review

The Diagnosis and Management of Hypertensive Crises*

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Severe hypertension is a common clinical problem in the United States, encountered in various clinical settings. Although various terms have been applied to severe hypertension, such as hypertensive crises, emergencies, or urgencies, they are all characterized by acute elevations in BP that may be associated with end-organ damage (hypertensive crisis). The immediate reduction of BP is only required in patients with acute end-organ damage. Hypertension associated with cerebral infarction or intracerebral hemorrhage only rarely requires treatment. While nitroprusside is commonly used to treat severe hypertension, it is an extremely toxic drug that should only be used in rare circumstances. Furthermore, the short-acting calcium channel blocker nifedipine is associated with significant morbidity and should be avoided. Today, a wide range of pharmacologic alternatives are available to the practitioner to control severe hypertension. This article reviews some of the current concepts and common misconceptions in the management of patients with acutely elevated BP. ***(CHEST 2000; 118:214–227)***

Key words: aortic dissection; β-blockers; calcium channel blockers; fenoldopam; hypertension; hypertensive crises; hypertensive encephalopathy; labetalol; nicardipine; nitroprusside; pregnancy

Abbreviations: ACE = angiotensin-converting enzyme; CBF = cerebral blood flow; DA = dopamine

Hypertension is a common clinical problem in the United States, and physicians of all types are likely to encounter patients with hypertensive urgencies and emergencies. Although various terms have been applied to these conditions, they are all characterized by acute elevations in BP.[1–8] Prompt but carefully considered therapy is necessary to limit morbidity and mortality.[9,10] Unfortunately, accelerated hypertension is among the most misunderstood and mismanaged of "acute" medical problems seen in clinical practice. Many physicians have an urgent need to rapidly lower an elevated BP without considering the pathophysiologic principles involved.

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Definitions

The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has classified hypertension according to the degree of BP elevation.[1] Stage 1 patients have a systolic BP of 140 to 159 mm Hg or a diastolic BP of 90 to 99 mm Hg. Stage 2 individuals have a systolic BP of 160 to 179 mm Hg or a diastolic BP of 100 to 109 mm Hg, whereas stage 3 includes a systolic BP pressure ≥ 180 mm Hg or a diastolic BP ≥ 110 mm Hg. Stage 3 hypertension has also been called severe hypertension or accelerated hypertension. The features and classification and of pregnancy-induced hypertension are included in Table 1.[11]

A number of different terms have been applied to severe acute elevations of BP. However, most authors have defined hypertensive crises or emergencies as a sudden increase in systolic and diastolic BP associated with end-organ damage of the CNS, the heart, or the kidneys; the term *hypertensive urgencies* has been used for patients with severely elevated BP without acute end-organ damage.[2–5,8,12,13] Table 2 lists those clinical conditions that meet the diag-

Table 1—*Classification of Preeclampsia

Variables	Mild	Severe†
BP	130/80 to 140/95 mm Hg	> 160/110 mm Hg
Absolute	Systolic ≥ 140 mm Hg Diastolic ≥ 90 mm Hg	
Relative	Systolic increased > 30 mm Hg Diastolic increased > 15 mm Hg	
Weight	< 5 lb/wk	> 5 lb/wk
Laboratory		
Proteinuria	300 mg/24 h	≥ 5 g/d; 3 + /4 + semiquantitative
Platelets	Normal	May be < $150{,}000 \times 10^9$/L
Liver function	Normal	Elevated AST/ALT
Clotting studies	Normal	May be prolonged
Bilirubin	Normal	May be elevated

*AST/ALT = aspartate transaminase/alanine transaminase.
†HELLP syndrome characterized by hemolysis, elevated liver enzymes, and low platelet count reflects those patients with the greatest risk for mortality and morbidity.

nostic criteria of hypertensive crises. It is important to note that the clinical differentiation between hypertensive emergencies and hypertensive urgencies depends on the presence of target organ damage, rather than the level of BP.

Another frequently encountered term, *malignant hypertension*, is defined as a syndrome characterized by elevated BP accompanied by encephalopathy or nephropathy.[1,14] Postoperative hypertension has arbitrarily been defined as systolic BP > 190 mm Hg and/or diastolic BP ≥ 100 mm Hg on two consecutive readings following surgery.[15,16] The transient nature of postoperative hypertension and the unique clinical factors present in the postoperative period require that this clinical syndrome be given individual consideration. A systolic pressure > 169 mm Hg or a diastolic > 109 mm Hg in a pregnant woman is considered a hypertensive emergency requiring immediate pharmacologic management.[17]

Epidemiology, Etiology, Pathogenesis

Hypertension is extremely common in the American population. Sixty million US inhabitants suffer from hypertension.[1] The vast majority of these patients have essential hypertension. Moreover, a large number of affected individuals are unaware of their hypertension. Three quarters of those affected do not have their BP well controlled. Fewer than 1% of these patients will develop one or multiple episodes of hypertensive crises.[18,19]

Table 2—*Hypertensive Emergencies*

Hypertensive encephalopathy
Acute aortic dissection
Acute pulmonary edema with respiratory failure
Acute myocardial infarction/unstable angina
Eclampsia
Acute renal failure
Microangiopathic hemolytic anemia

The incidence of hypertensive crises is higher among African Americans and the elderly.[10,13,20,21] The majority of patients presenting with hypertensive crises have previously received a diagnosis of hypertension, and many have been prescribed antihypertensive therapy with inadequate BP control.[10,13,20] The incidence of postoperative hypertensive crises varies depending on the population examined, being reported in 4 to 35% of patients shortly after the surgical procedure.[16,22,23] Like other forms of accelerated hypertension, a history of hypertension is common.

Preeclampsia (pregnancy-related hypertension) is a form of hypertension that deserves mention. The incidence of preeclampsia varies according to the patient characteristics. It occurs in 7% of all pregnancies. Of them, 70% are null-gravidas and 30% are multi-gravidas. In molar pregnancies, preeclampsia has been described in up to 70% of cases.[24]

The pathophysiology of hypertensive crises is thought to be due to abrupt increases in systemic vascular resistance that are likely related to humoral vasoconstrictors.[25,26] With severe elevations of BP, endothelial injury occurs and fibrinoid necrosis of the arterioles ensues.[25,26] This vascular injury leads to deposition of platelets and fibrin, and a breakdown of the normal autoregulatory function. The resulting ischemia prompts further release of vasoactive substances, completing a vicious cycle.[26]

It should be appreciated that most patients who present to hospital with an elevated BP are "chronically hypertensive," with a rightward shift of the pressure/flow (cerebral and renal) autoregulation

curve (Fig 1).[27] Furthermore, most patients with severe hypertension (diastolic pressure $\geq$ 110 mm Hg) have no acute, end-organ damage. Rapid antihypertensive therapy in this setting may be associated with significant morbidity.[28–30] There are, however, true hypertensive emergencies in which the rapid (controlled) lowering of BP is indicated (see below).[18,19,31]

Clinical Manifestations

The manifestations of hypertensive crises are those of end-organ dysfunction. Table 2 lists those conditions that, when associated with severely elevated BP, are referred to as hypertensive crises/emergencies. Organ dysfunction is uncommon with diastolic BPs $<$ 130 mm Hg, although it may occur.

It is important to recognize that the absolute level of BP may not be as important as the rate of increase.[7,9,32,33] For example, patients with long-standing hypertension may tolerate systolic BPs of 200 mm Hg or diastolic increases up to 150 mm Hg without developing hypertensive encephalopathy, while children or pregnant women may develop encephalopathy with diastolic BP $>$ 100 mm Hg.[17]

Headache, altered level of consciousness, and less-severe degrees of CNS dysfunction are the classic manifestations of hypertensive encephalopathy.[6,7] Advanced retinopathy with arteriolar changes, hemorrhages and exudates, as well as papilledema, are commonly seen on examination of fundi in patients with hypertensive encephalopathy. Cardiovascular manifestations of hypertensive crises may include angina or acute myocardial infarction. Cardiac decompensation may lead to symptoms of dyspnea, orthopnea, cough, fatigue or frank pulmonary edema.[10,34] Severe injury to the kidney may lead to renal failure with oliguria and/or hematuria.

In pregnancy, the presentation of a patient with preeclampsia may range from a mild to a life-threatening disease process. The clinical features of severe disease include visual defects, severe headaches, seizures, altered consciousness, cerebrovascular accidents, severe right upper quadrant abdominal pain, congestive heart failure, and oliguria. This process can be ended only by delivery. The decision to continue or to deliver the pregnancy should be made by consultation between medical and obstetric personnel.[11,24,35]

One syndrome warranting special consideration is acute aortic dissection. Propagation of the dissection is dependent not only on the elevation of the BP itself, but also on the velocity of left ventricular ejection.[31,36] For this reason, specific therapy aimed at both targets (BP and rate of pressure rise) is utilized for these cases (see below).

Initial Evaluation of the Patient With Hypertensive Crises

The key to successful management of patients with severely elevated BP is to differentiate hypertensive crises from hypertensive urgencies. This is accomplished by a targeted medical history and physical examination supported by appropriate laboratory evaluation.[19] Prior hypertensive crises, antihypertensive medications prescribed, and BP control should be ascertained. Particular inquiry should include the use of monoamine oxidase inhibitors and recreational drugs (*ie*, cocaine, amphetamines, phencyclidine). The BP *in all limbs* should be measured by the physician. In obese patients, appropriately sized cuffs should be used. Funduscopic examination is mandatory in all cases to detect the presence of papilledema.

A CBC count, electrolytes, BUN, creatinine, and

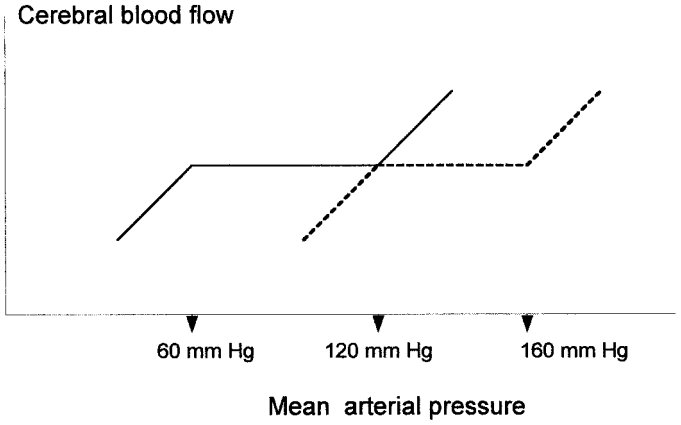

Figure 1. Cerebral autoregulation in normal and hypertensive patients.

urinalysis should be obtained in all patients presenting with hypertensive crises.[19] A peripheral blood smear should be obtained to detect the presence of a microangiopathic hemolytic anemia. In addition, a chest radiograph, ECG, and head CT are useful in patients with evidence of shortness of breath, chest pain, or neurologic changes, respectively. An echocardiogram should be obtained to assess left ventricular function and evidence of ventricular hypertrophy. In many instances, these tests are performed simultaneously with the initiation of antihypertensive therapy.

Therapeutic Approach

Patients with hypertensive emergencies require immediate control of the BP to terminate ongoing end-organ damage, *but not to return BP to normal levels*.[2–5,12,13,30] In patients with hypertensive urgencies, BP is lowered gradually over a period of 24 to 48 h, usually with oral medication. The elevated BP in patients with hypertensive emergencies should be treated in a controlled fashion in an ICU. Intraarterial BP monitoring is essential in all patients with hypertensive emergencies.

The use of sublingual nifedipine must be strongly condemned; this agent may result in a precipitous and uncontrolled fall in BP. Given the seriousness of the reported adverse events and the lack of any clinical documentation attesting to a benefit, the use of nifedipine capsules for hypertensive emergencies and "pseudoemergencies" should be abandoned.[37–46] Similarly, IV hydralazine may result in severe, prolonged, and uncontrolled hypotension, and it is therefore not recommenced. Rapid and uncontrolled reduction of BP may result in cerebral, myocardial, and renal ischemia/infarction.[29,30,37]

The immediate goal of IV therapy is to reduce the diastolic BP by 10 to 15%, or to about 110 mm Hg. In patients with acute aortic dissection, this goal should be achieved within 5 to 10 min. In the other patients, this end point should be achieved within 30 to 60 min.[28] Once the end points of therapy have been reached, the patient can be started on a regimen of oral maintenance therapy.

In pregnancy-related hypertension, IV drug therapy is reserved for those patients with persistent systolic BPs $>$ 180 mm Hg or persistent diastolic BPs $>$ 110 mm Hg (105 mm Hg in some institutions).[47] Prior to delivery, it is desirable to maintain the diastolic BP $>$ 90 mm Hg. This pressure allows for adequate uteroplacental perfusion. If diastolic BP decreases to $<$ 90 mm Hg, decreased uteroplacental perfusion may precipitate acute fetal distress progressing to an in-utero death or to perinatal asphyxia. After delivery, an acute, rapid decrease in BP usually means substantial blood loss and not a cure of the disease process.

It should be emphasized that only patients with hypertensive crises/emergencies (Table 2) require immediate reduction of a markedly elevated BP. In all other patients, the elevated BP can be lowered slowly using oral agents. In patients who have suffered a major cerebrovascular event, the BP should not be lowered, except in exceptional circumstances (see below).

Pharmacologic Management

A growing number of agents are available for management of hypertensive crises. The appropriate therapeutic approach will depend on the clinical presentation of the patient. However, agents that can be administered IV that are rapid acting, are easily titratable, and have a short half-life are recommended (Table 3).

Antihypertensive Drugs Used in Hypertensive Crises (Listed Alphabetically)

Clonidine

Clonidine is available as an oral and transdermal formulation. Oral clonidine (0.1 mg po every 20 min) has been used for the treatment of hypertensive urgencies.[48,49] The onset of action is within 30 min to 2 h, with a duration of action of 6 to 8 h. In a random, double-blind study, comparing the effects of oral nifedipine vs oral clonidine in 51 patients, clonidine was found to produce a more gradual decrease in BP than nifedipine.[48] Sedation was observed in those patients taking clonidine. This medication is an excellent choice for those patients in whom rapid control of BP is not required.

Diazoxide

This drug relaxes arteriolar smooth muscle and has been used in the treatment of severe hypertension.[50] When given IV, the onset of action is within 1 min, with a peak action at 10 min, and a total duration of action ranging from 3 to 18 h.[51] The dose of administration of diazoxide is a minibolus of 1 to 3 mg/kg, to maximum of 150 mg (single dose) injected over 10 to 15 min.[13] If the response is inadequate, repeated doses at 10- to 15-min intervals may be given. Diazoxide has significant side effects. Salt and water retention are commonly seen, and hyperglycemia and hyperuricemia may also occur.

Table 3—*Dosages of IV Antihypertensive Medications*

Drugs	Dosage
Diazoxide	IV injection of 1 to 3 mg/kg to maximum of 150 mg given over 10 to 15 min; may be repeated if inadequate response.
Enalaprilat	IV injection of 1.25 mg 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 500 μg/kg over 1 min, followed by an infusion at 25 to 50 μg/kg/min, which may be increased by 25 μg/kg/min every 10 to 20 min until the desired response to a maximum of 300 μg/kg/min.
Fenoldopam	An initial dose of 0.1 μg/kg/min, titrated by increments of 0.05 to 0.1 μg/kg/min to a maximum of 1.6 μg/kg/min.
Labetalol	Initial bolus 20 mg, followed by boluses of 20 to 80 mg or an infusion starting at 2 mg/min; maximum cumulative dose of 300 mg over 24 h.
Nicardipine	5 mg/h; titrate to effect by increasing 2.5 mg/h every 5 min to a maximum of 15 mg/h.
Nitroprusside	0.5 μg/kg/min; titrate as tolerated to maximum of 2 μg/kg/min.
Phentolamine	1- to 5-mg boluses; maximum dose, 15 mg.
Trimethaphan	0.5 to 1 mg/min; titrate by increasing by 0.5 mg/min as tolerated; maximum dose, 15 mg/min.

Enalaprilat

The use of angiotensin-converting enzyme (ACE) inhibitors for the treatment of hypertensive crises has been studied over the last 2 decades.[42,52–55] As angiotensin II has a pathogenetic role in the development of the malignant phase of hypertension, ACE inhibitors may have an important role in the treatment of these patients.[25,26] While sublingual captopril has been used in the treatment of hypertensive crises, enalaprilat, which is available in an IV formulation, has gained popularity for use in some hypertensive emergencies.[53,55,56–59] Enalaprilat has an onset of action within 15 min, with a duration of action of 12 to 24 h. Hirschl and colleagues[57] have demonstrated that the degree of the BP reduction with IV enalaprilat is correlated with the pretreatment concentration of angiotensin II and plasma renin activity. No adverse side effects or symptomatic hypotension has been reported with IV enalaprilat; however, ACE inhibitors are contraindicated in pregnancy.[53,57]

Esmolol

Esmolol is a cardioselective, β-adrenergic blocking agent that has an extremely short duration of action.[60–62] The metabolism of esmolol is via rapid hydrolysis by RBCs and is not dependent on renal or hepatic function. The onset of action is within 60 s, with a duration of action of 10 to 20 min.[60–62] The pharmacokinetic properties of esmolol, make it the "ideal β-adrenergic blocker" for use in critically ill patients. This agent is available for IV use, both as a bolus and as an infusion. It is of particular value for some supraventricular dysrhythmias, and recently has been used in patients with hypertensive crises and postoperative hypertension.[63–69] Esmolol has proven safe in patients with acute myocardial infarction, even those who have relative contraindications to β-blockers.[70] The recommended initial dose is 0.5 mg/kg followed by an infusion at 25 to 300 μg/kg/min.

Fenoldopam

This agent has recently been approved for the management of acute hypertension in the United States. It is a dopamine (DA)1 agonist that is short acting and has the advantages of increasing renal blood flow and sodium excretion. Fenoldopam has relatively unique actions and represents a new category of antihypertensive medication. While the structure of fenoldopam is based on DA, the former is highly specific for only DA1 receptors and is 10 times more potent than DA as a renal vasodilator.[71] The specific receptor activation is of paramount value in the differentiation of actions between DA and fenoldopam. As fenoldopam interacts only with DA1 receptors, its use is not associated with the adverse effects related to α_1- and β_1-activation.

Fenoldopam activates dopaminergic receptors on the proximal and distal tubules, inhibits sodium reabsorption, and results in diuresis and natriuresis.[72,73] Fenoldopam is rapidly and extensively metabolized by conjugation in the liver, without participation of cytochrome P-450 enzymes. The principal routes of conjugation are methylation, glucuronidation, and sulfation. Only 4% of the administered dose is excreted unchanged. Animal data indicate that the metabolites are inactive.[74] The onset of action is within 5 min, with the maximal response being achieved by 15 min.[75–77] The duration of action is between 30 to 60 min, with the pressure gradually

returning to pretreatment values without rebound once the infusion is stopped.[75–77] No adverse effects have been reported.[75] The dose rate of fenoldopam must be individualized according to body weight and according to the desired rapidity and extent of the pharmacodynamic effect. An initial starting dosage of 0.1 μg/kg/min is recommended.

Fenoldopam has been under clinical investigation since 1981, and has been administered IV to > 1,000 patients. In a prospective, randomized, open-label, multicenter clinical trial, Panacek and coworkers[78] compared fenoldopam with nitroprusside in the treatment of acute hypertension, concluding that both agents had equivalent efficacy. However, fenoldopam has been demonstrated to improve creatinine clearance, urine flow rates, and sodium excretion in severely hypertensive patients with both normal and impaired renal function, whereas these parameters fall in patients treated with nitroprusside.[73,79,80] Fenoldopam may therefore be the drug of choice in severely hypertensive patients with impaired renal function.[81]

Labetalol

Labetalol is a combined blocker of α- and β-adrenergic receptors. Given IV, the α/β-blocking ratio is 1:7.[82] The majority of the drug is metabolized by the liver to form an inactive glucuronide conjugate.[83] The hypotensive effect of labetalol begins within 2 to 5 min after an IV dose, reaches its peak at 5 to 15 min, and persists for about 2 to 4 h.[83,84] Heart rate is maintained or slightly reduced due to its β-blocking effect. Unlike pure β-blockers, which decrease cardiac output, labetalol maintains cardiac output.[85] Labetalol reduces peripheral vascular resistance without reducing peripheral blood flow; cerebral, renal, and coronary blood flow are maintained.[85–88] Little placental transfer occurs, mainly due to the negligible lipid solubility of the drug.[85]

Labetalol has been shown to be effective and safe in the management of hypertensive emergencies, as well as patients with acute myocardial infarction with systemic hypertension.[85,87,89] A loading dose of 20 mg is recommended, followed by repeated incremental doses of 20 to 80 mg given at 10-min intervals until the therapeutic goal is achieved. Alternatively, after the initial loading dose, an infusion commencing at 1 to 2 mg/min and titrated up to until the desired hypotensive effect is achieved may be particularly effective. Once the target BP has been achieved, oral therapy can be initiated. Large, bolus injections of 1 to 2 mg/kg have been reported to produce precipitous falls in BP and should therefore be avoided.[90]

Nicardipine

Over the last 5 years, an IV form of nicardipine has been available and approved in the United States for the treatment of severe hypertension. Nicardipine is a dihydropyridine-derivative calcium channel blocker. It differs from nifedipine by the addition of a tertiary amine structure in the ester side chain from position three of the hydropyridine ring and the movement of the nitro group to the meta position of the phenyl ring.[91,92] These differences make nicardipine 100 times more water soluble than nifedipine, and, therefore, it can be administered IV, making nicardipine a titratable IV calcium channel blocker. The onset of action of IV nicardipine is between 5 to 15 min, with a duration of action of 4 to 6 h.

Several studies have examined the acute effects of nicardipine when administered to patients with severe hypertension.[22,84,93–99] There have also been several studies published comparing the effects of nicardipine with sodium nitroprusside. Halpern and coauthors[95] conducted a multicenter, prospective, randomized study comparing the effect of this agent with nitroprusside in patients with severe postoperative hypertension. These authors reported nicardipine to be as effective as sodium nitroprusside. IV nicardipine, however, has been shown to reduce both cardiac and cerebral ischemia.[38] Its dose is independent of the patient's weight. The current recommended dosage for rapid BP control is 5 mg/h, increasing the infusion rate by 2.5 mg/h every 5 min (to a maximum of 15 mg/h) until the desired BP reduction is achieved.

Nifedipine

Oral/sublingual therapy with short-acting nifedipine has been widely used in the management of hypertensive emergencies, severe hypertension associated with chronic renal failure, perioperative hypertension, and pregnancy-induced hypertension.[39–43,100–103] Nifedipine is not absorbed through the buccal mucosa, but is rapidly absorbed from the GI tract after the capsule is broken and dissolved.[44] Nifedipine causes direct vasodilatation of arterioles, reducing peripheral vascular resistance. A significant decrease in BP is observed 5 to 10 min after nifedipine administration, with a peak effect at between 30 to 60 min and a duration of action of about 6 h.[100] This form of therapy, however, is not "benign."[37,38,45] As mentioned earlier, sudden reductions in BP accompanying the administration of nifedipine may precipitate cerebral, renal, and myocardial ischemic events that have been associated with fatal outcomes.[37] Elderly hypertensive patients with underlying structural vascular disease and target organ impairment tend to be more vulnerable to the

rapid and uncontrolled reduction in arterial pressure.[37] Because the hypotensive effects of nifedipine cannot be closely regulated, this drug *should not be used* for BP control in patients with hypertensive crises.

Nitroprusside

Sodium nitroprusside is an arterial and venous vasodilator that decreases both afterload and preload.[104–108] This drug reacts with cysteine to form nitrocysteine. The later activates guanylate cyclase, which, in turn, stimulates the formation of cyclic guanosine monophosphate that relaxes smooth muscle. When using this agent, cerebral blood flow (CBF) may decrease in a dose-dependent manner. Furthermore, both clinical and experimental studies demonstrate that *nitroprusside increases intracranial pressure*.[109–112]

Nitroprusside is a very potent agent. The onset of action of this drug is within seconds, with a duration of action of 1 to 2 min and a plasma half-life of 3 to 4 min.[104–108,113] If the infusion is stopped abruptly, the BP begins to rise immediately and returns to the pretreatment level within 1 to 10 min. In patients with coronary artery disease, a significant reduction in regional blood flow (coronary steal) can occur.[114] In a large randomized, placebo-controlled trial, nitroprusside was shown to increase mortality when infused in the early hours after acute myocardial infarction (mortality at 13 weeks, 24.2% vs 12.7%).[115]

Sodium nitroprusside is metabolized into cyanogen, which is converted into thiocyanate by the enzyme thiosulfate sulfurtransferase.[107] Nitroprusside contains 44% cyanide by weight. Cyanide is released nonenzymatically from nitroprusside, the amount generated being dependent on the dose of nitroprusside administered. Cyanide is metabolized in the liver to thiocyanate. Thiosulfate is required for this reaction.[107,116] Thiocyanate is 100 times less toxic than cyanide. The thiocyanate generated is excreted largely through the kidneys. Cyanide removal therefore requires adequate liver function, adequate renal function, and adequate bioavailability of thiosulfate.

Sodium nitroprusside has been demonstrated to cause cytotoxicity through the release of nitric oxide, with hydroxyl radical and peroxynitrite generation leading to lipid peroxidation.[117,118] Nitroprusside may also cause cytotoxicity due to the release of cyanide, with interference of cellular respiration.[119,120] Rauhala and colleagues[121] demonstrated lipid peroxidation in the substantia nigra of rats after the administration of nitroprusside. Lipid peroxidation has also been demonstrated in hepatocytes.[119] In addition, nitroprusside causes concentration and time-dependent ototoxicity.[122,123] Cyanide toxicity has been documented to result in "unexplained cardiac arrest," coma, encephalopathy, convulsions, and irreversible focal neurologic abnormalities.[108,124] The current methods of monitoring for cyanide toxicity are insensitive. Metabolic acidosis is usually a preterminal event. In addition, a rise in serum thiocyanate levels is a late event and not directly related to cyanide toxicity. RBC cyanide concentrations (although not widely available) may be a more reliable method of monitoring for cyanide toxicity.[107] An RBC cyanide concentration > 40 nmol/mL results in detectable metabolic changes. Levels > 200 nmol/L are associated with severe clinical symptoms, and levels > 400 nmol/mL are considered lethal.[107] Data suggest that nitroprusside infusion rates > 4 μg/kg/min for as little as 2 to 3 h may lead to cyanide levels that are in the toxic range.[107] The recommended doses of nitroprusside of up to 10 μg/kg/min result in cyanide formation at a far greater rate than human beings can detoxify.

Considering the potential for severe toxicity with nitroprusside, this drug should be used only when other IV antihypertensive agents are not available, and then only in patients with normal renal and hepatic function.[108] The duration of treatment should be as short as possible, and the infusion rate should not be > 2 μg/kg/min. An infusion of thiosulfate should be used in patients receiving higher dosages (4 to 10 μg/kg/min) of nitroprusside.[116] It has also been demonstrated that hydroxocobalamin (vitamin 12a) is safe and effective in preventing and treating cyanide toxicity associated with the use of nitroprusside. This may be given as a continuous infusion at a rate of 25 mg/h. Hydroxocobalamin is unstable and should be stored dry and protected from light. Cyanocobalamin (B12), however, is ineffective as an antidote and is not capable of preventing cyanide toxicity.

Phentolamine

Phentolamine is an α-adrenergic blocking agent that is frequently used for management of catecholamine-induced hypertensive crises (*ie*, pheochromocytoma).[3,7,18,32,33,36] This medication is given IV in 1- to 5-mg boluses. The effect is immediate and may last up to 15 min. Continuous IV infusions have also been used with variable effects. This agent may cause tachydysrhythmias or angina. Once the initial BP is under control, oral phenoxybenzamine, a long-acting α-adrenergic blocking agent, may be given.

Trimethaphan Camsylate

Trimethaphan camsylate is a nondepolarizing ganglionic blocking agent. It blocks the transmission of

impulses at the sympathic and parasympathic ganglia by competing with acetylcholine for cholinergic receptors.[7] This accounts for both its efficacy and its numerous side effects. The reduction in BP observed with this agent is caused by the adrenergic blockade resulting in vasodilatation. The onset of action is within 1 to 5 min, with a duration of action of 10 min. The administration is by constant IV infusion (500 mg is mixed in 500 mL of 5% dextrose water), and is given as initial dosage of 0.5 to 1 mg/min. The dose is then titrated to achieve the desired BP up to a maximum of 15 mg/min. Tachyphylaxis is a common side effect with this medication. It usually occurs within the first 2 days of administration.

Other Agents

Nitroglycerin and hydralazine are sometimes used in the treatment of hypertensive crises, and nitroglycerin may play a significant role in those patients with cardiac ischemia. However, it is important to emphasize that nitroglycerin is not an effective vasodilator.[125] Nitroglycerin is a potent venodilator, and only at high doses affects arterial tone. Nitroglycerin reduces BP by reducing preload and cardiac output, undesirable effects in patients with compromised cerebral and renal perfusion. In addition, it requires special tubing for administration.

Hydralazine has been used as an antihypertensive agent for $>$ 40 years. Following an IM or IV dose, there is an initial latent period of 5 to 15 min followed by a progressive (often precipitous) fall in BP lasting for up to 12 h.[126,127] Although the circulating half-life of the drug is about 3 h, the half-time of its effect on BP is about 100 h.[128] Hydralazine has been demonstrated to bind to the walls of muscular arteries.[129–131] This may explain the prolonged pharmacologic effect of the drug. Because of the prolonged and unpredictable antihypertensive effects of the drug, and the inability to effectively titrate its hypotensive effect, hydralazine should be avoided in the management of hypertensive emergencies. Other regimens utilizing medications such as reserpine, methyldopa, or guanethidine have largely been replaced by the agents described above.

Treatment in Special Situations

Acute Aortic Dissection

IV antihypertensive treatment should be started in the emergency department in all patients (except patients with hypotension) as soon as the diagnosis of acute aortic dissection is suspected (Table 4).[131] These patients must be admitted to an ICU as an emergency. Vascular pressures, urine output, mental status, and neurologic signs should be closely monitored for any deterioration owing to complications.

The aim of antihypertensive therapy is to lessen the pulsatile load or aortic stress by lowering the BP. Reducing the force of left ventricular contractions and, consequently, the rate of rise of aortic pressure retards the propagation of the dissection and aortic rupture. The combination of a vasodilator and a β-blocker is the standard antihypertensive regimen used in these patients; a vasodilator alone may cause an increase in velocity of ventricular contraction and lead to propagation of dissection. Esmolol is the β-adrenergic antagonist of choice.[132] Metoprolol is a suitable alternative.[133] While sodium nitroprusside has traditionally been used in patients with aortic dissection, nicardipine or fenoldopam is a less-toxic alternative.[133,134] Labetalol, an α- and β-adrenergic antagonist, is an alternative to the combination of nitroprusside and β-blocker.[135]

Trimethaphan, a ganglionic blocker as well as direct vasodilator, can be used when sodium nitroprusside is ineffective or poorly tolerated, or when the use of β-blockers is a relative contraindication due to preexisting conditions such as COPD, bradycardia, or congestive heart failure. An advantage over sodium nitroprusside is that it reduces both arterial pressure and its rate of increase, and therefore it does not require concurrent use of β-blockers. How-

Table 4—*Recommended Antihypertensive Agents for Hypertensive Crises*

Conditions	Preferred Treatments
Acute pulmonary edema	Nitroprusside or fenoldopam in combination with nitroglycerin (up to 200 μg/min) and a loop diuretic.
Acute myocardial ischemia	Labetalol or esmolol in combination with nitroglycerin (up to 200 μg/min). Nicardipine or fenoldopam may be added if pressure is controlled poorly with labetalol/esmolol alone.
Hypertensive encephalopathy	Labetalol, nicardipine, or fenoldopam.
Acute aortic dissection	Labetalol or combination of nitroprusside and esmolol.
Eclampsia	Hydralazine (traditional). In the ICU, labetalol or nicardipine is preferred.
Acute renal failure/microangiopathic anemia	Fenoldopam or nicardipine.
Sympathetic crisis	Nicardipine, verapamil, or fenoldopam.

ever, it is less predictable than sodium nitroprusside and has side effects of tachyphylaxis, severe hypotension, urinary retention, and ileus.

Cardiovascular surgical consultation is required in all patients with suspected aortic dissections. Surgery is indicated for all dissections involving the ascending aorta (type A dissection), with the exception of only a few patients with serious associated conditions contraindicating surgery.[136,137] Patients with hypotension suggesting aortic rupture are candidates for emergency surgical repair. Complications of type B dissections, such as leakage of blood from the aorta, impairment of blood flow to an organ or limb, or persistent pain despite an adequate medical regimen are best treated by surgery. Younger patients with Marfan's syndrome may benefit from surgery in the subacute phase and avoid rupture of a residual saccular aneurysm in the future.

Patients with uncomplicated distal dissections are best managed medically in the acute phase with antihypertensive therapy, as survival rate is around 75% whether patients are treated medically or surgically.[31] Also, these patients are generally in the older age group, with a history of cardiac, pulmonary, or renal diseases.

Hypertension After a Cerebrovascular Accident

In healthy humans, cerebral autoregulation maintains constant CBF between a mean systemic arterial pressure of 60 and 120 mm Hg. However, in patients with chronic hypertension, autoregulation is set at a higher level (approximately 120 to 160 mm Hg), presumably to protect the brain from the effects of persistent hypertension (Fig 1).[27] After a stroke, the normal mechanisms of cerebral autoregulation are impaired. Perfusion in the ischemic penumbra becomes pressure dependent. A rise in systemic arterial pressure may be an adaptive response to maintain the blood flow to this vulnerable area. In a series of 334 patients with acute stroke admitted to the hospital, Wallace and Levy[138] found that > 80% had elevated BP on the day of admission. The BPs fell spontaneously and gradually over the next 10 days. By the 10th day after the stroke, only one third of patients remained hypertensive. The mechanisms underlying hypertension after a cerebrovascular accident have not been fully elucidated. Activation of the sympathetic nervous system may be involved as part of a global metabolic response to cerebral infarction, cerebral hemorrhage, or associated edema.

There is no evidence that hypertension has a deleterious effect on the outcome of ischemic strokes during the acute phase.[32,139,140] Lowering the BP in patients with cerebral ischemia may reduce CBF, which, because of impaired autoregulation, may result in further ischemic injury. The common practice of "normalizing" BP is potentially dangerous. When a proximal arterial obstruction results in a mild stroke, a fall in BP may result in further infarction involving the entire territory of that artery.

The current recommendations of the American Heart Association is that hypertension in the setting of acute ischemic stroke should be treated only "rarely and cautiously."[141,142] It is generally recommended that antihypertensive therapy be reserved for patients with a diastolic pressure > 120 to 130 mm Hg, aiming to reduce the pressure by no more than an arbitrary figure of 20% in the first 24 h.[32,139,140,143]

In patients with intracerebral hemorrhage, the value of early antihypertensive therapy in preventing rebleeding or reducing vasogenic edema has not been demonstrated. However, with radiologic evidence of a major intracerebral bleed, cautious lowering of a systolic BP > 200 mm Hg or a diastolic BP > 120 mm Hg is generally suggested.[139,140,144] This recommendation is supported by a recent study that demonstrated that rapid decline in BP within the first 24 h after an intracerebral hemorrhage was associated with increased mortality.[145] In this study, the rate of decline in BP was independently associated with increased mortality. The effect was independent of other variables known to correlate with outcome after intracerebral hemorrhage, including hematoma volume, initial Glasgow Coma Scale score, and presence of ventricular blood.

To our knowledge, there are no data regarding the comparative effects of different antihypertensive drugs on CBF in ischemic stroke. In order to prevent a rapid reduction in BP, short-acting IV agents are preferred. These should be administered in an ICU under close BP monitoring. While nitroprusside is commonly used in this situation, this drug increases intracerebral pressure and has a very narrow therapeutic index, particularly in patients with renal dysfunction (cyanide poisoning). Labetalol is an effective agent; however, nicardipine or fenoldopam is a suitable alternative. IV or oral ACE inhibitors, oral or sublingual nifedipine, and hydralazine should be avoided due to their unpredictable and poorly titratable antihypertensive effects.

Preeclampsia

As mentioned previously, the presentation of a patient with pregnancy-induced hypertension may range from a mild to a life-threatening disease process. The process can be ended only by delivery. The decision to continue or to deliver the pregnancy will be made by consultation between medical and obstetric personnel.

Most preeclamptic patients are vasoconstricted and hemoconcentrated. After initial therapy, volume expansion and hemodilution occur. Magnesium sulfate is considered the standard of therapy as a prophylaxis for seizure activity[146,147]; the loading dose is 4 to 6 g in 100 mL dextrose 0.25 saline solution over 15 to 20 min. A constant infusion of 1 to 2 g/h should then be maintained depending on urine output and deep tendon reflexes that are checked on an hourly basis. Detailed intake and output records must be maintained. Since renal function is frequently impaired, an increase in total body water can result in pulmonary edema. In rare cases, if hyponatremia is allowed to occur, cerebral edema may be observed.

Hydralazine has been used traditionally in the treatment of eclampsia. However, once the patient is admitted to an ICU, labetalol or nicardipine is preferred. Both oral and IV formulations of labetalol and nicardipine appear to be safe and effective agents in hypertensive pregnant patients.[148–152]

Hypertensive Urgencies and Sympathetic Crises

Abrupt discontinuation of treatment with a short-acting sympathetic blocker (such as clonidine or propranolol) can lead to severe hypertension. Control of BP can be achieved in this setting by readministration of the discontinued drug. Should evidence of pulmonary edema of coronary ischemia be present, patients should be treated as outlined in Table 4.

In addition to drug therapy withdrawal, increased adrenergic activity can lead to severe hypertension in a variety of other clinical settings. These include the use of sympathomimetic drugs such as cocaine, amphetamines, phencyclidine, or the combination of a monoamine oxidase inhibitor and the ingestion of tyramine-containing foods, pheochromocytoma, and autonomic dysfunction, as in Guillian-Barré syndrome.

The use of β-blockers should be avoided in these patients, since inhibition of β–receptor-induced vasodilation results in unopposed α-adrenergic vasoconstriction and a further rise in BP. The use of β-blockers has been demonstrated to enhance cocaine-induced coronary vasoconstriction, increase BP, fail to control the heart rate, increase the likelihood of seizures, and decrease survival.[153–155] Although some patients have been treated with labetalol without adverse consequences, controlled experiments in animals and humans do not support its use.[156,157] In studies of cocaine intoxication in animals, labetalol increased seizure activity and mortality.[158,159] Furthermore, experimental studies have demonstrated that labetalol does not alleviate cocaine-induced coronary vasoconstriction.[160] Labetalol has been reported to have a hypertensive response in patients with pheochromocytoma.[161] Control of BP in these patients is best achieved with nicardipine, verapamil, or fenoldopam.[155,162,163] Phentolamine and nitroprusside are alternative agents.[164]

Hypertensive Crises in End-Stage Renal Disease

The most important cardiovascular complication of chronic renal failure is hypertension. The cause of hypertension in chronic renal failure is an increase in extracellular volume secondary to sodium retention by the diseased kidney, as well as vasoconstriction due to increased activity of the renin-angiotensin system.[25] Hypertensive crises may exacerbate renal failure and, therefore, need to be treated promptly. IV calcium channel blockers have been used for these patients with some success.[165] Patients may require emergent ultrafiltration in order to control the BP. Bilateral nephrectomy has been reported to "cure" malignant hypertension in hemodialysis patients.[166]

Conclusion

The key to the successful management of patients with severely elevated BP is to differentiate hypertensive crises from hypertensive urgencies. Patients with hypertensive urgencies have severe hypertension (diastolic > 110 mm Hg), but without clinical evidence of acute end-organ damage. Rapid antihypertensive therapy is not warranted in these patients. Hypertensive crises constitute a distinct group of clinicopathologic entities associated with acute target organ injury. These patients require immediate BP reduction to prevent progressive end-organ damage. Hypertension associated with cerebral infarction or intracerebral hemorrhage only rarely requires treatment. Patients with hypertensive crises are best treated in an ICU with titratable IV hypotensive agents. Several rapid-acting IV antihypertensive agents are available, including labetalol, esmolol, fenoldopam, nicardipine, and sodium nitroprusside. While nitroprusside is commonly used to treat severe hypertension, it is an extremely toxic drug that should be used only in rare circumstances.

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