintained until the patient has achieved neurological stability. This might not be the case for patients in special circumstances (such as increased intracranial pressure, progressive cerebral edema, and ongoing cerebral ischemia) where individualized management is advised.^{4,6}

Long-term antihypertensive therapy for patients after stroke might be best individualized based on patient comorbidities, compliance with medications, and ability to swallow.⁸ In general, more aggressive BP control can be initiated after the first week or when the patient has achieved neurologic stability, but long-term BP control is critical to prevent recurrent stroke.^{6,4,59}

Declaration of Conflicting Interests

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