Chapter 8
Acute Blood Pressure Management After Ischemic Stroke

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Elevation in blood pressure (BP) is common with an acute ischemic stroke; however, the acute management of the BP is a major unresolved issue. While there are clear benefits for BP reduction in the long-term for secondary stroke prevention, controversy exists in the period immediately following ischemic stroke. The main concern for the acute lowering of BP is the risk of worsening cerebral ischemia due to cerebral hypoperfusion surrounding the infarct core. Allowing the BP to be permissively elevated however may lead to an increase in the risk of hemorrhagic conversion and systemic complications. This chapter will review the current evidence that addresses the management of BP in the setting of acute ischemic stroke and how this affects neurological outcome.

Hypertension with Acute Ischemic Stroke

Incidence and Natural History

Many patients with acute ischemic stroke will present to the emergency department with BP elevation; however, it is unclear whether this represents a compensation for cerebral hypoperfusion or is related to systemic causes [1, 2]. Several studies have helped elucidate the natural history of BP changes following acute ischemic stroke.

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The incidence of an elevated BP has been reported to be 76.5 % in a large retrospective analysis of 276,734 patients presenting to the emergency room with acute ischemic stroke [3]. This is further supported by two large multicenter acute ischemic stroke trials, the Chinese Acute Stroke Trial (CAST) with 21,106 patients and the International Stroke Trial (IST) with 19,435 patients, that reported a systolic blood pressure (SBP) > 140 mmHg in 75 % and 80 % of patients, respectively. Furthermore, severe BP elevation, as defined as SBP > 180 mmHg, was reported in 25 % of patients in CAST and 28 % of patients in IST [4, 5].

Commonly this elevation in BP however is followed by a reduction over the next several days [1, 2, 6, 7]. A large stroke registry found that an early decrease of SBP by 20–30 % was associated with a complete neurological recovery [8]. Furthermore, an early decrease in SBP after acute ischemic stroke has been associated with recanalization of the affected vessel [9].

Effect of Hypertension on Outcome After Acute Ischemic Stroke

The optimal target for BP after acute ischemic stroke remains unclear, as several studies have demonstrated a U-shaped correlation between BP and poor outcome. Either an elevated or very low BP on admission has been associated with worse outcome.

A large observational study demonstrated early as well as late mortality in a U-shaped distribution in relation to the admission SBP. The relative risk of mortality at 1 month and 1 year increased with every 10 mmHg change in SBP above or below 130 mmHg [10]. Data from IST demonstrated that both high BP and low BP were independent prognostic indicators for poor outcome. A baseline SBP of 140–179 mmHg resulted in the lowest frequency of poor outcome [11].

Additional studies have demonstrated associations between elevated or low SBP and patient outcomes. One such study found that patients with a SBP less than 155 mmHg were more likely to die within 90 days compared to patients presenting with a SBP between 155 and 220 mmHg [12]. The Intravenous Nimodipine West European Stroke Trial found that a high initial BP, SBP greater than 160 mmHg, was a predictor for death or dependency at 21 days compared to patients who had a normal initial BP (SBP 120–160 mmHg and diastolic BP 60–90 mmHg) [13]. An analysis of the VISTA (Virtual Stroke International Stroke Trial Archive) collaboration examined the relationship between hemodynamic measures, variability in BP, and change in BP over the first 24 h after acute ischemic stroke. This study demonstrated that a persistently elevated SBP for up to 24 h was significantly associated with increased neurological impairment and poor functional outcome. Additionally, the magnitude of change in BP over this first 24 h was significantly related to poor outcome in which patients having large decreases (>75 mmHg) or increases (>25 mmHg) in BP had the highest risk of poor outcome [14]. Analysis of the Fukuoka stroke registry demonstrated that a SBP (averaged over first 48 h) range of 144–153 mmHg and above was associated with a lower probability of good neurological recovery. SBP elevation was also associated with an elevated risk of neurological deterioration

and poor functional outcome [15]. These studies suggest that hypertension on admission may be a marker of other factors, such as a higher severity of stroke or a sign of premorbid hypertension, rather than an independent prognostic sign [16].

Cerebrovascular Pathophysiology and Ischemic Stroke

Under normal physiological conditions, regional cerebral blood flow (CBF) is tightly regulated through cerebral autoregulation despite variations in regional cerebral perfusion pressure (CPP) [17]. Regional CPP is equal to the local mean arterial pressure (MAP) minus local intracranial pressure (ICP). In the absence of local arterial occlusion or stenosis or local increased ICP, regional CPP is equal to systemic MAP. The cerebral vasculature will either constrict or dilate maintaining stable CBF within a mean regional CPP range of 50–150 mmHg [18, 19]. When the regional CPP falls below the lower limit of autoregulation, regional CBF is reduced resulting in cerebral ischemia. Conversely, when the regional CPP increases above the upper-limit of autoregulation regional CBF is increased, which can lead to cerebral edema or hemorrhage. The autoregulation of CBF can be affected by chronic systemic hypertension with a resultant shift to the right in the autoregulatory curve. This shift may lead to cerebral hypoperfusion even when the MAP is within the normal physiologic range of 50–150 mmHg, but below the lower limit for the right-shifted curve. Prior to the advent of modern tomographic brain imaging modalities such as CT, PET, and MRI, CBF studies in humans using the technique of radiotracer injection into the carotid artery with radioactivity detection by scintillation crystals on the scalp showed abnormalities during the initial days following ischemic stroke. These abnormalities included non-focal hemispheric decreases in CBF in response to rapid reductions in MAP; however, it was not possible to determine whether these changes were in infarcted tissue, the peri-infarct region, or non-ischemic tissue [20–22]. These studies led to the widespread view that autoregulation of CBF in response to changes in systemic blood pressure is impaired in acute ischemic stroke. More recent data using tomographic imaging techniques for CBF measurement that have better spatial resolution have produced different results from the earlier studies. In the three studies that used intravenous agents to produce rapid reduction then stabilization of BP, there was no selective impairment of autoregulation in the peri-infarct region to reduced MAP in patients studied within 6 h or 1–11 days after onset of stroke [23–25]. Two additional studies using oral agents to produce blood pressure reduction over 6–8 h also failed to demonstrate impaired autoregulation in patients 2–8 days from onset of stroke. These studies did not address patients with large edematous infarcts causing increases in ICP or those with persistent large artery occlusion causing local reduction in MAP. In these situations, when local CPP is lower than systemic MAP, a reduction in systemic MAP within the 50–150 mmHg range could cause a reduction in local CPP below the autoregulatory limit with a consequent reduction in CBF even though the autoregulatory capacity of the cerebral blood vessels is normal.

Acute Management of Blood Pressure After Ischemic Stroke

Controversy

While the long-term treatment of hypertension clearly reduces the risk of recurrent stroke, controversy exists as to the management of BP elevation in the setting of acute ischemic stroke. An elevated BP may increase the risk of secondary complications of stroke such as hemorrhagic transformation and cerebral edema [26, 27]. Additionally, if the blood pressure is aggressively lowered then cerebral perfusion may decrease to a level that leads to further cerebral ischemia [19]. Several large prospective trials have been completed within the past several years aimed at addressing these questions.

Effect on Neurological or Functional Outcome

In 2008, a Cochrane review assessed the effect of altering BP in patients with acute ischemic stroke. Twelve small randomized studies, including a total of 1153 patients, were included in the review; however, the authors felt that there was insufficient evidence to determine an effect of lowering BP on clinical outcomes [28]. Since that publication however, several large prospective trials have been completed providing more definitive data (Table 8.1).

Controlling hypertension and hypotension immediately post-stroke (CHHIPS) was a randomized, placebo-controlled, double-blind trial that compared labetalol, lisinopril, and placebo for lowering BP in 179 patients with either acute ischemic or hemorrhagic stroke and a SBP greater than 160 mmHg. While BP was reduced by 21 mmHg in the active treatment and 11 mmHg in the placebo group, there was no significant difference in primary outcome of death or dependency at 2 weeks. While there was no difference in serious adverse events between the groups, the 3 month mortality was from 20.3 to 9.7 % in the treatment group (nominal $p = 0.05$, uncorrected for multiple comparisons) [29].

Angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST) was another randomized, placebo-controlled, double-blind trial conducted to determine if BP reduction with candesartan after acute ischemic or hemorrhagic stroke was beneficial. This trial included 2029 patients with acute stroke, 85 % of which were ischemic stroke, randomized to receive either candesartan or placebo for 7 days. Only a minimal SBP lowering effect was observed in the treatment arm, 5 mmHg lower in the candesartan group at day 7 compared to the placebo group. The trial did not demonstrate any significant difference in death, myocardial infarction, or recurrent stroke at 6 months between the groups while there was a slightly increased risk of poor functional outcome observed in the candesartan group at 6 months [30].

Recently, He and colleagues evaluated the impact of moderate BP reduction within 48 h of acute ischemic stroke onset on death and major disability at 14 days or hospital discharge in The Chinese Antihypertensive Trial in Acute Ischemic Stroke (CATIS) trial. CATIS randomized 4061 patients to receive either

Table 8.1 Studies evaluating the effect of blood pressure control after acute ischemic stroke

Trial	Design	Study arms/cohort	Number of patients	Time from onset to presentation (h)	Results
CHHIPS [29]	Randomized, double-blinded, prospective	Labetalol vs. lisinopril vs. placebo	179	<36	No difference in death or dependency at 2 weeks
					Reduced 3 month mortality in treatment arm
SCAST [30]	Randomized, double-blinded, prospective	Candesartan vs. placebo	2004	<30	Trend toward increased risk of poor functional outcome at 6 months in treatment group
CATIS [31]	Randomized, single-blind, blinded endpoint, prospective	Antihypertensive treatment vs. discontinue all antihypertensive medications	4071	<48	No difference in death or major disability at hospital discharge or at 2 weeks or 3 months
COSSACS [32]	Open, blinded-endpoint, prospective	Continue vs. discontinue preexisting antihypertensive drug	763	<48	No difference in death or dependency at 2 weeks
ENOS [33]	Randomized, single-blinded, blinded-outcome, prospective	Glyceryl trinitrate vs. no treatment; subset of patients taking antihypertensive agents on admission randomized to continue or stop these medications	4011	<48	No difference in modified Rankin Score at 90 days in either treatment comparison
					Patients continued on antihypertensive agents had increased risk of hospital death or have been discharged to an institution, and be dead or disabled
VENTURE [34]	Randomized, blinded-end-point, open-label, prospective	Valsartan vs. no treatment	393	<24	No reduction in death or dependency and major vascular events at 90 days
					Increased risk of early neurological deterioration

antihypertensive agents with a goal to lower SBP by 10–25 % within 24 h and a BP less than 140/90 mmHg within 7 days versus stopping all antihypertensive medications on admission. The primary endpoint was mortality and major disability at 14 days or at hospital discharge. While there was a significant reduction in BP in the intervention group of approximately 9 mmHg systolic from day 1–14, there was no difference in death or major disability at 2 weeks or 3 months [31].

Debate also exists whether to continue or stop antihypertensive medications that patients were receiving prior to admission with an acute ischemic stroke. The Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) assessed the efficacy and safety of continuing or stopping preexisting antihypertensive medications in patients who had an acute stroke. Patients were randomized to continue ($n=379$; 67 % ischemic stroke) or stop ($n=384$; 58 % ischemic stroke) their preexisting antihypertensive medications within 48 h of onset. The BP in the continue medication group was significantly lower at 2 weeks by 13/8 mmHg; however there was no difference in the primary outcome of death of dependency at 2 weeks. This trial provides data that indicates that continuing prior antihypertensive medications is safe; however, the results of this study should be taken with caution since the trial was underpowered due to the early termination of the trial and furthermore, patients with dysphagia were excluded, resulting in enrollment of a majority of patients with mild strokes (median NIHSS of 4) [32].

The Efficacy of Nitric Oxide in Stroke (ENOS) trial randomized patients with acute stroke, approximately 85 % ischemic and 15 % hemorrhagic, and elevated SBP to transdermal glyceryl trinitrate or no glyceryl trinitrate within 48 h of stroke onset. Also, a subset of patients taking antihypertensive medications prior to their stroke was also randomly assigned to stop or continue taking those previously prescribed medications. The primary outcome of this study was functional outcome as assessed via the modified Rankin Scale at 90 days. While there was a significant reduction in BP at 24 h in those receiving glyceryl trinitrate as well as those assigned to continue their previously prescribed antihypertensive agents, there was no difference in functional outcome in either group. However, patients that continued their prescribed antihypertensive medications were more likely to have died in the hospital or been discharged to an institution, and be dead or disabled by day 90 compared to those that stopped taking their antihypertensive medications on admission. Furthermore, those that continued their medications had lower cognition scores at follow-up as well as an increase in the risk for the development of pneumonia [33].

Valsartan Efficacy on Modest Blood Pressure Reduction in Acute Ischemic Stroke (VENTURE) was a randomized, open-label, blinded-end-point trial that assigned 393 subjects with acute ischemic stroke and elevated BP to either valsartan or no treatment for BP. The primary outcome was death or dependency at 90 days. Additionally, early neurological deterioration within 7 days and 90-day major vascular events were assessed. While the SBP did not differ between the two groups, the diastolic BP (DBP) was significantly lower during 7 days by approximately 2 mmHg in the treatment arm. The valsartan group did not have a reduced risk of death or dependency nor a reduction in major vascular events at 90 days, however there was a significantly increased risk of early neurological decline [34].

Based on the limited treatment data and the natural history of BP after ischemic stroke, we continue antihypertensive medications after admission either by mouth or by nasogastric tube. We often initially decrease the dose of a single medication or reduce the number of medications to guard against rapid drops in BP in the event of outpatient noncompliance. After 3 or 4 days we will begin to add medications back. For the patient with newly diagnosed hypertension or with previously known but untreated hypertension, we begin a single antihypertensive medication after 3–4 days following the Joint National Committee 8 guidelines [35]. Our practice is to avoid the use of intravenous antihypertensive medications for BP control unless there is a clear indication for rapid blood reduction, such as heart failure or myocardial ischemia. After discharge close follow-up is imperative to ensure the adequate long-term treatment of hypertension for secondary stroke prevention.

Blood Pressure Management in Patients Eligible for Thrombolytic Therapy

While the management of BP elevation in patients with acute ischemic stroke has been debated, BP lowering for patients with a BP > 185/110 mmHg is recommended for patients eligible for thrombolytic therapy.

A pilot study evaluating factors associated with intracerebral hemorrhage (ICH) following the use of thrombolytic therapy found that an increased risk of ICH was associated with elevated DBP [36]. Therefore, in the National Institute of Neurological Disorders and Stroke study, a strict BP of <185/110 mmHg was required for enrollment into the study and tight BP control was maintained for 24 h with a BP goal of <180/105 mmHg [37].

While subsequent observational studies evaluating the association of elevated BP and ICH formation have been variable [38], a study examining associations between protocol violations and outcomes in community-based recombinant tissue plasminogen activator (rt-PA) use found that when the NINDS protocol is strictly followed, hemorrhage rates are similar to those in the NINDS trial [39]. Additionally, results from the Safe Implementation of Thrombolysis in Stroke (SITS) registry demonstrated that an increased SBP 2–24 h after thrombolytic therapy was associated with worse outcome (symptomatic hemorrhage, mortality, functional dependence) at 3 months. The best outcomes were observed in patients with SBP values between 141 and 150 mmHg up to 24 h post-thrombolysis [40].

It is also important to note that thrombolytic therapy may be associated with improvement in systolic BP following successful recanalization. Mattle and colleagues reported that patients who underwent intra-arterial thrombolysis and had unsuccessful vessel recanalization had higher and sustained elevations in SBP compared to those patients with successful recanalization [9].

Guidelines for BP Management in Acute Ischemic Stroke

The current American Heart Association (AHA) and American Stroke Association (ASA) Guidelines recommend a cautious approach to lowering of BP after acute ischemic stroke. For those patients that receive thrombolysis, the BP should be reduced to less than 185/110 mmHg prior to initiation of treatment and should be maintained at less than 180/105 mmHg for 24 h after treatment. The use of intravenous labetalol and nicardipine are recommended as the first line agents although there is limited data to support this recommendation. For patients not receiving thrombolysis the guidelines recommend withholding medications unless the SBP is greater than 220 mmHg or DBP is greater than 120 mmHg. This recommendation is a consensus opinion however and not based on randomized studies [26].

The European Stroke Organization recommend similar guidelines for those treated with thrombolysis. For other patients, they do not recommend routine lowering of BP unless above 220/120 mmHg on repeated measurements, or if there is evidence of severe end-organ dysfunction [41]. The 2013 European Society of Hypertension/European Society of Cardiology Guidelines for the management of arterial hypertension recommend against BP lowering therapy in the first week after acute stroke "irrespective of BP level, although clinical judgment should be used in the face of very high SBP values" [42].

Choice of Antihypertensive Agents in Acute Ischemic Stroke

When BP reduction is required there are limited data that demonstrate the optimal antihypertensive for use in the setting of acute ischemic stroke. No large prospective comparison studies have been performed to date; however there are a few small retrospective and prospective studies evaluating efficacy and tolerability. Two comparative studies evaluated the therapeutic response and tolerability of labetalol and nicardipine following acute stroke [43, 44]. Both of these trials evaluated patients according to AHA and ASA guidelines regarding BP treatment after acute ischemic or hemorrhagic stroke and assessed patients for the first 24 h. The first study was a retrospective and non-randomized study that assessed BP reduction and BP variability between labetalol and nicardipine. Patients whom received nicardipine were more likely to achieve their BP goal at 1 h than patients whom received labetalol. Furthermore, patients treated with nicardipine required fewer dosage adjustments or need for rescue therapy with additional antihypertensive medications than those who received labetalol.

A follow-up study prospectively enrolled 54 acute ischemic or hemorrhagic stroke patients with elevated BP. The patients received either labetalol or nicardipine during the first 24 h after admission. Patients treated with nicardipine achieved a higher rate of meeting the goal BP within 60 min of drug initiation, had better maintenance of BP, and a greater percentage of time spent within the goal BP range. None of the patients randomized to nicardipine required rescue medication while 72.7 % of those randomized to labetalol required an additional agent to achieve BP goals [44]. Table 8.2 summarizes the preferred antihypertensive agents for use in the treatment of acute ischemic stroke-related hypertension.

Table 8.2 Rapidly acting antihypertensive agents for the treatment of hypertension immediately after acute ischemic stroke

Agent	Mechanism of action	Intravenous dose	Time to onset (min)	Considerations
Nicardipine	Dihydropyridine calcium channel blocker	Infusion at 5–15 mg/h	5–10	Titratable
				Invasive BP monitoring not required
				First line agent
Labetalol	Mixed α- and β-receptor antagonist	10–40 mg bolus every 15 min; max of 300 mg	5–10	May cause bradycardia
				No effect on cerebral blood flow
		Infusion at 0.5–2 mg/min		Second line agent
Hydralazine	Vasodilator	5–10 mg bolus	5–10	May increase intracranial pressure
Enalaprilat	ACE inhibitor	0.625–1.25 mg bolus every 6 h	15	Adjust dose based on renal function
				Duration of action 4–6 h

Data from [26, 40, 42]

ACE angiotensin converting enzyme

Conclusions

Blood pressure elevation after acute ischemic stroke is common and the management of this BP elevation is dependent on the clinical context. For patients that are candidates for thrombolysis, reduction and maintenance of the BP within the current guidelines is indicated as it likely reduces the risk of hemorrhagic complications. For all other patients, there is no clear benefit and potentially harm for acute blood pressure reduction.

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