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Reviews

Diagnosis and management of labile blood pressure during acute cerebrovascular accidents and other hypertensive crises

Joseph Varon MD*

The University of Texas Health Science Center at Houston, USA
The University of Texas Medical Branch, St. Luke's Episcopal Hospital, Houston, Texas, USA

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Abstract It is estimated that with more than 40 million adults in the United States having uncontrolled hypertension, the risk of developing ischemic or hemorrhagic stroke in this population is significant. In addition, roughly 1 of 100 patients with essential hypertension will experience a hypertensive crisis during their lifetime, and these accelerated hypertensive emergencies and urgencies complicate more than 27% of all acute medical problems in patients presenting to emergency departments (EDs) in the United States. Arterial hypertension, a prominent feature of acute stroke syndrome, usually declines spontaneously within a few days, but its presence at hospital admission or its acute development during hospitalization is often associated with worsening stroke outcome and early mortality. Control of hypertension in patients with subarachnoid and intracerebral hemorrhage, both forms of acute stroke, is directed at maintaining adequate cerebral blood flow to minimize ischemic damage and control intracerebral pressure while reducing the risk of rebleeding and developing cerebrovasospasm. Inappropriate lowering of the blood pressure in acute stroke may increase neurologic damage. However, adequate blood flow around the central area of the acute ischemic stroke or penumbra may result in ischemic cells being salvaged. Clinicians must be mindful that accelerated hypertension is associated with other types of patients seen in the ED, such as perioperative patients and patients with traumatic head injuries.

1. Introduction

Acute blood pressure (BP) elevations occur as the cause or consequence of acute stroke and require rapid assessment and management [1-4]. The goals of the management of acute BP elevations in stroke are to minimize brain damage and protect the brain from the impact of additional vascular ischemic damage [5]. Intracerebral hemorrhage (ICH), caused by an aneurysm or vascular malformation, is often associated with a sudden increase in systemic BP. Blood pressure management is an essential element of early treatment. Complicating the management of acute changes in BP are many systemic conditions (eg, renovascular disease or endocrine abnormalities) that may cause hypertension. Other conditions (eg, surgery or head injury) affect

* Corresponding author. Tel.: +1 713 669 1670; fax: +1 713 839 1467.
E-mail address: joseph.varon@uth.tmc.edu.

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BP so routinely that, for these conditions, BP monitoring is a fundamental part of patient management [6].

With acute ischemic stroke (AIS), an abrupt elevation of BP occurs as the vascular system of the brain compensates for increased resistance in intracranial vessels. Reflex mechanisms respond to blood vessel obstruction by increasing systemic BP. With ischemic stroke, the elevation of BP is typically self-limiting. Early elevation in arterial BP may stabilize in hours or days and return to a normal level within 2 days of stroke onset [7,8]. Even if BP elevations persist for longer, the poststroke hypertension is likely to remit spontaneously [9]. Treatment of acute elevations in BP associated with hemorrhagic stroke presumes that the risk of recurrent stroke or repeated hemorrhage is reduced by BP control [10-12].

It is generally agreed that for patients with subarachnoid hemorrhage (SAH), BP should be reduced from elevated levels until the aneurysm or other vascular malformation has been effectively treated [13]. Unfortunately, because of cerebrovasospasm, a complication of stroke, reflex constriction of cerebral arteries may occur [14]. Whereas vasospasm impedes cerebral blood flow (CBF), treatment may necessitate artificially elevating BP or expanding the intravascular volume to minimize ischemic damage [14,15].

Underlying the controversy about whether to treat elevated BP caused by stroke is the theory that elevation of BP is likely to be neuroprotective. With adequate blood flow around the central area of the stroke or penumbra, cells may be salvaged [5]. Upward or downward deviation of normal BP readings that persist for more than 2 days after a stroke may cause early mortality. It is unknown if elevated BP increases mortality or if it is a marker for more severe ischemic brain damage [10,16,17].

1.1. Methods

A National Library of Medicine literature search was conducted through the publication years 2000 to 2007 for articles concerned with the management of hypertension in acute stroke and other hypertensive crises. Original research using animal and human models investigating antihypertensive agents useful in acute stroke was considered. Pivotal articles published before the year 2000 were added as primary references. The bibliography has been annotated to identify the review articles and therapeutic guidelines in this area. For the original research articles provided in the reference list, the levels of evidence and strength of recommendation have been identified based on those adopted by the Stroke Council of the American Heart Association [17-20].

2. Epidemiology

2.1. Stroke data

There are more than 700,000 new or recurrent strokes each year in the United States, resulting in more than 160,000 deaths [1,21,22]. The mortality rate within 1 month of stroke onset was found in 1 review of worldwide population-based studies to vary between 17% (Japan) and 33% (Italy) [21]. In the United States, there are more than 4.8 million stroke survivors, and after stroke onset, 20% of these needed institutional care for more than 3 months, with 15% to 30% of survivors remaining permanently disabled [1,22].

Race, sex, and age, as well as numerous risk factors including chronic hypertension, diabetes mellitus, and cigarette smoking, contribute to the risk of ischemic stroke. African Americans are at higher risk than Hispanic Americans; however, both groups are at higher risk than Americans of central and northern European descent [1,22].

2.2. Hypertension data

High BP contributes substantially to the risk of developing ischemic or hemorrhagic stroke [1,4]. Because more than 60 million Americans have chronic hypertension (essential or idiopathic), the risk of stroke is significant [4,23,24].

Health statistics show that over 25% of noninstitutionalized Americans (≥20 years of age) were diagnosed with hypertension between the years 1999 and 2002 [25]. It is estimated that more than 40 million adults in the United States have uncontrolled hypertension [26]. In addition, roughly 1 of 100 patients with essential hypertension will experience a hypertensive crisis during their lifetime [27,28]. It has also been estimated that by the year 2025, one third of the global population will be having hypertension [29].

3. Classification of hypertension and stroke

Stroke is a vascular injury to the brain or spinal cord formally known as a cerebrovascular accident. Stroke is characterized by irreversible damage to nerve cells in the central nervous system (CNS) [30,31]. Interruption of critical blood flow to part of the brain causes ischemia (Table 1) [30-32]. Bleeding into or around the brain is referred to as ICH or SAH and is the most common presentation of a ruptured intracranial aneurysm [33,34]. Hemorrhagic strokes may produce ischemic injury by direct

Table 1 Distribution of ischemic stroke subtypes

Type	Subtype	Percent (N = 1805)
Infarctions	Unknown	32
	Lacunar	19
	Embolic	14
	Atherosclerotic	6
Hemorrhages	Intracerebral	13
	Subarachnoid	13
Other		3

Adapted with permission from Foulkes et al [32].

Table 2 Classification of hypertension in adults aged ≥18 years [4]

BP classification	SBP (mm Hg)	DBP (mm Hg)
Normal	<120	<80
Prehypertension	120-139	80-89
Stage 1 HTN	140-159	90-99
Stage 2 HTN	160-179	100-109

HTN indicates hypertension.

pressure of a blood clot on vessels feeding the neural tissues; by interrupting the supply of blood to tissues upstream from the bleeding site; or by inducing vasospasm in blood vessels exposed to the irritative effects of subarachnoid blood [30].

Cerebral ischemia results from inadequate blood flow, which prevents delivery of metabolic substrates and oxygen essential for survival of CNS tissue [30]. In addition, cerebral metabolic demands vary from region to region and from time to time; therefore, vulnerability and extent of damage to a specific part of the brain or even the spinal cord (eg, in the watershed area of the thoracic cord) vary. Once a central core of damage has occurred, toxic materials released by necrotic cells (ie, calcium ions and reactive free oxygen radicals) permeate the surrounding tissues, increasing cell vulnerability, although ischemia in outlying regions (penumbra) may not be as severe as in the original area of infarction [30,35].

Ischemic strokes may occur from atherosclerotic plaque occlusion of a major blood vessel or with clot or thrombus formation set free in the bloodstream (embolic stroke). Endothelial changes that develop in arterioles from chronic hypertension may lead to complete obstruction of blood flow, resulting in relatively small or lacunar injuries in the neural tissues [36]. These distinctions may be self-evident, but they are helpful in determining a BP management strategy.

Chronic hypertension is characterized by the severity of the elevation in systolic BP (SBP) and diastolic BP (DBP) (Table 2) [4,37]. Blood pressures of less than 120 mm Hg (systolic) and less than 80 mm Hg (diastolic) are normal, unless the individual is symptomatic (eg, syncope or easy fatigability) [4]. Systolic levels of 120 to 139 mm Hg and diastolic levels of 80 to 89 mm Hg are considered prehypertensive [4]. Stage 1 hypertension is characterized by systolic elevation between 140 and 159 mm Hg or diastolic elevation between 90 and 99 mm Hg [4]. Stage 2 hypertension is elevated with SBP 160 mm Hg or higher or DBP 100 mm Hg or higher [4]. Hypertensive crises and emergencies are defined by acute elevation of BP and clinical end-organ dysfunction (involving CNS, heart, or kidneys) [4,28]. Hypertensive urgencies show markedly elevated BP but may be without severe symptoms or progressive end-organ damage. [38] The differentiation between hypertensive emergencies and urgencies can be ambiguous [38].

4. Etiology of hypertensive crises

Hypertensive emergencies and urgencies complicate more than 27% of all acute medical problems presenting to emergency departments (EDs) [39]. The common denominator of hypertensive crises is peripheral vasoconstriction that may be associated with vasculitis, withdrawal of vasodilating antihypertensive medications, hormonal disturbances occurring with pregnancy or head trauma, or adverse reactions to medication (Table 3) [27,40].

The most common cause of hypertensive crisis is noncompliance with prescribed antihypertensive medications [27,41]. In other cases, patients are compliant, but outpatient treatment of elevated SBP is inadequate. Poor therapeutic response to effective BP medications targeting chronic elevations of SBP and medication noncompliance are independent risk factors for hypertensive crises [41,42].

Hypertensive crises are also seen in renal disease (ie, renovascular hypertension) [27], and some medications may induce hypertension (eg, amphetamines, tricyclic antidepressants [nortriptyline, amitriptyline], corticosteroids, and sympathomimetics [cocaine, pseudoephedrine]) [27,43-45]. Hypertension may also occur with head injuries. In this setting, an expanding intracranial mass may produce a paradoxical slowing of the pulse in association with a progressive elevation of SBP (Cushing effect) [46]. Posttraumatic hypertension also occurs independently of intracranial bleeding or hematoma formation. In addition, vasculitides (ie, lupus erythematosus) may produce hypertensive crises as an element of disease [27].

An international stroke study showed that with persistent elevations of BP after a stroke, there is an increased risk of recurrent stroke within 14 days of an initial ictus, as well as an increased risk of severe neurologic impairment or an increase in mortality [47].

4.1. Other forms of hypertension seen in the ED

4.1.1. Postoperative hypertension

Between 3% and 75% of patients undergoing surgical procedures will exhibit significant elevations of BP (eg, DBP ≥100 mm Hg and SBP ≥190 mm Hg on 2 consecutive

Table 3 Causes of hypertensive crises

- Abrupt increase in BP in patients with chronic hypertension
- Renovascular hypertension/renal disease
- Withdrawal from antihypertensive drugs
- Drug-induced hypertension (eg, amphetamines, diet pills, tricyclic antidepressants, street drugs [eg, cocaine]), drug withdrawal, pheochromocytoma
- Preeclampsia/eclampsia
- Head injury of any kind
- Vasculitis
- Scleroderma and other collagen-vascular diseases

Adapted with permission from Calhoun and Oparil [27].

postoperative readings 2-3 hours apart) [28,48,49]. Postoperative hypertension is often adequately managed with intravenous antihypertensives [48,50,51], and many different agents have been used for this purpose, including calcium channel blockers (eg, nicardipine) [50], nitrates, and sodium nitroprusside [48,50], However, considering the potential for severe toxicity, nitroprusside should be used only when other intravenous antihypertensive agents are not available [28]. The specific agent is chosen based upon the type of surgery performed and the patient's medical and medication histories.

4.1.2. Gestational hypertension

Pregnancy is associated with hypertensive disorders ranging from mild to life-threatening, and pharmacological treatment is complicated by concern for fetal and maternal safety [28,52,53]. The maternal mortality rate (≥20 weeks' gestation) from complications of preeclampsia and eclampsia have been shown in one 14-year study (N = 790) to be 19.6% [54]. Before delivery, DBP should be maintained at greater than 90 mm Hg to allow for adequate uteroplacental perfusion [28]. In patients with preeclampsia, intravenous drug therapy is reserved for those with a persistently elevated SBP of greater than 180 mm Hg or DBP of greater than 110 mm Hg [28].

4.2. Hypertensive encephalopathy

Because focal neurologic signs may occur with hypertensive encephalopathy, the distinction between AIS and the latter syndrome may be difficult. Hypertensive encephalopathy is relatively rare, subacutely progressive, and associated with generalized signs and symptoms of brain dysfunction (eg, headache, lethargy, or seizures) [10]. Hypertensive encephalopathy will routinely be associated with papilledema and uremia, whereas AIS is likely to be associated with changes in fundi [55,56].

5. Signs and symptoms of hypertensive emergencies

Diverse clinical signs and symptoms prompt patients with hypertensive crises to seek or be brought in for medical attention [4]. The cardiovascular characteristics of hypertensive crises include angina or acute myocardial infarction. In addition, cardiac decompensation may lead to shortness of breath, postural hypotension, or pulmonary edema [28]. The complaint of severe, catastrophic midline pain of the chest, back, or abdominal region is likely associated with aortic dissection [57]. Headache, altered consciousness, advanced retinopathy, and papilledema are often seen in patients with hypertensive encephalopathy; however, the patient may display only cognitive or other nonfocal neurological signs [28]. If serum creatinine is acutely elevated and urinary output is diminished, the patient may be developing acute renal failure.

Traditionally, accelerated hypertension has been defined as increased BP accompanied by acute encephalopathy or nephropathy [6,28,58]. The clinical characteristics associated with malignant hypertension include DBP greater than 140 mm Hg accompanied by various combinations of funduscopic findings (eg, hemorrhages, exudates, papilledema); neurologic findings (eg, headache, confusion, somnolence, stupor, focal deficits, seizures, coma); renal findings (eg, oliguria, azotemia); and gastrointestinal findings (eg, nausea, vomiting) [38].

6. Pathogenesis and pathophysiology

Humoral vascular constrictors are most likely the basis for the abrupt and self-propagating increase in systemic vascular resistance that leads to hypertensive crises [28,59,60]. Severe elevations of BP may result in endothelial injury and fibrinoid necrosis of the arterioles [28,59,60]. In most cases, vascular injury leads to platelet and fibrin endothelial deposition, breakdown of normal autoregulation, and, with ischemia, the release of toxic vasoactive substances [28,59,60]. Many individuals presenting to the hospital with chronic hypertension and an elevated BP are thought to exhibit a rightward shift of the pressure/flow autoregulation curve with no acute end-organ damage

Table 4 Renin levels in hypertensive emergencies

High Renin States
Malignant hypertension
Medium to high renin states
Unilateral renovascular hypertension
Renal vasculitis
Renal trauma
Renin secreting tumors
Pheochromocytoma
Cocaine abuse
Clonidine or methyl DOPA withdrawal
Probable medium to high renin states
Hypertensive encephalopathy
Hypertension with cerebral hemorrhage
Hypertension with (impending) stroke
Hypertension with pulmonary edema
Hypertension with acute myocardial infarction or unstable angina
Dissecting aortic aneurysm
Perioperative hypertension
Low renin states: sodium-volume overload
Acute tubular necrosis
Acute glomerulonephritis
Urinary tract obstruction
Primary aldosteronism
Low renin essential hypertension
Preeclampsia/eclampsia

DOPA indicates 3,4-dihydroxyphenylalanine.
Reproduced from Blumenfeld and Laragh [64].

[28,61,62]. After a study of hypercapnic dogs, a study in baboons confirmed that autoregulation remained intact until BP reached approximately 40% above baseline values [63]. The renin-angiotensin-aldosterone system plays a key role in the regulation of BP homeostasis [39,64]. Clinical syndromes associated with hypertensive crises are sometimes classified according to the serum renin level (Table 4) [64]. Excessive renin production by the kidney stimulates production of angiotensin II, a vasoconstrictor, which raises peripheral vascular resistance, thus increasing systemic BP [64]. Hypertensive crises appear to develop when the renin-angiotensin-aldosterone system spins out of control and progressively drives systemic BP higher [39,64].

The mechanism of hypertensive crises is thought by some to be associated with oxidative stress, endothelial dysfunction, and platelet aggregation. Reactive oxygen species can lead to vasoconstriction, presumably by decreasing intravascular nitric oxide production, which disturbs endothelial function. With decreased nitric oxide production, small-vessel dilatation may be impeded [65-67].

6.1. Hypertension in AIS

As previously mentioned, the acute elevation of BP seen with AIS may be a reflex adjustment to disturbed or impaired blood flow in the brain (Fig. 1) [6,10,68,69]. It is of constant concern that the mechanisms producing ischemic damage may result in expansion of the central core of ischemia if arterial BP is reduced precipitously [10,70]. Fine adjustments are constantly being made by an intrinsic system that regulates regional brain perfusion. This autoregulatory system is disrupted to varying extents after an AIS [10], and the most severe disturbances are likely in and about the ischemic core. One consequence of this focal disruption of autoregulation is that tissues needing additional blood flow may end up with reduced perfusion.

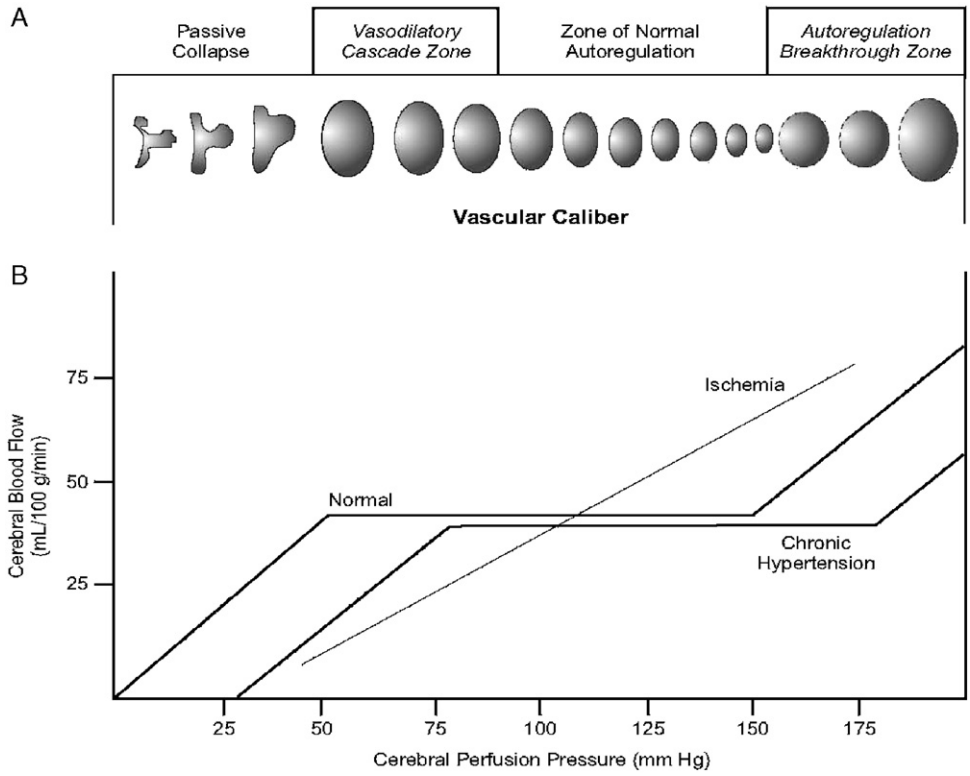

Fig. 1 A, Changes in vascular caliber that can be associated with cerebral autoregulation failure. Altered intracranial autoregulation due to an intracranial lesion and/or edema results from vasodilation in an effort to increase CBF. However, beyond the lower limit of autoregulation, vessels passively collapse, and ischemia results. Beyond the upper limit of autoregulation or the "breakthrough zone," increased intravascular volume and pressure results in vasogenic edema. Adapted with permission from Rose and Mayer [69]. B, Cerebral autoregulation in a healthy subject, a patient with chronic hypertension, and a patient with acute cerebral ischemia. Cerebrovascular autoregulation is a mechanism that maintains constant CBF (50 mL/100 g per minute) in spite of large changes in cerebral perfusion pressure (50-150 mm Hg). Cerebral perfusion pressure is a calculation of mean arterial pressure minus ICP or central venous pressure, whichever is greater. In healthy individuals, ICP and central venous pressure are minimal (ie, 5 mm Hg), and cerebral perfusion pressure is approximately equivalent to mean arterial pressure. Beyond the upper and lower limits of autoregulation, CBF passively and linearly follows changes in cerebral perfusion pressure. In patients with chronic hypertension, the autoregulation plateau and the upper and lower curves are shifted to the right. In patients with acute neurologic disorders (eg, traumatic brain injury, ICH, and SAH with vasospasm), CBF becomes pressure passive in areas of cerebral ischemic injury. Adapted with permission from Powers [10].

One recent study of 40 subjects with minor middle cerebral artery stroke assessed dynamic cerebral autoregulation with arterial BP and Doppler-measured CBF [71]. The findings, which "did not indicate a relevant impairment of dynamic autoregulation early after minor ischemic stroke," draw attention to the relationship between AIS and the disruption of autoregulation as seen in the subacute setting [71].

7. Diagnostic and laboratory evaluations in hypertensive crises

The key to the successful management of the patient with severely elevated BP are rapid identification of treatable causes and early introduction of intravenous antihypertensive agents where appropriate. It is important to differentiate hypertensive crises from hypertensive urgencies [6,28,72-74]. The targeted medical history must focus on possible causes of acute elevation of the BP. A thorough physical examination must be supplemented by appropriate laboratory evaluations, which include a complete blood count, electrolyte studies, blood urea nitrogen, and measurement of creatinine levels [6,28]. Women of childbearing age should have a pregnancy test. A urinalysis is essential, and a peripheral blood smear is also necessary to rule out microangiopathic hemolytic anemia as the basis for a hypertensive crisis [6,28].

The clinician should also inquire about prior hypertensive crises and antihypertensive medication use [6,28,75], and the fundi should be examined in all cases to detect papilledema as soon as possible. The patient should be asked specifically about the use of monoamine oxidase inhibitors, as well as the use of any recreational drugs such as cocaine or amphetamines [6,28]. Blood pressure should be checked in each limb; obese patients require use of the appropriately sized BP cuffs. Every patient should have a chest x-ray and electrocardiogram (especially in patients with shortness of breath, chest pain, or neurological signs) [57]. For patients with neurologic signs, computed tomography (CT) or magnetic resonance imaging (MRI) scan of the head is also necessary. Much of this evaluation may be performed at the same time that antihypertensive therapy is started [6,28,73].

7.1. Imaging modalities

Computed tomography scans and MRI studies have become routine and essential in the assessment of AIS. Because of its general availability, CT is the mainstay for diagnosis of most emergent neurological situations, and its main purpose is excluding hemorrhagic etiology [76,77]. Within 6 hours of the initial ictus, noncontrast, enhanced CT provides important clues to the ischemic nature of the deficit, which may include slight hypodensity, minimal mass effect, and loss of distinction between gray and white matter densities [76,77].

Magnetic resonance imaging provides high-resolution contrast, anatomic definition, multiplanar capabilities, and is especially suited to the evaluation of cerebral ischemia due to tissue swelling, which causes enlargement or distortion of brain structures [76,78,79]. Generally, routine spin-echo (SE) MRI is more sensitive than CT for imaging pathophysiologic changes occurring during a cerebral artery ischemic event. Although subtle signal intensity changes are seen within 6 hours post-ictus on T1-weighted SE images, conspicuous changes may not be seen for 1 to 3 days [76]. Signal changes on T2-weighted images are readily seen within 8 to 24 hours post-ictus; however, fluid-attenuated inversion recovery pulse sequences have even more sensitivity for detecting early cortical ischemic changes compared with routine SE imaging [76].

Diffusion-weighted imaging (DWI) is the most sensitive imaging technique for detecting acute ischemic changes [76,80-82]. This imaging technique identifies water diffusion as a 3-dimensional process. The apparent diffusion coefficient is calculated by using multiple gradient duration and amplitude values for data acquisition, resulting in an apparent diffusion coefficient map. After AIS, metabolic and cellular membrane breakdown causes the trapping of intracellular water in infarcted tissues. These areas of cytotoxic edema are visualized on DWI as areas of increased signal intensity [76,83].

Another MRI technique, perfusion-weighted imaging, uses contrast media (gadolinium) to determine mean transit times, time-to-peak arrival of contrast, and regional blood flow maps to identify cerebral microcirculation [76,84]. During dynamic signal acquisition, normal vascular perfusion reveals a transient signal drop as gadolinium passes through. Ischemic areas show delayed signal changes because contrast is not perfused in the normal acquisition phase. As a result, areas of contrast hypoperfusion are shown as bright signal intensity on the time-to-peak perfusion map [76].

Combining data from DWI and perfusion-weighted imaging scans provides an estimate of the cerebral ischemic penumbra. Areas of decreased or reduced contrast perfusion indicate ischemic tissue—information that may be helpful when considering therapeutic choices [76,85,86].

7.2. Differential diagnosis

Many thrombotic strokes are preceded by transient ischemic attacks, which are indicative of vascular disease. Transient ischemic attacks are occasionally confused with seizure activity, syncope, panic attacks, neurologic migraine, or attacks of labyrinthine vertigo. Evidence of bleeding on head CT scan and presence of blood in the cerebrospinal fluid characterize a hemorrhagic lesion [36]. Traumatic head injuries are likely candidates for accelerated-malignant hypertension and are an entity that should be ruled out. During patient examination, the "Cushing response" (decreased pulse and increased BP) should be

searched for. The patient's medical history of chronic hypertension and/or use of antihypertensive medications compel a clinician to carefully monitor BP.

8. Emergent management of hypertension

In the ED, intravenous nicardipine or labetalol may be first-line measures. Nicardipine is known for stability in regulating BP within a narrow range [87]. Labetalol easily controls BP reduction with use of mini boluses; however, it is contraindicated in cocaine use, asthma, and congestive heart failure (CHF) [88]. Nitroprusside has been used in the past, but it has the disadvantage of increasing intracranial pressure (ICP) [51,69,89]. Other agents used successfully in hypertensive crises in the past include clonidine (oral formulation); diazoxide (rapid-acting as intravenous formulation); enalaprilat (angiotensin-converting enzyme inhibitor, intravenous formulation); esmolol (β-adrenergic blocking agent); fenoldopam (dopamine-1 agonist); trimethaphan camsylate (nondepolarizing ganglionic blocking agent with many side effects); and phentolamine (α-adrenergic blocking agent that is helpful in catecholamine-induced hypertensive crises [eg, pheochromocytoma]) [28].

8.1. The patient in hypertensive crisis

The immediate goal of intravenous antihypertensive therapy is to reduce the DBP by 10% to 15% or to roughly 110 mm Hg. Which agent is used to accomplish this will largely be determined by clinical status of the hypertensive crisis (Table 5) [15,28]. If the patient is believed to have an aortic dissection, the reduction in DBP is accomplished over the course of 5 to 10 minutes [28]. In patients with a hypertensive emergency but no evidence of aortic dissection, the rate of reduction of the elevated BP can be more protracted. Dropping the DBP to roughly 110 mm Hg over the course of 30 to 60 minutes is desirable; however, precautions must be taken not to drop the BP any further in this short period because cerebral ischemic injury may occur. If the patient has a hypertensive urgency rather than a hypertensive emergency, BP is lowered over a more protracted period, which is often accomplished with oral medications (eg, clonidine) over 24 to 48 hours [6,28,69].

If a rapid adjustment in BP is warranted, intravenous medications such as labetalol, nicardipine, or sodium nitroprusside are used. Labetalol is a combined blocker of α- and β-adrenergic receptors with a hypotensive effect that begins within 2 to 5 minutes after intravenous dosing and reaches a peak in 5 to 15 minutes. The hypotensive effect persists with labetalol for about 2 to 4 hours. Maintenance of cardiac output and reduction of peripheral vascular resistance (without reducing peripheral, cerebral, renal, or coronary blood flow) are seen with labetalol [4,28,89].

Intravenous nicardipine has been shown to be as clinically effective as sodium nitroprusside in lowering BP in hypertensive crises, generally requires fewer dose adjustments, and produces fewer side effects [90]. Sodium nitroprusside is the most widely used parenteral agent for treating hypertensive crisis; however, cyanide toxicity, in some cases leading to end-organ damage, and increased ICP are associated side effects [89]. In addition, sodium nitroprusside infusion may result in increased renal blood flow, which is likely to cause rebound hypertension. Nicardipine, however, has a predictable onset of effect in 5 to 10 minutes with intravenous administration and fewer dosage adjustments [6,89].

Of the pharmacological agents currently under investigation in phase III trials, clevidipine shows the most promising results. Clevidipine is an ultrashort-acting dihydropiridine calcium channel blocker whose use is not yet approved in the United States [91].

When administering any antihypertensive intravenous agent, the recommended dosage must be strictly adhered to, and the patient must be closely monitored for adverse reactions (eg, abrupt changes in the heart rate or BP level or evidence of rash, fever, or seizure activity) (Table 6) [28]. Adverse reactions must be considered in the decision to continue or advance medication dosing [28,89].

Table 5 Recommended antihypertensive agents for hypertensive crises

Condition	Preferred treatments
Acute pulmonary edema	Fenoldopam or a combination of nitroglycerin (up to 60 μg/min) and a loop diuretic Nicardipine is a reasonable alternative
Acute myocardial ischemia	Labetalol or esmolol in combination with nitroglycerin (up to 60 μg/min)
Hypertensive encephalopathy	Labetalol, nicardipine, or fenoldopam
Acute aortic dissection	Labetalol or combination of nicardipine or fenoldopam and esmolol or combination of nitroprusside with either esmolol or intravenous metoprolol
Eclampsia	Labetalol or nicardipine; hydralazine may be used in a non-ICU setting
Acute renal failure/ microangiopathic anemia	Fenoldopam or nicardipine
Sympathetic crisis/cocaine overdose	Verapamil, diltiazem, or nicardipine in combination with a benzodiazepine

ICU indicates intensive care unit.
Reproduced with permission from Varon and Marik [6].

8.2. The patient with AIS

After AIS, cerebral autoregulation is impaired, and perfusion of the ischemic penumbra becomes directly

Table 6 Dosages of intravenous antihypertensive medications for hypertensive emergencies

Drugs	Dosage
Enalapril	1.25 mg, IV, over 5 min every 6 h, titrated by increments of 1.25 mg at 12- to 24-h intervals to a maximum of 5 mg every 6 h
Esmolol	Loading dose of 0.5 1 mg/kg over 1 min, followed by infusion at 50 $\mu g\ kg^{-1}\ min^{-1}$ and increasing to a maximum of 300 $\mu g\ kg^{-1}\ min^{-1}$, as necessary
Fenoldopam	Initial dose of 0.1 $\mu g\ kg^{-1}\ min^{-1}$ titrated by increments of 0.05-0.1 $\mu g\ kg^{-1}\ min^{-1}$ to a maximum of 1.6 $\mu g\ kg^{-1}\ min^{-1}$
Labetalol	20 mg, IV, bolus followed by boluses of 20-80 mg at 10-minute intervals or infusion starting at 1-2 mg/min uptitrated until hypotensive effect is achieved
Nicardipine	5 mg/h, IV, infusion, titrated if necessary by increasing by 2.5 mg/h every 5 min to a maximum rate of 30 mg/h
Nitroprusside	0.5 $\mu g\ kg^{-1}\ min^{-1}$, IV, titrated if necessary not to exceed 2 $\mu g\ kg^{-1}\ min^{-1}$
Phentolamine	1 to 5 mg boluses to a maximum dose of 15 mg

Reproduced with permission from Varon and Marik [28].

pressure dependent [6,28,92,93]. The sympathetic nervous system may be involved as part of a global metabolic response (known as sympathetic crisis) to cerebral infarction, cerebral hemorrhage, or associated intracranial edema [6,28]. Defective autoregulation may persist for days to weeks, during which there is overproduction of vasoconstrictive and vasodilatory substances [92-94]. With hypertensive encephalopathy, labetalol, nicardipine, or fenoldopam are the antihypertensive agents of choice [6]. If the clinical status is suggestive of a sympathetic crisis, verapamil may be just as effective in safely lowering BP as nicardipine or fenoldopam [6].

The Stroke Council for the American Stroke Association recommends considering antihypertensive treatment in individuals with ischemic strokes and DBPs of greater than 120 mm Hg or SBPs of greater than 220 mm Hg (Tables 7 and 8) [15,17,95]. There is general agreement that DBP should be reduced by 15% to 20% over the first 24 hours after a stroke if the DBP is 120 mm Hg or higher [6,15,28], and this can usually be achieved with labetalol or nicardipine [15]. If the DBP is greater than 140 mm Hg, a sodium nitroprusside infusion may be necessary [15]. If the patient is eligible for thrombolytic therapy, the BP must be maintained at desired levels (SBP ≤185 and DBP ≤110) [17].

Pharmaceutical agents that dramatically improve the outcome in stroke victims with hypertension are lacking, but there is preliminary evidence that candesartan cilexetil reduces cardiovascular morbidity and mortality in the stroke patient when given over the course of 7 days post-

Table 7 Approach to elevated BP in AIS

Clinical situation	Recommendation
SBP <220 mm Hg; DBP <120 mm Hg	Observe BP unless there is other end-organ involvement, such as aortic dissection, renal failure, or acute myocardial infarction
SBP >220 mm Hg or DBP 121-140 mm Hg	Labetalol 10-20 mg, IV, over 1-2 min, repeated or doubled every 10 min to a maximum dose of 300 mg or nicardipine 5 mg/h, IV, infusion as initial dose, titrated by increasing by 2.5 mg/h every 5 min to maximum infusion rate of 15 mg/h to achieve a 10%-15% reduction
DBP >140 mm Hg	Sodium nitroprusside 0.5 $\mu g\ kg^{-1}\ min^{-1}$, IV, with continuous BP monitoring to achieve a 10%-15% reduction

Adapted with permission from Adams et al [17].

ictus [96]. In the absence of unambiguous evidence supporting alternative medications, the consensus guidelines recommend the use of intravenous nicardipine for hypertensive episodes (DBP, 121-140 mm Hg) associated with AIS [18], as well as labetalol or nitroprusside in cases where the DBP is greater than 140 mm Hg [15]. However, patient management is substantially more complex if, after AIS, the patient received a thrombolytic agent such as recombinant tissue-type plasminogen activator (rtPA) [15].

8.3. Candidates for thrombolytic agents

To be a candidate for thrombolytic agents (ie, rtPA), the patient with an ischemic stroke must have a BP that is

Table 8 Levels of evidence

Level of evidence	
Level I	Data from randomized trials with low false-positive and low false-negative errors
Level II	Data from randomized trials with high false-positive or high false-negative errors
Level III	Data from nonrandomized concurrent cohort studies
Level IV	Data from nonrandomized cohort studies using historical controls
Level V	Data from anecdotal case series
Strength of recommendation	
Grade A	Supported by level I evidence
Grade B	Supported by level II evidence
Grade C	Supported by level III, IV, or V evidence

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185/110 mm Hg or less or respond to antihypertensive agents sufficiently to lower the BP to 185/110 mm Hg or less. Blood pressure adjustment to below 185/110 mm Hg may be achieved with labetalol 10 to 20 mg, IV, over 1 to 2 minutes or nitropaste (1-2 in). If 2 administrations of labetalol do not lower the BP to the target range, rtPA will usually not be administered [17].

After the thrombolytic agent has been administered, BP should be checked every 15 minutes for 2 hours, every 30 minutes for the subsequent 6 hours, and every hour for the after 16 hours [17,95]. If the DBP rises above 140 mm Hg, sodium nitroprusside at 0.5 μg kg^{-1} min^{-1}, IV, bolus followed by a titrated infusion may suffice to hold the BP in the desired range. With an SBP of greater than 230 mm Hg or a DBP of 121 to 140 mm Hg, nicardipine 5 mg/h, IV, initially, increasing to a maximum of 15 mg/h, if needed to drop the BP, is an option. The dose is increased every 5 minutes by an amount sufficient to increase the hourly dose by 2.5 mg if no response to the nicardipine is evident [17,95]. If this regimen fails, labetalol 10 mg, IV, may be infused over 1 to 2 minutes. The labetalol dose may be repeated or doubled every 10 minutes to a maximum cumulative dose of 300 mg. Alternatively, labetalol drip at 2 to 8 mg/min may be appropriate with systolic levels of 180 to 230 mm Hg or diastolic levels of 105 to 120 mm Hg after rtPA administration. If BP remains elevated despite nicardipine and labetalol administration, a nitroprusside drip may be warranted [17].

9. Conclusions

The debated issues of BP management remain an integral part of stroke prevention and poststroke care. It is well known that inappropriately lowering BP in the setting of an AIS may increase the neurologic damage associated with that stroke. More aggressive BP management is usually necessary with hemorrhagic strokes, especially if the source is an aneurysmal bleed. There is a consensus, however, that severe hypertension associated with ischemic stroke does warrant treatment [17,18]. The drugs of choice for acute hypertension associated with stroke are nicardipine and labetalol [95].

Management of a hypertensive crisis in the context of stroke or otherwise must be rapid, and observation in an intensive care setting is generally necessary. After an acute stroke, untreated hypertension appears to increase the risk of recurrent stroke and increases the probability of ICH or extension of ICH already associated with stroke within the first 24 hours post-ictus. The intravenous agents most likely to prove useful in the management of hypertensive emergencies associated with CNS disease include sodium nitroprusside (with a potential for increasing ICP or causing cerebral steal), labetalol, and nicardipine.

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*Highly recommended.
†Therapeutic guidelines.
‡Review article.
I-V = Levels of Evidence (see Table 8) [17].
A-C = Strength of Recommendation (see Table 8) [17].

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